POCKET NOTEBOOK

POCKET NEUROLOGY

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PREFACE

Most neurology residents, like most medicine residents, rely heavily on Pocket Medicine during their intern year in internal medicine. However, early during neurology residency, it becomes clear that no comparably concise and complete pocket handbook exists for Neurology house officers; hence was born the idea to write Pocket Neurology.

In this book, chapters have been written by neurology residents and beginning neurology fellows in collaboration with attending neurologists at the Massachusetts General Hospital, Brigham and Women's Hospital, Children's Hospital Boston, and Beth Israel Deaconess Medical Center. We have tried to make this book both a practical and a thorough guide to the process of working from neurologic signs and symptoms to differential diagnosis, to workup and diagnosis, to assessment of risks and benefits of available treatments, and finally to treatment and prognosis of the neurologic diseases residents encounter in the hospital and clinic. We have tried to imagine a scenario in which this book will be the only immediate source of information available, and accordingly we have worked to ensure that each chapter contains all the needed information, organized in a readily accessible way.

We hope that this book will serve as a valuable tool to any house officer in need of a comprehensive, quick reference when confronted with a challenging neurologic case.

Neurologic Emergencies: Quick Reference
ACUTE ISCHEMIC STROKE

Stroke: An acute neurologic event, secondary to ischemia or hemorrhage. Ischemic stroke is due to ischemia of brain tissue secondary to either thrombosis or emboli to the cerebral vessels. May p/w a variety of neurologic sx, such as weakness, numbness, aphasia, dysarthria or slurred speech, gaze deviations, ataxia, gait instability. Sx are usually acute onset, although they may fluctuate or "stutter" over several days. Risk factors: Age, hypertension, hyperlipidemia, smoking, diabetes, hypercoagulable states, cardiac arrhythmias such as atrial fibrillation, cardiomyopathy, & presence of a cardiac thrombus, among many others.

Initial steps in evaluating acute stroke: Determine time of onset. Note: If pt awakens w/ sx, time of onset is when they were last seen normal. Consider a stroke as amenable to possible acute therapy or intervention if:

- Symptom onset < 8 h prior to presentation
- Large basilar thrombus, large MCA, or large cerebellar infarct (>1/3 cerebellum or encroaching fourth ventricle) even if not w/in time window

Laboratory workup & tests: EKG, cardiac monitor, vital signs, accucheck, keep O_2 sat > 92%, CBC, ESR, T & S, PT-INR, PTT, Chem 7, LFTS, cardiac markers, STAT CT/CTA head & neck, & CT perfusion. If ordering MRI, make sure pt doesn't have pacer or metal in body.

- Obtain NIH stroke scale (NIHSS) & document vitals & time.
- Determine if pt meets criteria for IV TPA or intravascular procedure (IA TPA or mechanical clot retrieval, such as the MERCI or penumbra device). See below for the indications & contraindications of each.
- Contact neurointerventionalist or a facility w/ an interventional service to determine if pt may be a candidate for IA TPA or mechanical clot retrieval.

IV TPA

Indications: Age ≥ 18 yr; significant neurologic deficit expected to result in long-term disability; CT Brain that does not show a hemorrhage or well-established new infarct; acute ischemic stroke sx with time of onset clearly defined as <3 h. For cases where onset is 3-4.5 h, IV TPA may be considered (NEJM 2008;359:1317).

Contraindications to IV TPA: Hypodensity > 1/3 territory on head CT; blood on CT; recent stroke, head trauma, or intracranial procedure (<3 mo); h/o intracerebral hemorrhage (ICH), brain aneurysm, vascular malformation, brain tumor (may consider w/ CNS lesions w/ very low likelihood to bleed, such as small unruptured aneurysms or benign tumors w/ low vascularity); resolving or minimal deficit; suspicion of SAH; recent trauma or surgery (<15 days); active internal bleeding; h/o GI/GU bleeding (<22 days); recent LP or noncompressible arterial puncture (<7 days); bleeding diathesis (INR > 1.7; PT > 15; PTT > 40; platelets < 100, or known bleeding diathesis); uncontrollable HTN: SBP > 185, DBP > 110 despite medications to lower it; seizure at onset if deficits are believed to be due to postictal state. If dx of vascular occlusion made, then Rx may be given; for the 3-4.5 h window, other contraindications include: NIHSS > 25, h/o oral anticoagulant use, combination of previous stroke & DM.

Cautions w/ IV TPA (may have worse outcome w/ IV TPA but not necessarily contraindicated): Severe stroke deficit or NIHSS > 22; glucose < 50 or > 400; known L heart thrombus; conditions that increase risk of bleeding: pericarditis, endocarditis or high risk for septic emboli, liver or kidney disease causing increased bleeding risk, pregnancy, diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions; life expectancy <1 yr or severe comorbid illness.

IV TPA administration

- Initial workup & labs as above. Check list of contraindications. Double check time window (<4.5 h). Obtain consent from pt or family.
- TPA dose: 0.9 mg/kg w/ a max dose of 90 mg. Give 10% as bolus IV over 1 min & the remainder over 60 min.
- Maintain goal SBP < 180, DBP < 105. If BP needs to be lowered, use labetalol 5-20 mg IV q10-20min or nicardipine infusion 5-15 mg/h. Monitor pt in an intensive care unit for at least 24 h observation. Avoid arterial sticks, anticoagulation, antiplatelet agents for 24 h. During the first 24 h after TPA is given, check BP q15min × 2 h, then q30min × 6 h, then q1h for 24 h after starting Rx.
- F/u CT brain at 24 h. STAT CT if change in neurologic exam.

- When pt is stabilized, complete routine stroke workup. (See chapter on Stroke and Cerebrovascular Neurology.) (NEJM 1995;333:1581; MGH Acute Stroke IV/IA Thrombolysis Protocol 2005)

IA TPA/MECHANICAL THROMBOLYSIS

Indications for IA procedures: Significant neurologic deficit causing long-term disability; deficits attributable to large vessel occlusion (basilar, vertebral, internal carotid, or middle cerebral artery M1 or M2 branches); noncontrast CT scan w/o hemorrhage or well-established infarct; time of onset of ischemic stroke clearly defined. For anterior circulation, window is 6-8 h of nonfluctuating deficits. For posterior circulation, window less well defined & can be many hours or days of fluctuating, reversible sx.

Contraindications for IA procedures: ICH; well-established acute infarct on CT or MRI; major infarct > 1/3 cerebral hemisphere; CNS lesions w/ high likelihood of hemorrhage (brain tumors, abscess, vascular malformation); seizure at onset if deficits are believed to be due to postictal state (if dx of vascular occlusion made, then Rx may be given); suspicion of SAH.

Warnings for IA procedures (may be associated w/ unfavorable outcomes but not necessarily contraindicated): Recent surgeries or trauma (<15 days); recent ICH, spinal surgery, head trauma, or stroke (<3 mo); h/o ICH, brain aneurysm, vascular malformation, brain tumor (may consider IA infusion w/ CNS lesions w/ low likelihood of bleeding such as a small unruptured aneurysm or benign tumors w/ low vascularity); active internal bleeding or arterial puncture site (<22 days); platelet <100, PTT > 40 after heparin use, PT > 15, INR > 1.7, or known bleeding diathesis; stroke sx too severe; NIHSS > 22; glucose < 50 or > 400 mg/dL; left heart thrombus documented; increased risk of bleeding due to a variety of conditions (acute pericarditis, bacterial endocarditis, hemostatic defects due to hepatic or renal disease, pregnancy, diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions, septic thrombophlebitis or occluded AV cannula at seriously infected site, patients currently receiving oral anticoagulants, i.e., warfarin w/ INR > 1.7, advanced age, s/p full dose IV TPA); rapid improvement or stroke sx too mild; NIHSS < 8; life expectancy <1 yr or severe comorbid illness.

Preparing pt for IA TPA/mechanical thrombolysis: If pt is a candidate for IA TPA or mechanical clot retrieval, contact a neurointerventionalist or a facility with a neurointerventional service. Maintain O_2 sat > 92%. Treat fever w/ Tylenol. Keep pt NPO. Avoid placing Foley, NGT, femoral catheters, a-line, or central venous line unless necessary. Do not give heparin. Do not lower BP

unless MI or BP >220/120. If BP needs to be lowered, use labetalol 5-20 mg IV q10-20min or nicardipine IV 5-15 mg/h. Monitor BP q15min or continuously. Pt will need to be admitted to an intensive care unit for 24 h observation.

After IA TPA/mechanical thrombolysis: Pt will need STAT CT head right after procedure to evaluate for hemorrhage & admission to an ICU for post-TPA/intervention monitoring. F/u CT head at 24 h. When pt is stabilized, complete routine stroke workup; see chapter on Stroke and Cerebrovascular Neurology (JAMA 1999;282:2003).

INTRACEREBRAL HEMORRHAGE

Clinical presentation: Sx vary depending on the location w/in the brain or spinal cord. May include weakness, sensory loss, aphasia, field deficits, gaze deviation, neglect, altered mental status, headache, n/v, ataxia, & dysmetria. Typically sudden onset; may be more gradual w/ subdural hematoma (SDH) or occur over several hours or days if the hemorrhage is expanding. Common locations: cerebral lobes, basal ganglia, thalamus, pons, & cerebellum.

Risk factors or potential underlying causes: Hypertension, amyloid angiopathy, aneurysm, vascular malformation, trauma, neoplasm, venous sinus thrombosis, hemorrhagic conversion of a stroke, vasculitis, coagulopathy, cocaine, amphetamines, alcohol, a variety of infections among many others.

Dx: CT/CTA head & neck. Note the location & size of hemorrhage, degree of mass effect or herniation, & presence of intraventricular blood or hydrocephalus. Conventional angiogram in select cases to evaluate for vascular malformation, aneurysm, or vasculitis, which was not seen on CTA. Consider routine MRI brain to evaluate for underlying mass lesion or stroke.

Rx

- ABCs, intubation if depressed level of consciousness & inability to protect airway. A-line, goal SBP 100-160. Central line, if anticipated will need 23% saline or become hypotensive.

- Consider urgent neurosurgical evaluation, particularly if aneurysm rupture, AVM, dural AV fistula, symptomatic SDH, intraventricular extension, hydrocephalus, significant mass effect/herniation, cerebellar hemorrhage, depressed mental status. If intraventricular hemorrhage or hydrocephalus, urgent neurosurgical consultation for external ventricular device or intracranial pressure monitoring.

- Labs: CBC, Chem 7, PT-INR, PTT, blood bank sample, d-dimer, fibrinogen, LFTs. If INR > 1.3, correct coagulopathy STAT. Give Vitamin K 10 mg IV × 1 & FFP 2-4 Units STAT for a goal INR of < 1.3. Consider profilnine if available. Check coags q4h × 24 h & repeat FFP & Vitamin K if needed for goal INR < 1.3.
- To calculate volume of hemorrhage = (a × b × c)/2, where a = length, b = width, & c = number of cuts on CT brain (assuming cuts are 0.5 mm each). If significant mass effect, consider osmotic agents & hypertonic saline as needed. (See below for management of acute elevation in intracranial pressure.) Avoid corticosteroids. Surgical evacuation may be considered in select cases of cerebellar hemorrhages. No evidence of benefit from surgical evacuation of basal ganglia, thalamic, & pontine hemorrhages (Stroke 1997;82:2126).
- Consider admission to an intensive care unit for close monitoring. F/u CT brain in 6 h. STAT CT if change in neurologic exam (NEJM 2001;344:1450; Lancet 2009;373:1632; MGH Adult ICH Protocol 2008).

ACUTE ELEVATION IN INTRACRANIAL PRESSURE (ICP)

Elevated ICP is due to a variety of neurologic conditions, such as hemorrhage, tumor, encephalitis, hydrocephalus, stroke, global anoxic injury, trauma.

Sx: Headache, altered mental status, somnolence, motor or sensory deficits, speech or swallowing difficulties, seizures, n/v. Late findings: anisocoria, decerebrate or decorticate posturing, apnea, coma, Cushing triad (hypertension, bradycardia, & irregular respirations).

Dx: Clinical presentation/exam; CT brain to determine underlying cause or degree of mass effect on surrounding structures.

Rx:

- ABCs, consider intubation if depressed mental status or inability to protect airway, vital signs, cardiac monitoring, HOB elevated 30 degrees. Goal ICP is <20 mm Hg & cerebral perfusion pressure > 60-70. Consult neurosurgery for possible EVD or ICP monitor or hemicraniectomy posterior fossa decompression if lesion with significant mass effect.
- If herniation:
    - 1. STAT mannitol 100 g IV bolus, followed by 0.5-1 g/kg. Contraindications: low BP, anuria secondary to renal disease, serum osm > 340. Hold dose for Na > 160, serum osm > 340, or osm gap > 10. Osm gap = measured - calculated serum osms. Calculated

serum osms = 2Na + BUN/2.8 + Glu/18. Check Chem 7, serum osmolarity q6h.

- 2. Hypertonic saline: Goal sodium 145-155. For 23% saline, give 30 cc × 1 via central line over 20 min, followed by 15-30 cc q6h via central line if needed. For 3% saline, 40-50 cc/h can go through peripheral IV for up to 12 h, then needs a central line. Contraindications: Na > 160.
- 3. Hyperventilation: For goal pCO_2 ˜ 30

- If ICP due to tumor or infection, then dexamethasone 10 mg IV × 1, then 4 mg q6h.
- For any pt w/ a mass lesion, stroke, tumor, hemorrhage, keep goal sodium 145-155. Avoid free water in IVF, such as D5W, 1/2 NS, D5 1/2 NS, LR. This is especially important to monitor, since these are frequently used as maintenance fluids (J Emerg Med 1999;17:711-719).

ACUTE MENINGITIS AND ENCEPHALITIS

Clinical presentation: Si/sx: Fever, nuchal rigidity, n/v, headache, photophobia, seizure, altered or depressed mental status, papilledema, neurologic deficits, rash in meningococcus. Uncomplicated viral meningitis does not typically p/w neurologic deficits. Classic triad of fever, neck stiffness, & altered mental status w/ low sensitivity (˜44%). Almost all pts p/w at least two of following sx: headache, neck stiffness, altered mental status (GCS < 14), fever.

Dx: Labs: Chem 10, CBC, UA, CXR, blood cx × 2, coags. Consider PPD, HIV, ESR, CRP, further w/u for system infection depending on clinical history. When CT brain recommended before LP: altered mental status, seizures, immunocompromised state, abnormal neurologic exam, papilledema. If obtaining CT prior to LP, draw stat blood cultures & start empiric antibiotic coverage immediately (i.e., do not wait for LP to start antibiotics). (NEJM 2001;345:1727). Lumbar puncture: should obtain opening pressure, cell count & differential, protein, glucose, Gram stain, & culture. Consider wet mount for

fungal stain, AFB, India ink, VDRL, Lyme PCR, HSV PCR, PCR of other viruses, latex agglutination for specific bacterial infections depending on clinical history.

LP Results in Meningitis

Type	OP [cm H_2O]	WBC [cells/µL]	Diff	Prot [mg/dL]	Glu [mg/dL]	Sta cx, & O Tests
Bacterial	High (>18)	High (10-10,000)	PMN predom	High (>50)	Low (<40)	GS latex agglutin
Fungal	High	High (30-300)	Lymph predom	High	Low	Fur stains & India ink
Viral	Nml or mildly high (10-35)	High (25-500)	Lymph predom; PMNs in first 48 h	Nml to high (20-80)	Nml	PC CSF & serologi studies f specific viruses
Tb	High	High (10-500)	Lymph predom	High (10-500)	Low (20-40)	AF cx, PCR

OP, opening pressure; diff, WBC differential; prot, protein; glu, glucose; predom, predominance; lymph, lymphocyte; GS, Gram stain; sens, sensitivity.

Meningitis, Encephalitis, Brain Abscess, and Empyema. *Harrison's Neurology in Clinical Medicine*. ed. Hauser SL. McGraw-Hill, 2006:423-455.

Management

- Empiric coverage: Antimicrobial choice depends on age of pt, allergies, & clinical setting. Modify antimicrobial choice based on organism identification & sensitivities. Prophylaxis: recommended for close contacts of pts w/ meningococcal meningitis w/ either rifampin, ceftriaxone, ciprofloxacin, or azithromycin. Respiratory isolation for 24 h in cases w/ meningococcal meningitis.
- Consider dexamethasone for bacterial meningitis: dexamethasone 10 mg × 1 before or w/ first dose of antibiotics, then 10 mg q6h × 4 days. Avoid empiric dexamethasone if allergy/sensitivity, antibiotic therapy, head trauma, CSF shunt, or infection is not bacterial (NEJM 2002;347:1549).

Empiric Antimicrobial Coverage for Meningitis/Encephalitis

Clinical Scenario	Antibiotic	Organisms Covered
Age 16-50 yr	Vancomycin + third gen. cephalosporin	N. *meningitides, S. pneumoniae, H. influenzae*
Age > 50 yr	Vancomycin + third gen. cephalosporin + ampicillin	*N. meningitides, S. pneumoniae, L. monocytogenes,* GNR
Immunocompromised	Vancomycin + ampicillin + third gen. cephalosporin covering pseudomonas	*N. meningitides, S. pneumoniae, L. monocytogenes, H. influenzae,* GNR
Postneurosurgery/head trauma	Vancomycin + third gen. cephalosporin covering pseudomonas	*S. aureus, S. pneumoniae,* GNR
HSV encephalitis	Acyclovir	HSV

Note: For antibiotic coverage of specific organism, please see the chapter on *Neuro-Infectious Diseases*. (*NEJM* 2004;351:1849; *NEJM* 2006;354:44; *Bacterial Infections, Neurology in Clinical Practice,* Vol. II, 4th edition.

Editors: Bradley WG, Daroff RB, et al., 2004:1475-1514.)

NEOPLASTIC EPIDURAL SPINAL CORD COMPRESSION

Clinical presentation: Neck or back pain, weakness, numbness, loss of bowel or bladder function; hyperreflexia or hyporeflexia, decreased rectal tone, & Lhermitte's sign; malignancies that commonly metastasize to the cord: breast, lung, prostate, renal cell, & thyroid ca.

Dx: Clinical history & MRI spine w/ gadolinium; in pt w/ h/o malignancy, obtain imaging of entire spine.

Rx: If paraparesis & evidence of cord compression on imaging, give

dexamethasone 100 mg IV × 1, then 24 mg po qid × 3 days, followed by a taper over 10 days or when definitive Rx (surgery or XRT) is underway. For minor neurologic sx & no paraparesis & mild cord compression on imaging, administer dexamethasone 10 mg IV × 1, followed by 4 mg q6h, tapered over 10 days or when definitive Rx (surgery or XRT) is underway. Consult neurosurgery for possible surgical decompression, radiation oncology for XRT, & neuro-oncology for long-term follow-up/ monitoring (Lancet 2005;366:643; Neurology 1989;39:1255; Curr Oncol Rep 2008;10:78).

STATUS EPILEPTICUS

Clinical presentation: Status epilepticus (SE): >5 min of persistent, generalized convulsive seizure activity or ≥2 discrete seizures where there is incomplete recovery of consciousness in between. Diverse causes & clinical sx, including unresponsiveness, obtundation, repetitive rhythmic movements. May be convulsive or nonconvulsive. Approximately 7% generalized tonic-clonic seizures will progress to SE (J Intensive Care Med 2007;22:319).

Dx: Clinical presentation & EEG.

Rx

0-5 min: ABCs, O_2 sat, coma exam, ECG, IV access & draw labs for Chem 10, CBC, LFTs, PT-INR, PTT, AED levels, ABG, cardiac markers, urine & serum toxicology. Place pt on cardiac monitor.

6-10 min:

- Thiamine 100 mg IV followed by 50% dextrose 50 cc IV; consider naloxone.
- Lorazepam: 4 mg IV over 2 min (may give as 1-2 mg boluses); if still having seizures, may repeat × 1 in 5 min. Or diazepam 5 mg IV q3min × 4, while starting dilantin load. If no IV access, give diazepam 20 mg pr or midazolam 10 mg intranasally, buccally, or IM.

11-20 min: If seizures persist, give one of the following:

- Fosphenytoin: Load 20 mg/kg PE IV at 150 mg/min. Keep on cardiac monitoring. May give an additional 500 PE IV if no response.
- Dilantin 1,000 mg IV at <50 mg/min. May give an additional 500 mg IV if no response after 20 min. (Note: Do not give w/ glucose or dextrose due to precipitation.)
- Valproate 1 g over 15-20 min (20-40 mg/kg). Therapeutic level is 50-100. May give an additional 500 mg after 20 min.

21-60 min: If seizures persist, give one of the following four options (intubation is necessary except for valproate):

- IV midazolam: Load 0.2 mg/kg; repeat 0.2-0.4 mg/kg boluses every 5 min until seizures stop, up to a maximum loading dose of 2.9 mg/kg. Initial IV rate 0.1 mg/kg/h w/ a maintenance range from 0.05 to 2.9 mg/kg/h. If still having seizure, switch to or add propofol or pentobarbital.
- IV propofol: Load 1-2 mg/kg; repeat 1-2 mg/kg boluses every 3-5 min until seizures stop, up to a maximum total loading dose of 10 mg/kg. Initial IV rate: 2 mg/kg/h. IV dose range: 1-15 mg/kg/h. If still having seizures, switch to midazolam, valproate, or pentobarbital.
- IV valproate (if not given above): 40 mg/kg over ˜10 min. If still having seizures, give an additional 20 mg/kg over ˜5 min. If still having seizures, add or switch to IV midazolam or propofol.
- IV phenobarbital: 20 mg/kg at 50-100 mg/min. If still having seizures, add or switch to IV midazolam, propofol, or pentobarbital.

>60 min:

- IV pentobarbital: Load 5 mg/kg at up to 50 mg/min; repeat 5 mg/kg boluses until seizures stop. Initial IV rate: 1 mg/kg/h. IV dose range: 0.5-10 mg/kg/h; traditionally titrated to burst suppression on EEG but titrating to seizure suppression is reasonable as well.
- Pt will need to be admitted to an intensive care unit. Begin EEG monitoring as soon as possible if patient does not rapidly awaken or if any continuous IV Rx is used.
- Consider CT brain or MRI brain. Evaluate for & correct underlying causes.

Onset of action of AEDs: Lorazepam: 3-10 min; phenytoin IV: 20-25 min; fosphenytoin IV: 20-25 min; phenobarbital IV: 1-5 min.

Goal therapeutic level: (1) Phenytoin & fosphenytoin: 20-25 µg/mL for SE & 10-20 otherwise. Fosphenytoin levels should be checked >2 h after an IV load or >4 h after

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an IM load. (2) Valproate: 70-140 µg/mL for SE & 50-100 otherwise. (3) Phenobarbital: 30-45 µg/mL for epilepticus & 15-40 otherwise. (4) Carbamazepine: 4-12 µg/mL.

Side effects of AEDs used in SE

Phenytoin: Lethargy, abnormal movements, mental confusion, cognitive changes, gingival hyperplasia, acne, hirsutism, osteoporosis, rash/Stevens-Johnson/TEN. At levels >20 µg/dL, nystagmus, ataxia, dysarthria, & encephalopathy. At higher levels, can get cardiac dysrhythmias.

Phenobarbital/primidone: Sedation, memory loss, irritability, depression, aplastic anemia, hepatic failure, Stevens-Johnson/TEN. Connective tissue abnormalities w/ long-term use.

Valproic acid: Drowsiness, n/v, GI disturbances, tremor, weight gain, hair loss, fatal hepatotoxicity, pancreatitis, PCOS, Stevens-Johnson/TEN. May cause spinal bifida in children exposed to valproate neonatally.

Benzodiazepines: Drowsiness, ataxia, behavioral problems.

Contraindicated in generalized epilepsy syndromes: Carbamazepine, oxcarbazepine.

Renally cleared AEDs: Levetiracetam, topiramate (70%), gabapentin, pregabalin (Continuum: Epilepsy 2007:121).

GUILLAIN-BARRÉ SYNDROME

Clinical presentation: Rapid (days-1 mo) symmetric weakness, weak or absent deep tendon reflexes; may develop facial diplegia, poor swallowing or breathing, stocking/glove numbness in hands & feet. Sometimes proximal > distal weakness. Autonomic instability & diffuse back pain. May be a h/o infection, vaccination, or surgery 1-3 wk prior.

Variants: AIDP, Miller Fisher syndrome, acute motor sensory axonal neuropathy (AMSAN), acute motor axonal neuropathy (AMAN), acute pandysautonomia, sensory GBS. (See chapter on Peripheral Neuropathy for workup & differential dx.)

Rx: Place on monitor & watch for autonomic instability; NIFs & FVCs TID. Remember: O_2 sat is not sensitive & pt will become hypercarbic before becoming hypoxic. Intubate if FVC < 15 cc/kg or 1 L & NIF < 20 or rapid decline. If intubation >2 wk, consider tracheostomy. Plasma exchange or IVIg: benefit if given w/in 2 wk of symptom onset; see below for dosing (Lancet 1997;349:225). Narcotics for back pain; protect eyes from drying out; DVT prophylaxis; watch for SIADH.

Plasmapheresis: Five exchanges (40-50 mL/kg) qod w/ saline & albumin replacement fluid. Risks: Bleeding, infection, hematoma formation, pneumothorax w/ venous access. Contraindications: sepsis, active bleeding, cardiovascular instability.

IVIg: 0.4 /kg/day daily × 5 days. Check IgA level prior to administering IVIg. Pretreat w/ acetaminophen & diphenhydramine before each infusion & repeat the dose 6 h later if necessary. Risks: headaches, myalgias, arthralgias, flu-like sx, fever, & vasomotor reactions. Rare but serious complications: anaphylaxis in IgA deficient pts, aseptic meningitis, CHF, stroke, MI, renal failure. Contraindications: hyperviscosity, CHF, CRF, congenital IgA deficiency.

Prognosis: Fatal in <5%, 20% disabled, & 20% have permanent deficits; 3% recurrence; maximum deficit w/in 4 wk of onset. Poorer outcome w/ axonal variants, age > 60, bed-bound, intubated, rapid onset w/ max < 7 days, prior diarrheal illness, motor amplitude < 250 (J Clin Neurosci 2009;16:733).

MYASTHENIC CRISIS

Clinical presentation: Disease of the neuromuscular junction characterized by fatigable weakness & decreased number of nicotinic acetylcholine receptors on postsynaptic membranes. Most commonly due to autoimmune condition where antibodies are directed against components of the neuromuscular junction, most often the nicotinic acetylcholine receptors, although congenital myasthenic syndromes exist as well.

Sx: Ptosis, diplopia, dysarthria, dysphagia, weakness of the neck, shoulder, or facial muscles, overall fatigue, weakness of the extremities, & respiratory failure in severe cases. Often fluctuate & are usually worse at night or after significant use. Pts in myasthenic crisis may p/w worsening weakness with the risk of respiratory failure or death.

Triggers: Infection, medications (see below), stress/surgery/trauma, botox administration. (See chapter on Neuromuscular Junction Disorders for workup of a new dx & differential.)

Management: Place on cardiac monitor; consider monitoring in the intensive care unit. FVC & NIFs tid. Intubate for FVC < 15 mL/kg & NIF < -20 or rapid respiratory

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decline. O_2 sat is not sensitive & pt will become hypercarbic before becoming hypoxic. Remove precipitants: drugs, infection, heat.

Cholinergics: Neostigmine 0.5 mg IV push, followed by pyridostigmine 24 mg in 500 mL D5 1/2 NS.

Plasma exchange/IVIg: Plasma exchange: remove 2-3 L 3×/wk until improvement, usually five to six exchanges. (See section on GBS for side effects.) IVIg: 2 g/kg infused in divided doses over 2-5 days. Check IgA

before giving. Pretreat w/ Tylenol & Benadryl before each infusion & repeat the dose 6 h later if necessary. (See section on GBS for side effects.)

Steroids: Consider methylprednisolone 60 mg IV daily. Steroids may acutely worsen

weakness; so monitor closely.

Drugs to avoid: Beta-blockers, procainamide, lidocaine, quinidine, aminoglycosides, tetracycline, ciprofloxacin, clindamycin, phenytoin, lithium, trimethadione, chloroquine, D-penicillamine, & magnesium.

Lesion Localization in Clinical Neurology

CEREBRAL HEMISPHERES

LOBES: KEY FUNCTIONS & LESIONAL DEFICITS

Frontal lobe functions: Mvmt: Mediated by 1° and supplementary motor areas; voluntary mvmt of eyes to opposite side: mediated by frontal eye fields; attention, planning, judgment, insight, abstract thinking; Lang: See below.

Lesions involving the frontal lobe & clinical manifestations: Orbitofrontal synd: Disinhibition, impulsive behav; Frontal convexity synd: Apathetic, angry/aggressive behav. There may be assoc disturbances in mvmt. Medial frontal synd: Mutism, gait disturbances, & bladder incont.; Massive frontal lobe lesion: Akinetic, apathetic, & abulic state; Broca area: Inf frontal region in areas 44 & 45; resultant expressive aphasia characterized by nonfluent speech w/ rel intact comprehension & impaired repetition, reading, & writing.

Parietal lobe functions: Sensation: Somatosens area in postcentral gyrus. Attention: An inf parietal lesion, typ nondominant → contralat hemispatial neglect, anosagnosia.

Lesions involving the parietal lobe & clinical manifestations: Gerstmann synd: Lesion in dominant, inf parietal lobe → acalculia, alexia, finger agnosia, L-R confusion; Lesion of dominant angular gyrus: Alexia w/ agraphia; Balint synd: Bilat parietooccipital lesions; often due to watershed infarcts between PCA & MCA territories. Sx incl optic ataxia, ocular apraxia, visual inattention, simultagnosia.

Temporal lobe functions: Recognition of stimuli. Hearing: Mediated by 1° auditory areas in transv temporal gyrus & 2° auditory areas in sup temporal gyrus; Memory: Med by hippocampus; Lang: See below.

Lesions involving the temporal lobe & clinical manifestations: Prosopagnosia: Bilat or nondominant occipital temporal lesion → inability to identify or recognize faces. Kluver-Bucy synd: Bilat lesions of the medial temporal lobes or amygdala → hyperorality, hypersexuality, changes in emotional behav. Wernicke aphasia: Receptive lang disturbance w/ nonsensical fluent speech w/ poor comprehension & repetition.

Occipital lobe functions: Vision (calcarine cortex): Lesions may cause

blindness, vision loss, or visual agnosia.

Lesions involving the occipital lobe & clinical manifestations: Anton synd: Bilat parieto-occipital lesions → unaware of blindness. Preserved pupillary light reaction. Palinopsia: Persistence of visual image for several minutes despite gazing at another scene. Often 2° to occipitotemporal dz or during recovery from cortical blindness. Alexia w/o agraphia: Dom occipital lobe & splenium of corpus callosum. Often accom by a R homonymous hemianopia & color naming deficits.

Lateralization of cerebral hemispheres: Right hemisphere: Spatial & constructional skills, nonvisuospatial perception, emotional tone of speech. Left hemisphere: Lang, analytic & mathematic skills, reasoning.

Major white matter tracts connecting hemispheres: Corpus callosum, anterior commissure.

P.8

VISUAL PATHWAYS

Visual fields and pathways:

Optic nerve: Ipsi monocular visual field defects.

Optic chiasm: Bitemporal hemianopia. Anterior chiasm synd: Ipsi monocular visual loss + contralat sup temporal defect (junctional scotoma). Due to compression of ipsi optic nerve & contralat inferonasal fibers called Wilbrand knee, although the presence of this is controversial. Body of the chiasm synd: Bitemp visual field defects (w/ or w/o splitting of macula). Posterior chiasm synd: Bitemp scotomas w/ intact periph fields.

Optic tract: Contralat homonymous hemianopia.

Optic radiations, inf division or meyer loop: Travels through temporal lobe. Contralat sup quadrantanopia.

Optic radiations, sup division: Travels through the parietal lobe. Contralat inf quadrantanopia.

Occipital lobe: Contralat homonymous hemianopia w/ macular sparing.

Pupillary light reflex: When light is shined in one eye, pupil constricts in ipsi & contralat eye (direct & consensual response, respectively); mediated by cranial nerves (CN) II & III. Pathway: Retina → optic nerve → optic chiasm → optic tract → pretectum → Edinger-Westphal nucleus → pregang parasympathetic fibers in CN III → ciliary ganglion → pupillary constrictor muscles.

BASAL GANGLIA

Components: Caudate, putamen, external & internal globus pallidus, subthalamic nucleus, substantia nigra pars compacta (SNPc) & pars reticulata. Striatum = caudate + putamen, lentiform nucleus = putamen + globus pallidus.

Basal ganglia pathways: Control of posture & mvmt. Involves complex excitatory & inhibitory networks, which influence mvmt. Inputs to basal ganglia: From cortex, thalamus, substantia nigra, raphe nuclei. Outputs from basal ganglia: To globus pallidus, substantia nigra, thalamus, sup colliculus. Two pathways from input to output nuclei of basal ganglia: direct & indirect pathway. Net effect of direct pathway is excitatory to stimulate mvmt, & net effect of indirect pathway is to inhibit mvmt. Damage to basal ganglia may also result in cognitive deficits, incl diff w/ learning, particularly involv procedural memory, abulia, & ↓ executive function. Agitation, aphasia, neglect, obsessive-compulsive d/os have also been described w/ basal ganglia lesions. Huntington dz: Loss of neurons projecting from striatum to globus pallidus externus → loss of inhibitory effect of indirect pathway.

Influence of the SNPc: Modulate activity of caudate & putamen (striatum). Two types of dopaminergic receptors in striatum: D1 & D2. D1: Excitatory to direct pathway. D2: Inhibitory to indirect pathway. Net effect of D1 & D2 activity is excitatory (or to decrease inhibitory influence of basal ganglia). In Parkinson’s dz, there is loss of dopaminergic neurons of SNPc.

Lesions involving the basal ganglia & clinical manifestations: Subthalamic nucleus: Contralat hemiballismus. Caudate nucleus: Contralat choreoathetosis. Globus pallidus: Contralat hemidystonia, hemiparkinsonism, tremor. Substantia nigra: Parkinsonism. Unilat basal ganglia: Falling to contralat side & slow mvmts.

THALAMUS

Thalamus is relay & integrative center connecting multiple areas of brain, include cortex, basal ganglia, hypothalamus, cerebellum, & brainstem.

Thalamic nuclei: Anterior nucleus: Memory. Projects to the cingulate gyrus. Receives connections from mammillary bodies via mammillothalamic tracts. Anterior nucleus or dorsomedial nucleus of thalamus may be affected in Wernicke-Korsakoff synd. Dorsomedial: Emotions, sleep-wake cycle, executive function. Receives input from prefrontal cortex & limbic structures. Major thalamic relay for info traveling to frontal association area. Ventral anterior: Motor control. Receives input from globus pallidus & projects to thalamus & frontal cortex. Ventral lateral: Motor control. Receives motor input from cerebellum & basal ganglia & projects to motor, premotor, & supplementary motor cortex. Ventral posterior medial & lateral: Relays sens

info from face & body respectively to primary somatosens cortex. Medial geniculate: Relays auditory info from inf colliculus to transverse temporal (Heschl's) gyrus. Lateral geniculate: Relays visual info from visual pathway to the calcarine cortex. Pulvinar: Modulates occipitotemporo-parietal cortical attention/visual processing. Reticular: Relays info between thalamic nuclei.

Vascular supply of the thalamus: Tuberothalamic artery: Arises from PCA. Paramedian artery: Branch of basilar & PCA. Posterior choroidal artery: Branch of P2 segment of PCA. Inferolateral artery (aka thalamogeniculate artery): From P2 segment of PCA.

Lesions involving the thalamus & clinical manifestations: Dejerine Roussy synd: Thalamic pain synd w/ hemisens painful sensation. Korsakoff dementia: Degen of dorsomedial and anterior nuclei of thalamus, mammillothalamic tracts, mammillary bodies due to thiamine deficiency → memory loss, confabulation. Lesions in thalamus cause a significant variety of deficits, depend on location; include hemisens loss, hemiparesis, abnormal mvmts, behav Δs, akinetic mutism, somnolence, changes in mood, apathy, memory disturb, neglect, deficits in ocular motility, visual field deficits, & lang difficulty/aphasia.

CEREBELLUM

Integrates sens info & sends outputs to the cerebral cortex, brainstem, & spinal cord to coordinate mvmt. Lesions result in ataxia/irreg uncoord mvmts. Composed of vermis & two hemispheres. Vermis lesions → truncal ataxia; hemisphere lesions → limb ataxia. Ataxia is typically ipsi to the lesion. Cerebellar lesions may also result in ↓ intellectual function & cerebellar cognitive affective synd, characterized by ↓ executive function, diff w/ visuospatial ability, flattened affect, & inapprop behav.

Cerebellar anatomy: Cerebellar cortex: Three layers: molecular, Purkinje cell, granule cell. Cerebellar peduncles: Connect cerebellum to brainstem. Sup: Efferent pathway. Deep cerebellar nuclei send efferents in the superior cerebellar penduncles to synapse in thalamus; thalamocortical projections complete the cerebellar-cerebral feedback circuit. Middle: Afferent pathway. Fibers from cortex & sup colliculus project to cerebellum via pons & middle cerebellar peduncle. Inf: Afferent & efferent. Efferents project to vestibular nuclei & reticular formation & afferent info from vestibular nuclei, spinal cord, & brainstem tegmentum. Deep cerebellar nuclei: Outputs from cerebellar cortex travel through deep nuclei to regulate upper motor neurons in cerebral cortex, brainstem, & spinal cord. Cerebellar nuclei from lateral to medial are dentate, emboliform, globose, & fastigial nuclei.

Vascular supply to cerebellum: Sup cerebellar artery (SCA): Sup portion. Anterior inf cerebellar artery (AICA): Middle portion. Posterior inf cerebellar artery (PICA): Inf portion.

BRAINSTEM

MIDBRAIN

Clinical synds & localization points in midbrain: Claude's: Third + contralat ataxia due to involv of CN III & rubrospinal tract. Weber's: Third + contralat hemiplegia due to involv of CN III & corticospinal tract. Benedict's: Third + contralat ataxia & hemiplegia. Top of the Basilar: See below. Parinaud's: Dorsal midbrain: Supranuclear paralysis of vert gaze, impaired convergence, convergence retraction nystagmus, light-near dissoc of pupils, Collier sign or lid retraction, skew deviation.

PONS

Clinical synd & localization points in the pons: Basis pontis: Anterior pons incl corticospinal tracts; may result in contralateral ataxic hemiparesis, dysarthria-clumsy hand, or pure motor hemiparesis. Millard-Gubler: Ventral pons affecting fascicles of VI, VII, & corticospinal tract → ipsi facial palsy, ipsi lateral rectus palsy, contralat hemiplegia. Foville: Pontine tegmentum affecting fascicles of CN VI, VII, PPRF, & the corticospinal tract → ipsi peripheral seventh, gaze palsy to ipsi side, contralat hemiplegia. Raymond: Ventromedial pons; affects VI, corticospinal tract. Raymond Cestani Chenais: Dorsal pons, cerebellum → ataxia & contralat hemisens loss. Marie Foix: Lateral pons → ipsi cerebellar ataxia, contralat hemiparesis, contralat hemisens loss. AICA/lateral pontine: See stroke synds. Locked in: Bilat ventral pons → quadriplegia, aphonia, impaired horiz eye mvmts although vert eye mvmts & blinking may be intact due to sparing of supranuclear oculomotor pathways; pt may be awake due to sparing of reticular formation.

MEDULLA

Clinical synds & localization points in the medulla: Lateral medullary "Wallenberg": due to PICA or vert artery infarct ipsi → facial numb, contralat body numb, ipsi ataxia, gait instability, N/V/vertigo, Horner synd, ipsi palate deviation. Medial medullary: Tongue deviation toward the side of the lesion, contralat paralysis of arm & leg, ↓ touch &

proprioception contralat body. Hemiplegia cruciata: Crossed motor hemiparesis; paralysis of ipsi arm & contralat leg due to lower medullary lesion compromising crossed fibers to arm & uncrossed fibers to leg.

CRANIAL NERVES

I: Olfactory nerve: Smell. May be damaged due to head injury, tumors, neurodegenerative dz. Foster-Kennedy synd: Tumor/mass lesion compressing olfactory bulb & optic nerve causing ipsi anosmia & optic atrophy & contralat papilledema.

II: Optic nerve: Vision; afferent pupillary light reflex.

III: Oculomotor nerve: Motor: Innervates sup, medial, & inf rectus, inf oblique, levator palpebrae supis muscles. Autonomic: Efferent pupillary light reflex; accommodation of lens.

Clinical synds & localization points involving the third nerve: INO (internuclear ophthalmoplegia): due to MLF lesion; ipsi adduction paresis w/ contralat abducting nystagmus. WEBINO (wall-eyed bilat INO): due to midbrain lesion involving both medial recti & both MLFs. Common in MS. One & a half synd: MLF + PPRF or MLF + sixth nuclear lesion causing ipsi adduction paresis w/ gaze deviation to ipsi side, w/ only mvmt being contralat abducting nystagmus. Horner synd: Clinical findings: Classic triad: Ptosis, miosis, anhidrosis. Other possible findings: (1) “upside down ptosis” due to sympathetic denervation to the lower eyelid retractors, (2) heterochromia iridis (diff in eye color b/w two eyes) in congenital causes, and (3) apparent enophthalmos. First order neurons: Descend from hypothalamus to intermediolateral cell column (ILC) at C8-T2. Second order neurons (preganglionic): Ascend from ILC through cervical sympathetic chain over lung apex, then along common carotid artery to synapse at sup cervical ganglion. Third order neuron (postganglionic): Travels w/ carotid artery up cavernous sinus to form nasociliary branch of trigeminal nerve & reaches eye as long & short ciliary nerve. Dx: If Horner’s present, cocaine fails to dilate pupil. (Cocaine blocks reuptake of norepinephrine.) Hydroxyamphetamine dilates a miotic pupil if lesion is first or second order, but not if lesion is third order. (Hydroxyamphetamine causes release of norepinephrine from intact nerve endings.) Orbital apex: CN II, III, IV, VI, V_1, proptosis. Sup orbital fissure synd: CN III, IV, VI, & V_1. Cavernous sinus synd: CN III, IV, VI, V_1, V_2, & sympathetics.

IV: Trochlear Nerve: Motor: Innervates sup oblique muscle. Depresses eye when adducted or intorts eye when abducted. Bielschowsky sign: Head tilt to side of weak sup oblique increases diplopia.

V: Trigeminal Nerve: Motor: Innervates muscles of mastication. Sens: Three divisions V_1: Forehead, corneal, eyelids, nose, scalp; V_2: Nose & cheeks, upper gums, nasal cavity; V_3: Chin, lower jaw & teeth, cheek, anterior

tongue.

VI: Abducens Nerve: Motor: Innervates lateral rectus muscle; abducts eye.

VII: Facial Nerve: Motor: Motor branches exit from stylomastoid foramen to innervate facial muscles involved in mvmts & expression. Motor branches also innervate the stapedius & dysfxn leads to hyperacusis. Sens: (nervus intermedius) supplies taste in anterior 2/3 of tongue & sensation of acoustic meatus. Autonomic: Autonomic branches (greater petrosal nerve, chorda tympani) supply glands for lacrimation & salivation.

Clinical synds & localization points involving the seventh nerve: Supranuclear lesion: Contralat facial wkns w/ sparing of the forehead, due to bilat supranuclear innervation of forehead. Nuclear or fascicular lesion: Ipsi wkns of face & forehead. Cerebellopontine angle lesions (e.g., meningiomas, schwannomas) & lesions of meatal segment of the facial nerve: Ipsi peripheral facial nerve palsy incl loss of taste over ipsi anterior 2/3rds of tongue w/o hyperacusis due to assoc eighth CN palsy w/ ipsi tinnitus, deafness & vertigo. Geniculate ganglion lesions (Ramsay Hunt synd-latent VZV): Facial palsy of LMN type w/ hyperacusis & loss of taste assoc w/ geniculate neuralgia & herpetic vesicles in ear drum, external auditory meatus or palate. Lesions proximal to nerve to stapedius: Hyperacusis along w/ ipsi facial wkns & loss of taste. Lesions proximal to the greater petrosal nerve: Impaired lacrimation. Gradenigo synd: Lesion of CN VI & VII w/ retro-orbital facial pain due to lesion in petrous apex (may be compl of otitis media/mastoiditis & nasopharyngeal carcinoma). Lesions at or distal to stylomastoid foramen: Isolated facial motor paralysis w/o hyperacusis or impaired taste/lacrimation. Aberrant regeneration of seventh nerve: Causes crocodile tears or Bogorad synd; gustatory sweating or Frey synd.

VIII: Vestibulocochlear nerve: Sens: Equilibrium & hearing. Composed of vestibular & cochlear nerves. Cochlear nerve: Deficits result in tinnitus, deafness. Vestibular nerve: Vertigo: Often positional (see table below); Nystagmus: vert/horiz/rotatory; General sx: Diaphoresis, nausea, vomiting, tachycardia, hypotension.

Si/Sx to Distinguish Peripheral Vs. Central Vertigo

Si/Sx	**Peripheral**	**Central**
Severity	Intense	Less intense

Paroxysmal/continuous	Paroxysmal (usually)	Continuous
Positional	**Yes**	No
Nausea, vomiting	Usually present	Usually present but may be less pronounced
Direction of nystagmus	Horiz, torsional, never vert	Horiz, torsional, vert, may be variable
Intensity of nystagmus affected by gaze fixation	Decreased	Unaffected
Fatigability	Decreases/disappears	Not fatigable
Neurologic si/sx	Absent	Present usually
Latency before onset of nystagmus/vertigo	Present	Absent

IX: Glossopharyngeal nerve: Motor: Palate elevation, swallowing. Sens: Taste in posterior 1/3 of tongue, palate sensation. Autonomic: Parasympathetic innervation to parotid gland. Jugular foramen synd: Involvement of CN IX, X, XI due to mass lesion or compression of jugular foramen.

X: Vagus nerve: Motor: Palate elevation, swallowing, innervation of vocal cords. Sens: Epiglottis and laryngeal sensation. Autonomic: Parasympathetic innervation to trachea, GI tract, heart.

XI: Spinal accessory nerve: Innervates trapezius & sternocleidomastoid, responsible for shoulder shrug, neck mvmt.

XII: Hypoglossal nerve: Motor: Tongue mvmt.

SPINAL CORD

(For details, see chapter on Spine and Spinal Cord Diseases)

Vascular supply of the spinal cord: Upper (cervicothoracic) region: Supplied by ant spinal artery & artery of cervical enlargement arising between C4 & C8. Intermediate (midthoracic) region: Supplied by branches of intercostal arteries. Also known as watershed of the spinal cord. Lower

(thoracolumbosacral) region: Supplied by ant radicular artery of Adamkiewicz.

Common Spinal Cord Synds

Synd	Presentation	Anatomic Basis
Transverse myelopathy 	*Motor*: LMN wkns at level, UMN wkns below level *Sens*: Loss of pain, temperature, vibration, proprioception, & touch, two to three segments below level, hyperesthesia/pain at the level *Reflexes*: Hyporeflexia at the level, hyperreflexia below the level	Complete or nearcomplete transection of the corticospinal, spinothalamic, & dorsal columns
Brown-Sequard synd 	*Motor*: LMN wkns at level, UMN wkns below level *Sens*: Ipsi loss of proprioception, vibration & touch below the level, contralat loss of temperature & pain two to three segments below the level; ipsi hyperesthesia at the level of the lesion *Reflexes*: Ipsi hyporeflexia at the level & hyperreflexia below the level	Ipsi damage to corticospinal, posterior columns, & spinothalamic tracts
Anterior cord synd 	*Motor*: LMN wkns at the level of lesion *Sens*: Pain & temperature loss below the lesion (intact light touch, vibration, & proprioception)	Vascular compromise to anterior spinal artery causes damage to anterior 2/3rds of the cord incl anterior motor neurons & decussating pain & temperature fibers in front of the central canal

	Reflexes: Hyporeflexia at the level of lesion	
Central cord synd 	*Motor*: Wkns at the level. May cause a “man in the barrel synd” if at the cervical level *Sens*: Cape distribution of pain & temperature loss *Reflexes*: Hyporeflexia at the level	Damage of anterior horn cells or corticospinal tracts at one or more levels. Medial cervical fibers are damaged preferentially over lateral T/L/S fibers leading to UE > LE involvement

Clinical Features of Conus Medullaris & Cauda Equina Synd

Conus Medullaris Synd	**Cauda Equina Synd**
• Due to lesion of conus medullaris • *Sx*: Flaccid LE paralysis, urinary retention & decreased anal tone, variable sens loss but more often symmetrical, saddle anesthesia, diminished ankle reflexes, UMN & LMN findings. *Causes*: Spinal stenosis, trauma, herniated disc, abscess, neoplasm, hemorrhage, and vascular malformation	• Lesion of lumbar & sacral roots below L3 • *Sx*: Asymmetric & flaccid wkns of LE, urinary retention (later finding), asymmetric sens loss, which may be in a radicular pattern, saddle anesthesia, knee & ankle reflexes often absent, LMN findings. *Causes*: Herniated disc, epidural compression from bony collapse, epidural hematoma, meningeal carcinomatosis meningitis, tumors, trauma, and infection

RADICULOPATHY, PLEXOPATHY, & PERIPHERAL NEUROPATHY

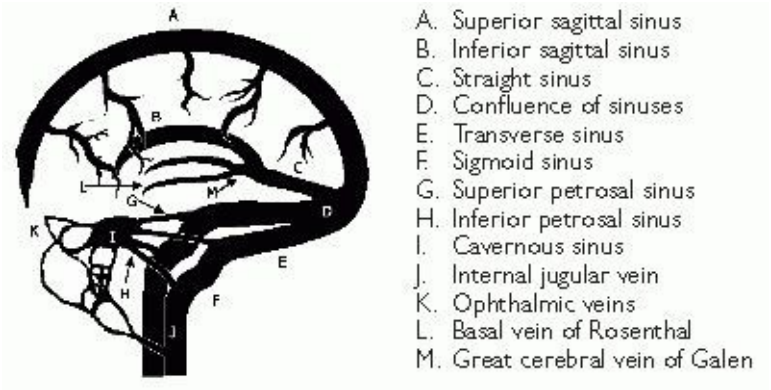
Please see chapters on Radiculopathy and Plexopathy and Peripheral Neuropathy.

VENTRICULAR SYSTEM

CSF flow: Produced by choroid plexus & flows from lateral ventricles →

Foramen of Monro → third ventricle → aqueduct of Sylvius → fourth ventricle → foramen of Luschka (lateral) & Foramen of Magendie (midline) → subarachnoid space.

VENOUS ANATOMY



STROKE SYNDS

MCA: Wkns & sens loss of contralat face, arm, & to lesser degree leg, dysarthria, global aphasia and apraxias in dominant hemisphere, neglect in nondominant hemisphere. Homonymous hemianopsia. Gaze deviation (looking toward lesion).

Sup division: Supplies rolandic & prerolandic areas. Dense sensorimotor deficit involv contralat face, arm & to lesser extent leg. Deviation of eyes toward lesion. If dominant side: initial global aphasia which changes to Broca aphasia, or Broca aphasia from outset.

Inf division: Supplies lateral temporal & inf parietal lobes. If dom side, causes Wernicke aphasia. Sup quadrantanopia or homonymous hemianopia. For R sided lesion: left sided visual neglect & other signs of amorphosynthesis, agitated confusional state may occur w/ temporal lobe damage.

ACA: Contralat leg wkns & sens loss. If both ACAs involved, may have bilat paraparesis, abulia, gegenhalten (paratonic rigidity), contralat grasp, & urinary incont.

Anterior choroidal: Supplied internal segment of globus pallidus & posterior limb of internal capsule & contiguous structures. Contralat hemiplegia, hemihypesthesia, homonymous hemianopsia.

PCA: Precommunal PCA (P1): Infarct often involves P1 perforators to midbrain, subthalamus, & thalamus (see below). Postcommunal PCA (P2): Cortical temporal & occipital lobe signs, hemianopia w/ macular sparing,

memory disturbances. Dominant occipital lobe + splenium of the corpus callosum: Alexia w/o agraphia. Visual agnosia for faces, objects, mathematical symbols, & colors. Peduncular hallucinosis: Highly vivid visual hallucinations due to lesions of midbrain/tegmentum. Anton synd. Balint synd. Palinopsia.

SCA: Ipsilateral upper & lower extremity dysmetria, dysarthria, gait ataxia, & nystagmus. Variable vertigo, nausea, vomiting & headache.

Basilar artery: Branches supply pons & sup cerebellum. Small vessel perforators include paramedian, short circumferential, long circumferential. Top of basilar synd: (1) somnolence/altered mental status, (2) lid retraction/Collier sign, (3) akinetic mutism, (4) peduncular hallucinations, (5) ptosis, d/os of ocular mvmt, paralysis of vert gaze, (6) convergence retraction nystagmus; pseudo-abducens palsy, and (7) skew deviation.

AICA: Supplies lateral pons, middle cerebellar peduncle, anterior cerebellar hemispheres, CN VII & VIII. Stroke may lead to hearing loss & facial palsy together with ipsilateral limb dysmetria, gait ataxia, nausea, vomiting & vertigo.

Vertebral arteries: Arise from subclavian arteries proximally, join distally to form basilar. Four segments: V1: From subclavian artery to C6; V2: From C6-C2; V3: From C2 to atlanto-occipital joint; V4 (intradural segment): Pierces dura at foramen magnum to enter intracranial cavity, travels to pontomedullary junction, where they merge to form basilar. Occlusion → brainstem or cerebellar dysfunction. Sx include limb or truncal ataxia, nystagmus, ipsi Horner synd, ipsi light touch & proprioception, contralat pain & temp sensation, ipsi tongue deviation, hemiparesis, INO, lateral medullary synd (see below).

PICA: Supplies inf and posterior aspects of cerebellar hemispheres & inf vermis. PICA strokes p/w headache & vestibular sx of n/v & vertigo; cognitive & affective changes can occur. If anterior lobe is spared then dysmetria & ataxia may be mild or absent. Cerebellar posterior lobe edema from PICA infarcts can lead to herniation & brainstem compression. PICA lesions may cause lateral.

Selected small vessel/lacunar syndromes: Hemisens loss & hemiparesis: Thalamocapsular. Pure hemisens loss: Thalamus. Pure motor hemiparesis: Internal capsule, corona radiata, & basis pontis. Dysarthria/clumsy hand: Genu of the internal capsule & basis pontis. Ataxic hemiparesis: Pons, midbrain, or internal capsule, or parietal white matter.

Neuroimaging

TIPS FOR REVIEWING SCANS

Review all images & sequences. Be systematic: Eval gyral-sulcal pattern, gray & white structures, ventricles & CSF spaces, vessels, bones, sinuses & soft tissues. Look for patterns of abnormalities, asym., mass effect, shift of midline structures. Note whether lesion involves gray matter, WM, or both.

COMPUTED TOMOGRAPHY (CT)

Signal measured in Hounsfield units. From black (hypodense) to white (hyperdense): Air, -1,000; fat, -50; CSF, +15; brain, +40s; blood, +100; bone, +1,000. CT w/ contrast (iodine-based) enhances vessels & areas of BBB breakdown (necrosis, infxn, acute demyelination, many tumors). Delayed post-contrast images to assess temporal dynamics of enhancement (e.g., chronic brain abscess). CT angiography (CTA) uses timed boluses of IV contrast to enhance arteries. CT venography (CTV) uses timed IV contrast to

enhance veins. CT perfusion (CTP) measures cerebral blood flow (CBF), cerebral blood volume (CBV), & mean transit time (MTT), used to define an area of tissue w/ infarction or down arrow perfusion at risk of infarction (i.e., ischemic penumbra surrounding an infarct). Can also be used to demonstrate ↑ perfusion to a tumor or other highly vascular or hypermetabolic lesion. Relative CBF = Relative CBV/Relative MTT.

MAGNETIC RESONANCE IMAGING (MRI)

Signal from applying magnetic field & measuring relaxation times of hydrogen nuclei. Gadolinium: paramagnetic, causes “T1-shortening” (hyperintensity). Enhances vessels & areas of BBB (necrosis, infxn, acute demyelination, many tumors). Delayed post-contrast images to assess temporal dynamics of enhance. Lesions that ring-enhance usually neoplastic, pustulent, or bloody.

MRI sequences: T1: Gray matter darker than WM, CSF dark. T2: WM darker than gray, CSF bright. FLAIR (fluid-attenuated inversion recovery); T2-weighted sequence, but CSF signal suppressed (dark). “Fat saturation” or STIR: Helps differentiate diff tissue densities by suppressing bright signal from fat. DWI/ADC (diffusion-weighted imaging/apparent diffusion coefficient): Assesses for acute ischemia or cytotoxic injury (restricted diffusion is DWI bright, ADC dark); many processes besides acute infarction

show restricted diffusion. GRE (gradient echo, aka “susceptibility”): Dark signal corresponds to heavy metals (Fe, Ca, Mn, melanin), including iron-containing blood products; useful for chronic hemorrhage (hemosiderin). Diffusion tensor imaging (DTI): Useful for WM tracts. MR angiography (MRA): Uses timed-boluses of gado to enhance arteries. “Time of flight” angios are non-contrast-based vessel reconstructions of flow void signal, more subject to artifact. MR venograms (MRV): Venous study, without contrast. MR perfusion (MRP): Times contrast bolus to measure perfusion parameters (e.g., for “ischemic penumbra”): CBF, CBV, MTT. MR spectroscopy (MRS): Compares measures of neuronal integrity (N-acetyl aspartate, NAA), cellular metabolism (creatinine, Cr), cell membrane synthesis (choline, Cho) w/in selected foci. In diseases w/ ↑ cell turnover, Cho is ↑‘d. In neurodegenerative diseases, NAA is ↓‘d. Functional MRI (fMRI): Blood oxygen level-dependent (BOLD) T2-based measurements of oxy- & deoxy-Hb. OxyHb is hyperintense compared to deoxyHb on T2-weighted images. W/ high perfusion to active brain tissue, oxyHb levels rise & deoxyHb fall. Net effect is hyperintense signal in metabolically active tissue. Used in surgical planning to localize eloquent cortex adjacent to infiltrating tumors.

Bright & Dark on CT & MRI

On	Hyperintense/Dense	Hypointense/Dense
CT	↑ Protein content or cellularity, blood, bone, metals (e.g., calc)	Air, fat, infarction, edema, gliosis
T1	Fat, cholesterol, ↑ protein content or cellularity, methemoglobin, metals (Fe, Ca, Mn, melanin), gado, intravascular blood flow	Water/CSF, air, bone, calc, hemosiderin, chronic demyelination, gliosis
T2	Water/CSF, vasogenic edema, subacute to chronic infarction, gliosis, intravascular slow flow or thrombus	↑ Protein content, ↑ nucleus to cytoplasm ratio (as in some tumors), deoxyHb, intravascular flow void
DWI	Cytotoxic edema w/ failure of Na/K pump (as in acute stroke), necrosis, pyogenic abscess, ↑	

	cellularity	
ADC	“T2 shine-through” effect due to vasogenic edema, gliosis, chronic demyelination, etc.	Cytotoxic edema (acute stroke), abscess, lymphoma, szs, spreading depression (migraine), ↓glycemia
GRE		Blood (any age), metals (Fe, Ca, Mn, melanin), air, thrombosis, telangiectasias

THINGS THAT ENHANCE

- Patent vessels, breakdown of BBB (e.g., w/ in cytotoxic processes: infarction, necrosis, infxn, acute demyelination, expanding tumors).
- Ring-enhance: Fungal or parasitic infxn, abscess, demyelinating plaques, granuloma, infarction, lymphoma (in immunocompromised host), radiation necrosis, GBM, subacute ICH. (Mnemonic: “MAGIC DR”: Metastases, Abscess, Glioma (& lymphoma), Infarction, Contusion, Demyelination, Resolving hematoma/Radiation necrosis.)
- Pachymeninges (dura & outer arachnoid): CSF leak or intracranial hypotension, SAH, infxn, inflammation, mets.
- Leptomeninges (inner arachnoid & pia): Acute stroke, infxn, inflammation, mets.

- Cauda equina or roots: GBS, disc herniation, Charcot-Marie-Tooth, mets, neurofibromas, Schwannomas, arachnoiditis, granulomatous disease, Lyme, CMV, schistosomiasis.

OTHER IMAGING TECHNIQUES

Conventional angiography: Intra-arterial (IA) contrast to study indiv vessels; allows | focal Rx (coiling, embolization, IA tPA). Resolution ˜0.5 mm.

Ultrasound: Helpful to evaluate anatomy, stenosis, & flow (direction & quality). Carotid Doppler: Extracranial carotids and verts; Transcranial Doppler: Intracranial vessels.

Positron emission tomography (PET): Indirectly measures metabolism by uptake of a radioactively-labeled biologically active compound, e.g., glucose (tumors & abscesses are hypermetabolic; atrophy & gliosis are

hypometabolic). Can be combined w/ CT or MRI to improve anatomical resolution of lesions.

Single-photon emission computed tomography (SPECT): Eval distribution of a radiologically-active compound by emission of gamma rays to study perfusion & metabolism.

Myelography: Intrathecal injection of contrast to assess cord & nerve root anatomy (e.g., protruding discs & other masses).

IMAGING PROTOCOLS, INDICATIONS, & CAUTIONS

- Acute focal neurologic deficit: Acute head/neck trauma, concern for stroke/SAH: I-CT.
- Acute stroke: I-CT (w/ CTA & CTP if available).
- Subacute stroke: MRI w/ DWI & GRE, & head/neck MRA.
- Multiple sclerosis: MRI brain, cervical, & thoracic spine w/ DWI & gado.
- Neoplasm: MRI w/ DWI, GRE, gado.
- Cranial nerve or brainstem lesion: FIESTA or CISS sequence, w/ thin cuts through brainstem & detailed views of CNs.
- Optic nerve lesion: Brain & orbital MRI w/ gado.
- Aneurysm: CTA (MRA has slightly lower resolution).
- Dissection: CTA or MRA w/ T1 fat-saturated images (to visualize intramural hematoma).
- Conventional angiogram: Gold standard for vascular imaging & dissections, residual lumen, vasculitis, vasospasm, Moya Moya. Invasive, risk of stroke ˜1%.

NEURORADIOLOGY OF SPECIFIC DISEASES

HEMORRHAGE

CT: Hyperdense (bright) & surrounded by hypodensity (edema, extruded serum). Note: Hyperacute/chronic subdural hematomas & hygromas can be isodense.

Blood on MRI: T1/T2 appearance depends on “age” of blood (see table). Blood, hemosiderin & other substances containing metal (Fe, Ca, Mn, melanin) hypointense on GRE.

ABC/2 formula for estimating hematoma volume: (A × B × C)/2, where A =

max hematoma transverse diameter, B = max hematoma AP diameter, C = no. of axial slices containing hematoma × slice thickness (usually 1/2 cm).

Mnemonic for determining age of intraparenchymal hematoma on MRI: “i be iddy biddy baby doodoo” (or “i bleed, i die, bleed die, bleed bleed, die die”).

Stage (Age)	Hemoglobin	Compartment	T1
Hyperacute (<24 h)	Oxyhemoglobin	Intracellular	**I**so
Acute (1-3 days)	Deoxyhemoglobin	Intracellular	**I**so
Early subacute (>3 days)	Methemoglobin	Intracellular	**B**right
Late subacute (>7 days)	Methemoglobin	Extracellular	**B**right
Chronic (>14 days)	Hemosiderin	Extracellular	**D**ark

Epidural: Biconvex shape; cannot spread past suture lines (dura adherent to skull).

Subdural: Concave shape; cannot spread past dural reflections (falx, tentorium).

SAH: Aneurysms most often located at branch points around circle of Willis (ICA-PCom, PCA-PCom, ICA-ophth, etc.); depending on artery & extent of bleed, blood can track into parenchyma, ventricles, cisterns, & along tentorium. If SAH seen, CTA indicated.

ICH: HTN: Most commonly basal ganglia & cerebellum. Cerebral amyloid angiopathy (CAA): Typically lobar. Mets that commonly hemorrhage include breast and lung (by

incidence) Melanoma, Renal cell ca, Choriocarcinoma, Thyroid papillary ca (“MR/CT”) (by propensity).

Venous infarct: Does not respect arterial territory, extensive edema, var hemorrhage.

Intraventricular: Typically seen w/ SAH and hypertensive hemorrhage.

Hemorrhagic Transformation of an Infarct: Graded by Severity

Grade	Features
HI-1	Small petechiae w/in or along margins of infarct w/o mass effect
HI-2	Confluent petechiae w/in infarct w/o significant mass effect
PH-1	Hematoma <30% of infarct w/ some mass effect
PH-2	Hematoma >30% infarct w/ mass effect or any hemorrhage outside infarct

Clues to secondary hemorrhage: Aneurysm rupture: ICH&SAH; Coagulopathy: Fluid-fluid level (=nonclotting blood) w/in hematoma; TBI: Soft-tissue edema of scalp, fractures, or other injury overlying SAH or ICH. Look for coup & contra-coup effects.

INFARCTION

Noncontrast CT: Can use high contrast windowing (30/30) to assess for early infarction—loss of grey-white differentiation, parenchymal hypodensity. Hyperdensity w/in a vessel may represent a thrombus. Soft thrombus appears hypodense compared to calcified atherosclerotic plaque (hyperdense). CTA: Vessel cutoff/stenosis; flame-like tapering suggests dissection. CTP defines ischemic penumbra.

MRI: DWI-bright & ADC-dark acutely. MRA, MRP: Interpreted like corresponding CT studies. Wallerian degeneration can be seen following infarctions involving parent neurons; output tracks appear DWI hyperintense acutely, T2-hyperintense chronically.

Age-based MRI Appearance of Infarctions

Stage (Age)	T1	T2/FLAIR	DWI	ADC
Hyperacute (0-6 h)	Iso	Iso	Bright	Dark

Acute (6 h-4 days)	Dark	Bright	Bright	Dark
Subacute (4-14 days)	Dark	Bright	Iso/bright	Pseudo-normal
Chronic (>14 days)	Dark	Bright	Iso	Bright

OTHER VASCULAR DISEASES

Microvascular disease: Aka leukoaraiosis: 2/2 lipohyalinosis & arteriosclerosis of small vessels. Subcortical sym T2-hyperintense lesions, usu. punctate but confluent w/ more advanced dz. Binswanger disease: SC WM process a/w HTN & lacunes; spares U-fibers 2/2 to collaterals from cortical arteries.

Developmental venous anomaly (DVA or venous angioma): Dilated veins which converge radially (like a caput medusa) to a draining vein. W/ contrast, early venous filling, persistence of venous phase. Low risk hemorrhage.

Capillary telangiectasias: Capillaries surrounded by nl brain, predilection for pons. Most never hemorrhage. Enhance on CT/MRI, GRE hypointensity.

Cavernous angiomas/hemangiomas/malformations: Congenital vasc hamartoma of vessels w/o interspersed nl brain parenchyma. Can have assoc DVA. Hyperdense on CT w/ calc. T1 hyperdense & T2 hypodense; GRE: Dark ring (hemosiderin). “Popcorn” appearance.

Arteriovenous malformation (AVM): Arterialization of veins, large feeding arteries, absent or abnl capillaries, & enlarged draining veins. Often has aneurysms of feeding vessels. CT: Hyperdense, enhances. MR: Irregular serpentine flow voids on T2, enhances. Conventional angiogram: Early venous phase 2/2 absence of capillary phase.

Dural arteriovenous fistula (AVF): Dural-based AVM a/w venous hypertension. Can occur anywhere in CNS. In spine, mostly in thoracolumbar area. Cord infarction w/ necrotizing myelopathy can occur causing paraparesis. (Foix-Alajouanine syndrome, spinal cord appears T2 hyperintense, tangle of T2 flow voids posterior to spinal cord.)

Aneurysms: Focal arterial dilations typically at branch points; fusiform (atherosclerotic dilation), saccular/berry (branch points), mycotic (infectious), neoplastic, pseudoaneurysm (traumatic, dissection).

Dissections: Flame-shaped tapering of vessel lumen, sometimes in corkscrew or spiral orientation on CTA, MRA, or conventional angiography. T1 fat-saturated images may

demonstrate thrombus w/in false lumen, but CTA is superior (AJNR 2008;29:1753-1760). Note whether dissection extracranial or intracranial, whether there is intradural extension (risk for SAH). Carotid: Tend to occur near C2-3 vertebral level, 2-3 cm superior to bifurcation. Vertebral: Tend to occur where artery is nearest bone, at C1.

CAA: Lobar ICHs & evidence of prior microhemorrhages in SC WM, T2 hyperintense & GRE hypointense.

Moya moya: Stenosis or occlusion of ICAs → development of abnl network of collateral capillary circulation arising from ACA, MCA, or PCA branches, lenticulostriates, or ECA transdural anastamoses. Angiography: ICA stenosis, proximal ACA/MCA occlusion w/ extensive collaterals & dilation of perforating lenticulostriate arteries (“puff of smoke”).

CADASIL (cerebral autosomal dominant arteriopathy w/ subcortical infarcts & leukoencephalopathy): Sym T1 hypointense & T2 hyperintense lesions in anterior temporal lobes, external capsules, & widespread subcortical WM.

Fibromuscular dysplasia (FMD): Large vessel (ICA & renal artery) “string of beads” appearance; diameter of beading greater than diameter of artery; commonly spares first few cm of ICA (unlike atherosclerosis).

Vasculitis: Segments of circumferential vessel narrowing (atherosclerotic lesions usu. more eccentric & focal c/w vasculitic lesions); multiple areas of cortical & subcortical infarction, hemorrhage, & nonspecific WM T2-hyperintensities. Differentiate from reversible cerebral vasoconstriction syndrome and vasospasm via clinical presentation.

Migraine: Nonspecific SC T2 hyperintensities, “UBOs” (“unidentified bright objects”).

Transient global amnesia (TGA): Punctate foci of restricted diffusion within limbic structures, typically reversible.

Susac syndrome (retinocochleocerebral vasculopathy): “Punched out” punctate T1 hypointense and T2 hyperintense lesions in the corpus callosum and deep gray nuclei.

DEMYELINATING & OTHER WHITE MATTER DISEASES

Multiple sclerosis: Focal, ovoid WM lesions of PV>SC (perpendicular

“Dawson’s fingers”) hemispheric WM, corpus callosum, optic nerves, brainstem (esp medial longitudinal fasciculus), cerebellum (esp middle cerebellar peduncle), optic nerves, spinal cord (<2 spinal segments); old lesions T1 dark; acute lesions enhance w/ gado (ring, incomplete ring, or diffuse), may be DWI bright. Rare cortical & deep gray matter lesions.

ADEM: Multiple lesions of same age; round, enhancing SC T2 bright lesions in hemispheric WM (& brainstem & cerebellum).

Acute MS or ADEM variants: Acute hemorrhagic leukoencephalitis (Weston Hurst disease): confluent T2 bright WM signal w/ mass effect & minimal enhance; hemorrhage on GRE (or CT). Marburg variant of MS: Large region of T2 bright signal in hemispheric WM w/ mass effect & periph enhancement. Balo concentric sclerosis: Alternating concentric rings of T2 bright & dark signal (& alternating rings of enhancement) in hemispheric WM w/ var mass effect. NMO (Devic disease): Longitudinal cord T2 bright lesion (>3 spinal seg, central or occupying entire cross section) w/ optic nerves & chiasm T2 bright lesions; all lesions expansile with var enhance; var PV WM T2 bright lesions.

Ddx of White Matter Disease Based on MRI Characteristics (Not Comprehensive-See Below for More Ddx)

Multifocal

Demyelinating diseases (PML, MS, NMO, ADEM)

Vasculopathies (CADASIL, Fabry disease, Susac syndrome)

Congenital CMV

Brucellosis

Mucopolysaccharidoses, Galactosemia, L2 hydroxyglutaric adicuria

Neuroaxonal leukodystrophy with spheroids, Lowe syndrome

Chromosomal abnormalities, mosaicism

Confluent

Frontal	Alexander disease; metachromatic leukodystrophy; leukodystrophy with axonal spheroids
Parieto-occipital	Krabbe disease; X-linked adrenoleukodystrophy; early onset peroxisomal disorder; neonatal hypoglycemia
Periventricular predominance	Metachromatic leukodystrophy; Krabbe disease; SjögrenLarsson syndrome Periventricular leukomalacia HIV encephalopathy Later onset neuronal degenerative disorders e.g., neuronal ceroid lipofuscinosis Adult polyglucosan body disease Leukoencephalopathy with brainstem and spinal involvement and lactate elevation
Subcortical predominance	Kearns-Sayre syndrome; Canavan disease; urea cycle defects; L2 hydroxyglutaric aciduria; propionic academia
Diffuse cerebral	End stage of all progressive WM diseases Some mitochondrial disorders (MELAS) Vanishing white matter (VWM) disease Others: Megalencephalic leukoencephalopathy with subcortical cysts (MLC), merosin

	deficient congenital muscular dystrophy, etc.
Cerebellum + middle cerebellar peduncles	Heroin/cocaine toxicity Alexander disease; histiocytosis; premutation Fragile × syndrome; autosomal dominant leukodystrophy Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation Early onset maple syrup urine disease; peroxisomal disorders; Cerebrotendinous xanthomatosis (CTX)
Brainstem	Peroxisomal disorders; Wilson disease; Alexander disease

Delayed myelination or hypomyelination

T2: hypointensity of WM less marked

T1: hyperintensity of WM less marked

No Typical PNS Involvement	**Typical PNS Involvement**
Pelizaeus Merzbacher disease Galactosemia Early onset degenerative disorders e.g., early onset GM1 and GM2 gangliosidoses, infantile neuronal ceroid lipofuscinosis, Alpers syndrome	Hypomyelination syndromes (e.g., Cockayne)

Adapted from Schiffman and van der Knapp, *Neurology* 2009;72:750-759.

OTHER DEMYELINATING DISEASE

SLE/APLA: SC WM (posterior predilection) T2 bright lesions; may be in vascular distribution & true infarct may occur (DWI bright); relative PV sparing; cortical lesions & diffuse atrophy also seen; T2 bright signal in cord (transverse myopathy).

Sjögren: SC & PV WM T2 bright lesions; also w/ basal ganglia T2 bright lesions; corpus callosum involvement less common.

Behcet: Multifocal or confluent hemispheric WM T2 bright lesions w/ var enhancement; usually w/ concurrent diencephalon & upper brainstem lesions (often edema & enhancement); occassional cortical vein thrombosis/infarctions (var hemorrhage).

Sarcoidosis: Focal, multifocal, or confluent T2 bright lesions of WM w/ var enhancement; also enhancement and thickening of pachymeninges w/ parenchymal infiltration (pituitary- hypothalamus, optic nerve, optic chiasm).

Primary CNS vasculitis: Acute lesions DWI bright in hemispheric white (& gray) matter (may follow clear vascular territory), a/w stenoses & aneurysms; var lesional, meningeal & perivascular enhancement; chronic lesions w/ T2 bright hemispheric WM.

Immune reconstitution inflammatory syndrome (IRIS): Confluent, multifocal T2 bright diffuse WM lesions w/ areas of focal enhancement & mass effect.

Inflammatory CAA: Predominantly cortical & SC microhemorrhages (on GRE) w/ extensive asym & confluent ↑ T2 & ↓ T1 signal of SC WM w/ minimal enhancement (Neurology 2007;68(17):1411-1416).

Tolosa Hunt: Idiopathic granulomatous dz typically involving cavernous sinus, orbital apex & adjacent structures, lesions are T1/T2 isointense & strongly enhance. Paraneoplastic disease: a/w multiple systemic ca’s incl SCLC, testicular germ cell, ovarian, etc. Sym T2 hyperintensity w/ edema.

PRES & hypertensive encephalopathy: b/l, sym T2 bright WM lesions in posterior hemispheres at MCA-PCA border zones; other regions may be affected (frontal &

temporal, brainstem, cerebellum, gray structures); var restricted diffusion & peripheral enhancement.

Metabolic diseases: B_{12} deficiency: Scattered PV T2 bright WM lesions; ↑ T2 signal in posterior cord. Marchiafava-Bignami syndrome: Acutely, central T2 & DWI bright lesions of corpus callosum; chronically, central cavitation; var

mass effect & enhancement. Osmotic demyelination: b/l, sym T2 bright lesions of central pontine WM (var sparing of corticospinal tracts), & var SC WM, midbrain, & deep gray lesions w/o enhance or mass effect. Hypoxia-ischemia: b/l, sym diffuse DWI & T2 bright confluent lesions after resp or cardiac arrest; predilection for SC WM (involves U-fibers), corpus callosum, capsules (internal & external), globus pallidi hippocampus, cerebellum. High altitude encephalopathy: b/l, sym posterior deep WM > SC WM & corpus callosum T2 bright lesions; var DWI bright lesions. Acute intermittent porphyria (AIP): Similar to PRES (above).

Toxic diseases: Chemotherapy (cyclosporine, tacrolimus, methotrexate): (1) Acutely, PRES (see above); (2) chronically, b/l, sym, confluent, diffuse, deep T2 bright WM lesions (spares U-fibers). Radiation: (1) w/ focal exposure, T2 bright WM lesion (often spares corpus callosum) w/ var mass effect & ring enhancement. Ddx: Tumor recurrence (choline peak on MRS, may involve corpus callosum); (2) w/ diffuse exposure, b/l, sym, confluent T2 bright deep & PV lesions w/o enhancement or mass effect. Illicits: b/l, sym lesions; (1) IV or inhaled heroin: diffuse WM high T2 signal (sparing U-fibers), high convexities; (2) cocaine: scattered T2 bright WM lesions; stroke; ICH; vasculitis; (3) MDMA: globus pallidi & diffuse WM high T2 signal. Organic solvents: b/l, sym, confluent, diffuse T2 bright lesions; (1) toluene: corpus callosum & cerebellum; (2) methanol: SC WM, putamen, & optic nerve; (3) ethylene glycol: thalamus & pons. Mercury: b/l, sym, postcentral gyrus, occipital lobe & cerebellar T2 bright WM lesions w/ cortical atrophy in chronic phase. Carbon monoxide (CO) poisoning: Similar to hypoxic-ischemic injury (above), but sparing SC region & T2 bright globus pallidi lesions typical.

Infectious diseases: PML/JC virus: Often begins asym, usually evolves into b/l sym dz; parietal & occip (but may occur anywhere) SC (involves U-fibers) T2 bright confluent nonenhancing WM dz w/ var pontocerebellar WM lesions; no mass effect. HIV/AIDS: b/l, sym PV T2 bright lesions, nonenhancing; diff atrophy. CMV: (1) AIDS-related: Ventriculitis w/ PV T2 bright lesions & subependymal enhance; assoc lumbosacral meningeal & nerve root thickening & enhancement, (2) Congenital CMV: Temporal SC & PV T2 bright lesions w/ cystic regions. VZV: (1) Immunocompromised pts (small vessel vasculitis): Diffuse, patchy T2 bright multifocal WM lesions; angiographic abnormalities (proximal MCA-ACA); (2) Immunocompetent pts (large vessel vasculitis): Acute stroke from VZV-vasculitis w/ DWI bright lesions in deep WM & cortex; var enhancement. HTLV-1 & 2: Small, multifocal T2 bright SC WM lesions; in early stages of spinal disease, multifocal enhancing T2 bright thoracic lesions w/ var mass effect. Lyme: Scant T2 bright PV WM lesions; meningitis, polyradiculitis & cranial neuritis

(with enhancement of corresp structures). SSPE (rubeola/measles): Early stages, posterior SC (spares U-fibers) T2 patchy bright lesions w/ adjacent gray matter involvement; var enhancement & mass effect; mid-stages w/ PV & putamen and pontocerebellar T2 bright lesions w/ regression of SC lesions; late stages w/ atrophy & worsening PV T2 bright lesions.

Hereditary diseases: Metachromic leukodystrophy: Diffuse, sym T2 bright signal of cerebral (+corpus callosum, -U-fibers) & cerebellar WM; tigroid WM pattern; predom frontal involvement in adult-onset forms. Pelizaeus-Merzbacher: Diffuse, sym T2 bright signal of WM w/ var T2 dark signal in deep gray nuclei, midbrain, & cerebellum; “eye of the tiger” sign. X-linked ALD: Sym SC & deep WM T2 bright signal (U-fiber sparing); begins parietal & occip w/ enhancement at leading edge & var mass effect; involves corpus callosum; progresses anteriorly & posteriorly. Krabbe (globoid cell): Parietal & cerebellar WM T2 bright signal; var bright lesions in deep gray (thalami), WM & cortex. Alexander disease: (1) Childhood forms: begins w/ T2 bright signal in frontal lobes w/ enhancing edge, followed by cystic changes; macrocephaly; var bright lesions in caudate on CT; (2) adult form—var PV T2 bright lesions; upper cervical cord & medulla atrophy. Canavan dz: SC (involves U-fibers) & deep gray T2 bright signal; macrocephaly; ↑ NAA peak on MRS. Vanishing WM (VWM) disease: Sym, diffuse T2 bright signal in cerebral & cerebellar hemispheres (loss of WM; rel temporal lobe & U-fiber sparing); nl head size. Megaloencephalitic leukoencephalopathy: Temporal T2 bright signal w/ cysts; macrocephaly. Aicardi-Goutiere’s: Diffuse, T2 bright signal in hemispheric WM; basal ganglia calc on CT. Tuberous sclerosis: Cortical tubers & areas of dysmyelination: T2 bright SC lesions (in adults); subependymal enhancing lesions (small hamartomas, large giant cell astrocytomas [SEGA]).

NONINFECTIOUS IMMUNE/INFLAMMATORY DISEASE

Meningeal Enhance

Finding	Description	Etiologies
Pachymeningeal enhance	Dural thickening & enhancement (var nodules) Leptomeningeal sparing	Low ICP Syphilis, TB Sarcoid Wegener granulomatosis

		GCA Idiopathic Lymphoma & leukemia Metastatic carcinoma Old SAH[a] Superficial siderosis[a]
Diffuse meningeal enhance	Dural enhancement & thickening Leptomeningeal enhancement (follows gyral & sulcal pattern)	Syphilis, TB, other bacteria, viruses Sarcoid Lymphoma & leukemia Metastatic carcinoma

[a] Enhancement not expected, meninges dark on GRE.

INFECTIOUS DISEASES

Bacterial meningitis: See table; FLAIR bright signal (pus) in subarachnoid spaces; concurrent ventriculitis (subependymal enhance, ventriculomegaly, & PV T2 bright signal) & empyema (DWI & T2 bright; T1 dark; enhances); listeria w/ predilection for brainstem & cerebellum (rhombencephalitis).

Bacterial abscess: Solitary or multiple; MCA territory (frontoparietal) gray-white junction

- 1. Early cerebritis (days): ill-defined T1 dark, T2 bright region;
- 2. Late cerebritis (weeks): similar to early, but increasing enhancement;
- 3. Early capsular (1-2 wk): T2 bright, T1 dark lesion w/ surrounding T2 bright signal (edema) & early ring enhancement;
- 4. Late capsular (>2 wk): less surrounding edema (T2 bright signal) & increasing capsule (ring enhancement); DWI bright core; concurrent paranasal or mastoid sinus dz on CT.

Bartonella henselae (cat scratch disease): Var thalamic & deep WM T2 bright lesions, optic disc edema w/ macular star (ODEMS) on funduscopy/retinography.

Treponema pallidum (syphilis)

- 1. Pachymeningitis: see table
- 2. Meningovascular syphilis: anterior > posterior circulation infarcts w/ meningitis
- 3. Gummas: enhancing mass lesions of dura w/in cerebral hemispheres or CNs
- 4. Tabes dorsalis: high T2 signal of posterior cord
- 5. Parenchymal syphilis: diffuse atrophy.

Mycobacterium tuberculosis

- 1. Meningitis: pus in basal cisterns (T2 bright); skull base dural thickening & enhancement; basal ganglia & internal capsular infarcts.
- 2. Tuberculoma: solitary or multiple T2 bright masses adjacent to dura (may occur anywhere) w/ enhancement (ring or diffuse).

Borrelia burgdorferi (Lyme): See WMD.

Tropheryma whippelii (Whipple dz): Diencephalic & thalamic T2 bright lesions w/ enhancement.

HSV-1 (adult): Early DWI gray & white matter changes (medial temporal, orbitofrontal, insular); later T2 bright signal (cingulate, capsules); spread to putamen (w/o involving it); var hemorrhage (by CT or GRE), mass effect, & enhancement; pseudo-hyperdense MCA sign; spares deep gray nuclei; occasional pontine & CN V involvement. HSV-2 (neonate): Diffuse hemispheric gray & WM T2 bright & T1 dark changes—loss of gray-white differentiation, var enhancement, occas cerebellar & brainstem involvement; WMD difficult to apprec in neonate brain; no predilection for temporal lobes; calc (after weeks).

VZV: Zoster paresis: Dorsal root enhancement on T1 & dorsal cord T2 bright signal (short segment) with enhancement; immunocompetent (large vessel vasculitis): see WMD; immunocompromised (small vessel vasculitis): see WMD; may evolve into

diffuse encephalitis (gyriform enhancement, hemorrhages) & ventriculitis (subependymal enhancement).

EBV: (1) ADEM: likely represents most brain cases; see WMD; (2) meningitis: see table.

CMV: Congenital: PV calc; anterior temporal & subependymal cysts, ventriculomegaly w/ vol loss, neuronal migration abnormalities (e.g., polymicrogyria, pachygyria, lissencephaly), cerebellar hypoplasia, & PV WM T2 bright signal; adult (immunocompromised): ventriculitis w/ deep WM & PV T2 bright signal + subependymal enhancement (owl eyes); lumbosacral nerve root enhancement & conus enlargement w/ ↑ T2 signal and enhancement; rarer brainstem & cerebellar lesions.

HIV/AIDS: see WMD; basal ganglia calc & proximal vasc ectasia in women/children.

EEE (eastern equine encephalitis): Thalamic & basal ganglia T2 bright lesions; var upper brainstem lesions; lack of enhancement.

JE (Japanese encephalitis): Thalamic, basal ganglia, upper brainstem, hippocampal & deep WM T2 bright lesions; ±hemorrhage (by CT or GRE) in thalami; no enhancement.

SSPE: See WMD.

Aspergillosis: Parenchymal T2 bright lesions (often poorly-defined capsule) w/ surrounding T2 bright signal (edema), var enhancement; var adjacent hemorrhage (by GRE) & infarction (tends to be angio-invasive).

Mucormycosis: Paranasal bony sinus & soft tissue changes w/ var bony changes on CT; meningeal thickening & enhancement; stenoses & dilation by angio (vasculitis & aneurysms); anterior > posterior DWI bright lesions (infarctions).

Cryptococcus: (1) Meningitis: dilated Virchow-Robin spaces, enhancing nodules w/in leptomeninges, choroid plexus, parenchyma; lack of diffuse meningeal thickening & enhancement (2) Cryptococcomas: concurrent meningitis; T2 bright lesions of midbrain & basal ganglia.

Candidiasis: Small, scattered parenchymal T2 bright lesions; parenchymal & meningeal enhancing nodules; meningeal thickening & enhancement; abscesses (similar to bacterial above).

Coccidioidomycosis: Meningitis: base of skull predominant meningeal changes; granulomatous lesions, similar to TB; cerebellar predilection.

Cysticercosis: (1a) Early stages (w/o encephalitis): T2 bright, T1 dark cysts (w/ central scolex) w/ thin capsule & minimal surrounding edema (T2 bright

signal) or enhancement; cysts in parenchyma, ventricles & subarachnoid space; (1b) early stages (w/ encephalitis): Diffuse nodular enhancing lesions w/ marked surrounding edema (T2 bright signal); hydrocephalus; (2) Middle stages: Diffuse T1 bright & T2 dark or isointense lesions w/ enhancement of thickened capsule & var surrounding edema; encephalitic changes may occur; (3) Late stages: Lesion calc (bright on CT or T1, dark on GRE).

Toxoplasmosis: Deep gray nuclei T2 bright, enhancing lesions w/ surrounding edema (T2 bright signal); ring enhancement; var hemorrhage (by CT or GRE).

Echinococcus: Parietal > other lobar cystic lesions (T2 bright, T1 dark core) w/ central parasitic contents visualized.

Malaria: Loss of gray-white differentiation, diffuse cerebral edema & WM changes including corpus callosum (T2 bright signal), & cortical stroke (by DWI).

CJD (Creutzfeldt-Jakob disease): Cortical ribbon, putamen, caudate, thalamic DWI bright lesions; T2 bright lesions follow.

Variant CJD: Bithalamic (pulvinar) DWI bright lesions; T2 bright lesions follow.

GSS (Gerstmann-Sträussler-Scheinker): Similar to CJD.

FFI (fatal familial insomnia): Limited data, but T2/FLAIR & DWI may be normal; possible ↑ ADC values & MRS abnormalities w/n thalami.

INTRACRANIAL NEOPLASIA & OTHER MASS LESIONS

Determine compartment containing the lesion

- Extra-axial lesions: Intradural (e.g., meningioma, w/ dura between lesion & underlying brain) or extradural (e.g., bone metastasis). Inward buckling of underlying parenchyma, expansion of subarachnoid space adjacent to lesion, inward displacement of meningeal vessels.
- Intra-axial lesions: E.g., metastases or primary brain tumors. Absence of expansion of subarachnoid space, superficial position of meningeal vessels, intraparenchymal mass effect or blurring of anatomic boundaries.

Extra-axial tumors

- Meningioma: Looks like egg w/ dural tail, hyperdense on CT, isointense

to gray matter on T1-weighted MRI, w/ homogenously bright enhancement due to high vascularity. Typical locations: parasagittal dura, convexities, sphenoid wing, cisterns, & olfactory groove. Can encroach vessels; commonly see adjacent overlying bony Δs including hyperostosis. Typically makes obtuse angle w/ dura or bone. Less common features: Calc, cysts, necrosis, hemorrhage. Multiple meningiomas can be seen in NF2.

- Nerve sheath tumors (Schwannomas, neuromas, neurofibromas): T2 hypo or hyperintense depending on tumor density. Vestibular schwannomas often expand internal auditory canal & can have intracanalicular &/or cisternal components. Typically makes acute angle w/ bone. Assoc arachnoid cysts occur w/ larger tumors. Less common features include cysts & hemorrhage. Schwannomas, if b/l, suggest NF2. Plexiform neurofibromas most often affect skin & subcutaneous tissue & are a/w NF1. Neuromas are post-traumatic neuronal prolif.
- Choroid plexus tumors: Papilloma: WHO grade I, typically in atria of lateral ventricles, less commonly in third ventricle or cistern; p/w obstructive hydrocephalus (due to block of CSF outflow) or communicating hydrocephalus (due to overproduction of CSF). CT hyperdense, T1 hypointense, T2 mixed intensity, enhances, can hemorrhage. Carcinoma: WHO grade III, also in lateral ventricles, appears similar to papilloma, metastasizes via CSF.
- Chordoma: Malignant tumor of notochord remnants, destructive bone lesion usually in clivus or sacrum/coccyx, differential includes chondrosarcoma
- Primary or metastatic disease: Can involve meninges & subarachnoid space. On MRI, nodular or diffuse pachy- &/or lepto-meningeal thickening & enhancement (carcinomatous meningitis). Primary CNS tumor: Think glioma & lymphoma. Metastatic disease: Think melanoma, lung, breast, GI, prostate cancer, hematologic malignancies (leukemia, lymphoma), chloroma (granulocytic sarcoma a/w myelogenous leukemias).
- Non-neoplastic mass lesions: Lipoma: Congenital developmental abnormality from neural crest, composed of lipid, CT hypodense, T1-hyperintense, T2-hyperintense. Epidermoid: Desquamated ectodermal remnants that appear homogenous, commonly found near cerebello-pontine angle & not midline. Slow growing. CT hypodense (brighter than CSF), MRI nonenhancing, T2-hyperintense w/ restricted diffusion. Can have calc & can scallop adjacent bone. Resemble arachnoid cysts but arachnoid cysts do not restrict diffusion. Dermoid:

Ectodermal/mesodermal remnants contain lipid & calc, heterogeneous appearance, commonly found at or near midline. Male predominance. Look for fat intensity. Can rupture. Teratoma: Ectodermal/mesodermal/endodermal congenital tumors, endodermal component forms cysts, commonly in midline near pineal or suprasellar areas. Heterogeneous appearance w/ enhancement.

Intra-axial tumors

- Pituitary adenoma: T1-hypointense, homogenous w/ delayed enhancement, & mass effect on neighboring structures.
- Craniopharyngioma: Typically suprasellar; cysts, calc, & homogenous enhancement in a T2-hyperintense lesion. Benign Rathke cleft cysts do not commonly calc or enhance.
- Pilocytic astrocytoma: WHO grade I, most common juvenile infratentorial primary tumor. Well-defined margins, CSF-intensity cyst w/ enhancing vascular mural nodule.
- Brain stem astrocytoma: WHO grade II, more common in children than adults, var enhancing T2-hyperintense lesion.
- Pleomorphic xantroastrocytoma (PXA): WHO grade II, most common juvenile supratentorial primary tumor, typically in temporal lobe, often w/ clear borders, enhancing w/ meningeal attachment.
- Primitive neuro-ectodermal tumor (PNET): Aka medulloblastoma, WHO grade IV, common juvenile infratentorial lesion, M>F, midline vermis lesion which extends into superior & inferior vela of fourth ventricle. CT hyperdense, heterogeneous enhance; also include ependymoblastoma, medulloepithelioma, neuroblastoma.
- Ependymoma: WHO grade I-II depending on site; fourth ventricle > spine, supratentorial.
- Sub-ependymomas: WHO grade I, present in adulthood, mostly located along lateral ventricle wall, CT isodense, T1-isointense, T2-hyperintense, var enhancement.
- Ganglioglioma: Mixed neuronal/glial, low-grade tumor, young & female predominance. Well defined margins, calcified, cystic mass w/ minimal edema, var enhancement.
- L’Hermitte-Duclos: Dysplastic gangliocytoma (WHO grade I), T2-hyperintense nonenhancing cerebellar “tigroid” lesion affecting gray & WM.

- Hemangioblastoma: Most common infratentorial intraparenchymal primary tumor in adults. Cystic mass w/ mural nodule w/ flow voids from feeding vessels.

P.23

- Gliomas: Infiltrating lesions,grading is based pathologically on presence of necrosis, vascular endothelial proliferation, mitoses, nuclear pleomorphism, & cellular density.
    - Astrocytoma: Grade II, most common supratentorial intraparenchymal primary tumor in adult. CT hypodense, non- or low-enhancing, T1-hypointense, T2-hyperintense, lower CBV on perfusion imaging.
    - Oligodendroglioma: Grade II, often calc, T1-hypointense, T2-hyperintense, minimal edema, var enhancing.
    - Anaplastic astrocytoma: Grade III, poorly-defined borders w/ extensive edema & enhancement w/o necrosis.
    - Glioblastoma (GBM): Grade IV, mass effect & extensive edema, follows WM tracts such as corpus callosum, irregular poorly-defined borders, ring enhancement w/ internal necrosis (restricted diffusion), higher CBV on perfusion imaging.
- Gliomatosis cerebri: Neuroepithelial tumor, diffuse infiltration of at least two lobes of cerebral hemispheres w/o mass effect, T2-hyperintense gray & WM throughout, min enhancement.
- Germinoma: Germ cell origin, also known as seminoma, typically in pineal or suprasellar regions, male & Asian predominance (female predominance when tumor is suprasellar), sometimes multifocal, CT hyperdense & enhancing, T2-hypointense.
- Choriocarcinoma: Typically hemorrhagic, male predominance, subarachnoid seeding common, can occur w/ retinoblastoma.
- Neurocytoma (aka neuroepithelioma): neural mass typically extending into the lateral ventricle and adjacent to septum pellucidum, “bubbly” appearance, heterogenous enhancement, var vascularity.
- Pineal tumors: More common in childhood, pineocytoma (WHO grade II), pineoblastoma (WHO grade IV), calc, enhance, hemorrhage in pineoblastoma. Important to distinguish from benign pineal cysts which, unlike cystic tumors, should not have a solid component.
- Primary CNS lymphoma: More common in immunocompromised host,

lesions usually supratentorial w/in deep gray nuclei or PV WM. Spread across corpus callosum is common. May coat ventricles. Lesions are heterogeneous (T2 iso- to hypo-intense w/ marked enhancement & restricted diffusion); ring enhancement seen in immunocompromised but not immunocompetent hosts. May radiographically disappear following treatment w/ steroids.

- Intravascular lymphoma (IVL): Proliferation of malignant large B-cell lymphoma w/in lumen of small blood vessels, w/o extravascular mass. Lesions resemble small infarcts w/ focal parenchymal or meningeal enhancement; multifocal WM dz common.
- Intraparenchymal metastatic disease: Multifocal T1-hypointense, T2-var intensity (depending on presence of cysts, necrosis, calc, etc.), enhancing lesions w/ clear borders & marked surrounding edema most commonly at or near gray-white junction, more commonly in anterior circulation (especially MCA), often a/w skull (bony) mets. Mets which hemorrhage: Breast, lung, melanoma, renal cell, choriocarcinoma, retinoblastoma, thyroid carcinoma.
- Non-neoplastic mass lesions: Colloid cyst: Near foramen of Monro in anterior third ventricle. Highly proteinaceous (T1-hyperintense), T2-hyperintense, well defined borders.

TOXIC & METABOLIC DISEASES & CONDITIONS

Acquired metabolic diseases

(Note: see WMD section for CNS dz caused by B_{12} deficiency, Marchiafava-Bignami syndrome, osmotic demyelination, hypoxia-ischemia, high altitude encephalopathy.)

- Hepatic encephalopathy: b/l, sym T1 bright lesions in basal ganglia (metallic deposits).
- Hypoglycemia: b/l & sym DWI & FLAIR bright signal of cortex, hippocampus, & basal ganglia; var DWI & FLAIR bright signal of WM.
- Thiamine (vitamin B_1) deficiency (Wernicke encephalopathy): Sym, b/l T2 bright in medial thalami, mam bodies, reticular formation, & periaqueductal gray matter; var microhemorrhages in affected structures (GRE dark, T1 bright).

Hereditary metabolic diseases

- Wilson disease: Sym caudate, putamen, thalamus, sup cerebellar

peduncle T2 bright, T1 dark signal; central pontine T1 dark region (central metallic dep); globus, red nuclei T2 dark.

- Pantothenate kinase deficiency (formerly Hallervorden-Spatz syndrome): b/l globus, red nucleus, substantia nigra T2 dark lesions; globus w/ central T2 bright portion (eye of tiger); var cortical atrophy.
- MELAS: Acutely DWI bright (ADC typically isointense) cortical & SC lesions; often posterior; lesions do not respect vascular territories.

- Leigh syndrome: b/l, sym putamen > thalamus, caudate, globus, brainstem, WM T2 bright lesions.
- Kearns-Sayre syndrome: b/l, sym basal ganglia T2 bright signal; CT bright & GRE dark basal ganglia lesions (calcs); diffuse atrophy.
- Mucopolysaccardidoses: Diffuse atrophy, WM T2 bright lesions (cystic changes), dural thickening w/ var mass effect on brain stem, var macrocephaly & thickened skull.
- Amino acidopathies: Early diffuse swelling; delayed/absent myelination; later diffuse atrophy; var neuronal migrational abnormalities.

Acquired toxic diseases

- EtOH: Chronically, midline cerebellum > diffuse cerebral atrophy. Diffuse WM dz.
- Manganese: b/l globus pallidus T2 bright lesions.
- Lead: Chronically, b/l basal ganglia calcs (CT hyperdense, GRE hypointense).
- Arsenic: B/l T2 bright lesions around cerebral aqueduct & midbrain tegmentum.
- Kernicterus: Early, b/l globus pallidus T2 & T1 bright lesions; later, T2/FLAIR bright & T1 dark; b/l subthalamic nucleus T2 bright lesions; var ↑ T2 signal in WM & gen atrophy.
- Cyanide: Acutely, b/l putamen DWI bright lesions & diffuse cerebral swelling.

NEURODEGENERATIVE DZ & HYDROCEPHALUS

- Alzheimer disease: Hippocampal, amygdala, & temporal lobe atrophy, ↓ NAA on MRS. With hippocampal atrophy, temporal horns of lateral

ventricles enlarge ex vacuo. Also, ↓ metabolism in posterior parietal areas on FDG-PET, & Pittsburgh compound B (PIB, binds to amyloid protein). PIB to distinguish from fronto-temporal lobar degeneration (FTLD), which has no abnl PIB signal.

- Lewy-body dementia: Substantia nigra, posterior cortical, & brainstem atrophy.
- Parkinson disease: Atrophy of substantia nigra.
- Parkinson plus syndromes:
    - Progressive supranuclear palsy (PSP): Midbrain tectum atrophy, abnl periacqueductal signal, ↑ iron in putamen (T2 hypointense), ↓ NAA on MRS.
    - Cortical-basal ganglionic degeneration (CBGD): "Knife-blade" atrophy of structures near central sulcus & superior parietal lobe.
    - Multiple systems atrophy (MSA): Olivopontocerebellar atrophy (OPCA): "Hot cross bun" sign on axial images of pons.
    - Striatonigral degeneration: Caudate, putamen, & substantia nigra atrophy.
- FTLD:
    - Frontal variant: Asym frontal & anterior temporal atrophy.
    - Semantic variant: Asym temporal lobe/pole & parahippocampal atrophy.
    - Progressive nonfluent aphasia: Perisylvian, insular, & superior temporal atrophy.
- Huntington disease: Head of caudate atrophy (loss of convex shape) w/ ex vacuo "rounding" of anterior lateral ventricles, best seen on axial images.
- Multi-infarct "vascular" dementia: White & deep gray matter lacunes, multiple strokes of different ages, ↓ NAA on MRS.
- HIV/AIDS: Diffuse atrophy, hyperintense basal ganglia structures, superimposed PML, lymphoma, toxoplasma, IRIS, etc.
- CJD: Hyperintense basal ganglia structures & diffuse cortical restricted diffusion.
- Amyotrophic lateral sclerosis (ALS): Anterior horn cell atrophy, & T2-hypointense motor cortex & corticospinal tract.

VENTRICULOMEGALY & ICP ABNORMALITIES

Ventriculomegaly

- Hydrocephalus (obstructive & communicating): Flattened sulci, ↑ PV & periaqueductal T2 signal (transependymal flow), elevated & thinned corpus callosum, dispropor enlarged temporal horns, convex third ventricle w/ enlarged anterior recess, var fourth vent enlargement.
- Cerebral atrophy (ex vacuo): Enlarged sulci, sym involvement of ventricles (depending on underlying disease; AD also has temporal horn enlargement); concave third ventricle w/ nl anterior recess, fourth ventricle nl size (unless concurrent, marked cerebellar atrophy).
- Normal pressure hydrocephalus (NPH): Diffuse ventricular enlargement out of proportion to enlarged sulci, minimal ↑ PV & periaqueductal T2 signal (transependymal flow).
- Pseudotumor cerebri: nl or slightly ↓ventricles, ↑ T2 signal (CSF) round optic nerves, flat pituitary gland & posterior sclera, compressed venous sinuses, reverse

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cupping of optic discs (papilledema), enlarged optic nerve sheath, greater than average freq empty sella.

NPH	Cerebral Atrophy
Ventricular dilatation > sulcal dilatation	Ventricular = sulcal dilatation
Enlarged temporal horns	Nl or atrophic temporal horns
Convex third ventricle	Concave third ventricle
<1 cm mammilo-pontine distance	>1 cm mammilo-pontine distance
Distended thin corpus callosum— flattened cortical sulci	Nl or atrophic corpus callosum Enlarged cortical sulci
Evidence of transependymal flow (acute	No evidence of transependymal flow (though can resemble microvascular ischemic

only) disease)

NEURODEVELOPMENTAL & GENETIC DISEASES

Migrational disorders

- Heterotopia: Diffuse, subcortical, or PV region isointense to cortex (area of ectopic gray matter.
- Cortical dysplasia: An area of ectopic gray matter.
- Pachygyria: Abnormally thick cortical mantle.
- Polymicrogyria: Excessive or redundant abnl folding of cortical mantle.
- Lissencephaly: Abnl “smoothness” (lack of nl gyral pattern) of cortex.
- Porencephaly: Cyst, cleft, or cavity lined by WM, disrupts nl cortical architecture.
- Schizencephaly: Cyst, cleft, or cavity lined by heterotopic GM, disrupts nl cortical architecture.
- Holoprosencephaly: Failure of forebrain development.

Other developmental disorders

- Dandy-Walker malformation: Usually obstructive hydrocephalus, cerebellar vermis agenesis, cystic enlargement of fourth ventricle w/ enlargement of posterior cranial fossa.
- Chiari malformation: (1) Type 1: Low-lying cerebellar tonsils (>5 mm below foramen magnum); var assoc hydrocephalus, high T2 signal in central cord (syringomyelia); (2) Type 2: Hydrocephalus, small posterior fossa w/ compression of cerebellar structures, elongated cerebellar tonsils & fourth ventricle, beak-shaped midbrain tectum, kinking of medullocervical region; assoc protrusion of lumbar spinal cord through meningeal defect (lumbar myelomeningocele) & syringomyelia; (3) Type 3: As in type 2 + occipital encephalocele or cervical myelomeningocele.
- Joubert syndrome: Dysgenesis of cerebellar vermis, “molar tooth” sign on axial MRI, corresponding to lateral displacement of superior cerebellar peduncles & lack of decussation of these fibers.
- Vermian hypoplasia: Can be incidental or a/w Dandy-Walker malformation.
- Septo-optic dysplasia: partial or complete absence of the septum

pellucidum and/or optic nerves or chiasm.

Other disorders

(Note: see WMD section for CNS dz caused by TS.)

- NF-1: (1) Neurofibromas: T1 isointense (to brain) & T2 bright skin, soft tissue, bone, & nerve lesions w/ enhancement; (2) Schwannomas: T1 isointense (to brain) nerve lesions w/ enhancement; (3) Anterior visual pathway gliomas: Enlargement of optic nerve, chiasm, or tract w/ minimal enhancement; (4) Tectal glioma: Enlargement of midbrain tectum w/ minimal enhancement; var hydrocephalus (5) Myelin vacuolization (children): T2 bright lesions of WM; regress in teenage years; (6) Bony abnormalities: Macrocephaly; sphenoid wing hypoplasia, creates defect for temporal lobe to protrude; (7) Other: Dural calcs (by CT or GRE); aneurysms.
- NF-2: (1) Schwannomas: T1 isointense (to brain) nerve lesions w/ enhance; b/l or u/l CN VIII lesions; other cranial nerves, which may be multiple; (2) Meningiomas: T1 isointense (to brain) dural lesions w/ enhancement; often multiple.
- Sturge Weber syndrome (SWS): Cortical & meningeal calcs (by CT or GRE) w/ hemispheric volume loss & cranial thickening; region of meningeal thickening & enhancement (hemangioma).
- Von-Hippel Lindau (VHL): Cerebellar hemangioblastoma: Cystic-appearing (T2 hyperintense cyst) w/ nodular enhancement; var regions of hemorrhage; may be multiple.

Vascular Neurology

TRANSIENT ISCHEMIC ATTACKS

General: TIA: brief, reversible episode of focal neuro sxs (by definition <24 h, most <1 h). Newer definition: Brief, reversible episode of focal neuro sxs due to ischemia w/ a negative MRI. Often hard to diagnose, given large differential. Longer TIAs more likely to be from an embolus, repeated TIAs w/ similar sxs suggest impending vessel occlusion. Most TIAs should be worked up urgently, whether inpt or outpt. Early w/u & treatment of TIA/minor stroke reduces risk of recurrent stroke by up to 80% (Lancet Neurol 2007;370:1432).

ABCD2 Score (*Lancet* 2007;369:283)

- Help determine urgency of stroke w/u, score ≥ 4 might benefit from admission & expedited w/u

Stroke Risk

Score 2	Day	Day 7 90	Day
<4	1%	1.2%	3.1%
4-5	4.1%	5.9%	9.8%
>5	8.1%	11.7%	17.8%

- Age ≥ 60 yr: 1 point
- BP ≥ 140/90: 1 point
- Clinical features: U/l weakness (2 pts), speech Δ w/o weakness (1 pt)
- Duration: 10-59 min (1 pt); ≥60 (2 pt)
- DM: 1 point

APPROACH TO TRANSIENT NEUROLOGIC SYMPTOMS

Top 3: TIA, sz, migraines. Others: Syncope, compressive neuropathy, anxiety, conversion, malingering, prior stroke sx re-manifested by metabolic derangement/infxn, amyloid spells.

- TIA: Pts: Older, M > F, stroke risk factors (HTN, DM). Sx: Negative. If multiple modalities (i.e., sensory, motor) usu occur all at once. HA: Sometimes. Duration: Brief (usu ˜15 min).

- Seizures: Pts: Younger. Sx: Begins w/ positive (tingling) → negative (e.g., paresis, aphasia) postictally. Duration: Very brief (seconds-minutes). Negative can sometimes last hours.
- Migraines: Pts: Younger, F > M, +FHx. Sx: HA after attack, N/V, photo-/phonophobia. Begins (+) sxs (bright lights), followed by (-) sxs. Slowly evolving (e.g., tingling spreads up arm). Modalities affected sequentially (e.g., vision → sensory/motor) Duration: Longer (30 min-several hrs).

ISCHEMIC STROKES

Etiologies: Embolic: Sudden onset sxs, maximal at onset. Occasionally pt reports getting up to go to bathroom & developing symptoms. Thrombotic: Full main deficit sometimes preceded by warning signs (either TIAs or minor symptoms) or stuttering course (progressive neurologic worsening over several hour).

Main Subtypes

Large artery atherosclerosis (˜18%)	• Most common sites: Carotid bifurcation, vertebrals at origin or at the vertebrobasilar junction, MCA at stem/bifurcation • Rare for plaques to occur beyond first branching point • Risk factors: HTN, DM, dyslipidemia, smoking
Cardioembolic (˜21%)	• Afib, MI, CHF, prosthetic valves, rheumatic heart disease • Most often lodge in MCA (especially superior division) or PCA territory • Small embolus → cortical/penetrating arteries; large → main branches
Small vessel (lacune) (24%)	• Due to atherosclerosis → thrombosis of small penetrating vessels • Infarcts up to 2 cm in size • Often a/w HTN

Other causes

Vasculitis: Due to autoimmune disease, arteritis (temporal, Takayasu), infectious (Tb, syphilis, VZV), or primary CNS vasculitis.

Dissections: Strokes typically in younger pts (35-50 yr).

Fibromuscular dysplasia: Uncommon, affects women (30-50 yr). Imaging: String of beads (segmental narrowing & dilations of arteries), usu B/L. Arteries affected: Renal,

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ICA > vert > intracranial a. Stenosis causes thrombosis or dissection. Rx: Antiplatelet therapy.

Moyamoya: Best studied in Asians, but occurs worldwide. Occlusion of large arteries (usu distal ICA or main stem MCA/ACA) → lenticulostriate develops collaterals. Angio: Collaterals = “puff of smoke” = moyamoya in Japanese. Stroke 2/2 large artery occl, ICH 2/2 breakdown/fragility of collaterals. Rx: Surgical (↓ ischemic stroke): Bypass (first line) or EDAS (if bypass not feasible, involves laying branch of STA onto affected brain hoping it’ll grow into brain).

Drugs: Amphetamines & cocaine, cause either acute HTN or drug-induced vasculopathy.

Subcortical vascular dementia: Elderly w/ longstanding HTN; multiple subcortical infarctions → dementia. MR: Extensive white matter changes. Rx: Alzheimer meds not found to be helpful (Lancet Neurol 2008;7:310).

CADASIL (Cerebral autosomal dominant arteriopathy w/ subcortical infarcts & leukoencephalopathy): 30-50 yr, inherited (incomplete penetrance), Notch 3 mutation. P/w: Lacunar strokes, progressive dementia, h/o migraine w/ aura. MR: Extensive WM Δs. Hypercoagulable states: see below.

Unknown causes: “Paradoxical embolism”: technically “cryptogenic” (not lacunar, no clear cardioembolic (e.g., afib)/large artery source. 2/2 PFO, see below for Rx.

ISCHEMIC STROKE WORKUP

Urgent ED studies

CBC, BMP, PT, PTT, Cardiac Enzymes q8h ×3; Non-contrast head CT: r/o ICH (only required imaging for IV rt-PA)

Studies for secondary risk prevention

Labs: Fasting lipid panel, including lipoprotein(a); hemoglobin A1c (looking for underlying DM, glucose may be elevated s/p stroke); homocysteine; TSH: Looking for hyperthyroidism (increases risk of afib); ESR & CRP if suspecting vasculitis or endocarditis; hypercoagulable panel → before starting heparin for pts <50 yr (antiphospholipid antibodies, lupus anticoagulant, prothrombin G20210A gene mutation, factor V leiden, protein C/protein S/antithrombin III deficiencies, β-2 microglobulin).

Imaging: CTA: For endovascular intervention/medical therapy (e.g., dissection, atherosclerosis, vasculitis), comparable to U/S for ICA stenosis. MRI/MRA: Not needed emergently, Se 95% w/in first few hours of stroke. Carotid U/S: If CTA or MRA not done.

Other tests: Holter: 24-h Holter, looking for atrial fibrillation, in pts w/ high suspicion of afib can do extended cardiac monitoring for 7-14 days (or longer) as outpt. Echocardiogram: Ruling out PFO or atrial septal aneurysm (ASA) (in cryptogenic stroke), CHF, thrombus, left atrial dilatation (↑'s risk for afib), LV hypokinesis, valvular abnormality. Consider TEE: For younger pts w/o clear cause, better for looking at valves. May be less sensitive for PFO detection than TTE if pt unable to Valsalva due to sedation. CT Venogram of lower extremities: For + PFO & cryptogenic stoke, to rule out DVTs; LE U/S do not evaluate for DVT in iliac veins. MRV or CTV of pelvis may be necessary.

Early management of acute lschemic strokes

Thrombolysis: IV rt-PA in first 3 h of sx onset (dose: 0.9 mg/kg, 10% as bolus). NNT for improvement: 3; number needed to harm: 30. Not used in minor/mild sxs, rapidly resolving symptoms, other contraindications (hemorrhage, AVM, endocarditis, abscess). Sooner Rx → better outcome (˜2 million neurons lost every minute) (Stroke 2006;37:263). BP prior to & during rt-PA: BP ≤ 185/110 (if BP ↑, give Labetalol IV, if BP remains stable at target, then can give rt-PA). Post rt-PA precautions for 24 h: No NG tube, NPO. No arterial sticks in noncompressible sites. No antiplatelets or anticoagulation (including DVT dosing of heparin & LMWH). Use TEDs/pneumoboots for DVT ppx. CT scan at 24 h to determine if hemorrhage present, earlier w/ any clinical worsening. Hemorrhagic transformation: Important complication of rt-PA: ↑risk w/ → NIHSS: score ≥ 20 → 17% risk, <10 → 3% risk. Sxs: ↑ somnolence, HA, neurologic deterioration. If suspected: stop rt-PA, STAT noncontrast CT, coagulation panel, type & cross-match 6-8 units platelets & cryoprecipitate. Negative CT: Resume rt-PA (if still w/in 3 h window); Positive CT: Transfuse, neurosurgery consult. Angioedema (orolingual) in 5% receiving rt-PA, usu mild (Rx: steroids & antihistamine)

Heparin: Guidelines do not recommend heparin; some centers consider it for large artery etiology (including actively embolizing carotid, some evidence) or for afib (little evidence); others: LV thrombus, mechanical heart valve, dissection, cerebral venous thrombosis. Do not give heparin if coma, large infarction, mass effect or ICH on CT, MAP > 130, NIHSS > 15.

Endovascular treatments: See “Interventional Neurology” chapter

ASA: ASA 81 mg qd (full dose not proven more effective). No other antiplt tested acutely (e.g., clopidogrel, ticlopidine, dipyridamole). Two large trials showed (non

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significant) ↓ in death or disability w/ ASA w/in 48 h (CAST & IST; Lancet 1997;349:1641; Lancet 1997;349:1569). Meta-analysis of both trials → modest/significant benefit: 7 strokes prevented/1,000 pts treated, 4 deaths/1,000; likely no effect on severity of current stroke but ↓ recurrent ones.

Statins: For 2° prevention. Some rec high dose statin (as in ACS) acutely (for atherosclerotic stroke—see AHA/ASA Guidelines 2008). Only one small study testing acute statin use, safety & efficacy trial, statin started <12 h, not powered to detect clinical benefit, no difference in mortality or outcome. Recent statin withdrawal study: (Neurology 2009;69:904): Stopping outpt statin → worse outcome (˜5 × ↑ in death/dependence) & worse infarct volume; statin withdrawal perhaps triggers prothrombotic/inflammatory response.

Induced HTN: Small clinical trials, useful in select group of pts, use w/ caution. Possibly ↑ BP restores perfusion to penumbra. How to do trial of HTN: Consider in pts w/ fluctuating exam w/ BP changes (i.e., worse when ↓ BP). Exclude pts w/ h/o CAD, PVD, CHF, ischemic, ICH/midline shift, rt-PA, SBP > 200, heparin drip. ↑ admission SBP by 20% (max SBP 200) w/ phenylephrine drip, titrate to neurologic improvement. If NIHSS ↓ by 2 points after 30 min, continue drip. Daily attempt to titrate drip off, only if neurologic sx do not worsen during titration. Should be seen as bridge to more definitive therapy (e.g., stent, CEA, bypass).

General medical care

Hypertension: >60% of stroke pts have SBP > 160. Rx BP > 220/120, in pts not receiving t-PA, or if end-organ damage (kidney, heart, eye). Rx BP > 185/110 in pts receiving rt-PA. Don’t ↓ BP by >15%. Can initiate HTN meds w/in 24 h of stroke.

Hypotension: Worse outcomes, esp < 100/70. Rx underlying cause of

hypotension (volume depletion, arrhythmia, blood loss, sepsis). Rx: Fluids, pressors.

Glucose: Hypoglycemia: Goal BG 80-140, Rx w/ ISS or insulin drip. 1/3 stroke pts affected, a/w poor outcomes, few studies in stroke pts, studies extrapolated from other scenarios (Medical/Surgical ICU). Hyperglycemia: Promptly correct hypoglycemia (may mimic strokes).

Temperature: Fever: ↑ mortality, seek cause of fever & Rx w/ antipyretic. Hypothermia: ↓ mortality, insufficient data for use of cooling in stroke.

Oxygenation: Keep O_2 sats ≥ 92%. Pts needing intubation have 50% mortality at 30 days. Aspiration PNA important complication & leading cause of death.

ACUTE STROKE TREATMENT EVIDENCE

Rt-PA

NINDS rt-PA (NEJM 1995;333:1581): 624 pts, placebo v. rt-PA w/in 3 h, 2 parts: Part 1: No diff in neuro improvement at 24 h v. placebo. Part 2: Favorable outcome v. placebo at 3 mo (OR for favorable outcome 1.7). ↑ benefit for pts treated w/in 90 min, no difference in mortality.

ECASS (JAMA 1995;274:1017): European trial, multicenter, 620 pts, placebo v. rt-PA w/in 6 h, sl. larger rt-PA dose. Overall no difference at 3 mo in rt-PA v. placebo, ↑ mortality w/ rt-PA. Post hoc analysis: (nonsignificant) trend → better outcome w/ pts Rx'd w/in 3 h.

ECASS II (Lancet 1998;352:1245): 800 pts, same dose as NINDS (0.9 mg/kg), w/in 6 h. No benefit w/ rt-PA, not enough pt to see if Rx w/in 3 h makes a difference.

ATLANTIS (JAMA 1999;282:2019): Rt-PA 3-5 h, 613 pts. No difference in functional outcome & mortality, extending window > 3 h not beneficial.

ECASS III (NEJM 2008;359:1317): 821 pts, Rt-PA 3-4.5 h. Rt-PA → sl. better outcome at 90 days.

Heparin

IST (Lancet 1997;349:1569): Tested heparin SC at two doses (5,000 U BID or 12,500 U bid) w/in 48 h of stroke. Not all pts received a baseline CT before randomization. Heparin no effect on mortality at 14 days & 6 mo. Significantly ↓ ischemic strokes, but offset by ↑ in hemorrhagic stroke; DVT rate significantly lower.

TOAST (JAMA 1998;279:1265): Rx w/ IV LMW Heparin (danaparoid) started w/in 24 h for 7 days. No difference in outcome at 3 mo, ↑ risk for

major bleeding & ICH. Strokes due to large artery athero outcomes better in pts receiving anticoag (no difference in pts w/ cardioembolic stroke), but this was a subgroup analysis w/ small numbers. Risk of recurrent stroke in trial 1.5%/wk (not ↑ w/ pts w/ cardioembolism), so urgent anticoag may not be needed.

Other trials (1) Small study of heparin w/in 3 h showed a benefit (authors argued that previous trials heparin given too late & that early Rx helpful) (Stroke 2005;36:2415). (2) Multicenter Asian trial of LMWH in pt w/ large artery atherosclerosis showed no benefit (Lancet Neurol 2007;6:407). (3) Cochrane meta-analysis of ˜22,000 pts (done before Italian study) showed no benefit for anticoagulation in acute stroke (Cochrane

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Syst Dat Rev 2008;CD000024); prevents 9 ischemic stroke per 1,000 pts but causes an equal amount of ICH. (4) HAEST: 449 pts, LMWH v. ASA in pts w/ afib + stroke w/in 30 h for ˜14 days (after which anticoag started at discretion of clinician), no difference in preventing recurrent stroke in first 14 days or outcome at 14 days or 3 mo (Lancet 2000;355:1205). (5) Cardioembolic stroke meta-analysis: (Stroke 2007;38:423): Arguably strongest reason for urgent anticoag (to prevent further embolism), stroke rate for afib 0.1% to 1.3%/day. Early anticoag no benefit (no difference in death, increase risk of ICH, nonsig decrease in ischemic stroke).

Complications of ischemic stroke

Ischemic brain swelling: See Neuro ICU section. Hemorrhagic transformation: ˜5% of infractions → symptomatic ICH. Rx: Depends on extent. Szs: risk ˜2%, ↑ w/ cortical strokes, no need for prophylactic AED, most commonly partial sz (± secondary generalization).

SECONDARY STROKE PREVENTION

Antiplatelets

ASA: High & low-dose equal efficacy. ↑ ASA dose doesn’t ↓ stroke risk but ↑s risk of bleeding.

Dipyridamole & ASA: French Toulouse Study/AICLA: No benefit of adding dipyridamole to ASA. ESPS-2 trial: ASA ↓ relative stroke risk by 18%, ASA/ext.-release dipyridamole by 37%; neither affected mortality (J Neuro Sci 1996;143:1). HA most common SE of dipyridamole (↓ this by giving med qd w/ baby ASA × 1 wk then dropping ASA & switching med to BID).

Clopidogrel: Used if pt allergic to ASA, conflicting evidence. CAPRIE: (Lancet 996;348:1329): Clopidogrel more effective than ASA in a composite

risk of ischemic stroke, MI, or vascular death. But in pts w/ prior strokes, the benefit was not statistically significant, nor was stroke as an outcome reduced for the total population. CHARISMA: ASA v. ASA + clopidogrel in vascular pts & those w/ vascular risk factors, no difference in composite risk stroke, MI, or vascular death, but sig increase in bleeding events (NEJM 2006;354:1706). MATCH: Clopidogrel v. ASA + clopidogrel in stroke pts, no difference for stroke or other endpoints, combination caused increased bleeding (Lancet 2004;364:331). Profess: Clopidogrel equivalent to combination ASA + dipyridamole in >22,000 stroke pts (Lancet 2008;7:875).

EXTRACRANIAL ATHEROSCLEROSIS

Carotid endarterectomy (CEA): Indications: Symptomatic stenosis: Stenosis 70%-99% & life expectancy >5 yr. 50%-69% stenosis: Men w/ at least 5 yr life expectancy; women → no CEA, medically manage. Asymptomatic stenosis: Medically stable men w/ stenosis 60%-99% w/ life expectancy of at least 5 yr. Women → no CEA, medically manage.

Carotid artery stenting (CAS): Few trials, mixed results (neg results 2/2 lack of technical expertise), no evidence CAS better than CEA. CAS may be appropriate for surgical high risk pts. CAS → ↑ risk periprocedural stroke (w/in 30 days); stroke risk after similar to CEA (Lancet Neurol 2008;7:885). Current guidelines: CAS for high risk surgical pts w/ stenosis > 70% & sx.

Extracranial/intracranial bypass: Used in carotid occlusion: superior temporal artery anastomosed to MCA. 1985 International EC/IC bypass: no benefit (Stroke 1985;16:397). (Criticism: pts w/ completed infarctions included, no perfusion studies). Bypass may benefit pts w/ misery perfusion or carotid occlusion (i.e., complete stenosis).

Misery perfusion tested via: Acetazolamide challenge: pre-postacetazolamide images taken (MR or CT), Rx dilates vessels & ↑s CBF, vessels already max dilated will show little/no ↑ blood flow. OEF PET scan: Shows O2 extraction fraction, ↑‘d extraction where vasodilation can’t meet cerebral demand. Japanese EC-IC bypass trial used misery perfusion as inclusion criteria (other criteria: stenosis ≥70%, small or no infarct), surgery significantly ↓‘d stroke rate at 2 yr.

Complete Carotid Artery Occlusion (CAO): (Neurology 2000;54:878): asx CAO stroke risk: 0% at 2 yr, 4.4% at 3 yr (i.e., benign prognosis). Sx CAO stroke risk: 19% at 2 yr, 21% at 3 yr → reasonable to consider intervention.

INTRACRANIAL ATHEROSCLEROSIS

Medical Rx: Antiplatelets or warfarin. ASA usu given, but if severe flow-limiting → consider anticoag to ↓ progression. ˜10% strokes & TIAs 2/2

intracranial stenosis (50%-99% stenotic).

P.30

WASID Trial (NEJM 2005;352:1305): ASA vs. warfarin for intracranial stenosis: No difference in outcome. Pts on warfarin: Therapeutic 63.1% of the time (little better than real life PCP monitoring). When INR in range, rate of ischemic stroke reduced from 25/100 to 5/100.

Angioplasty/stenting: See “Interventional Neurology” chapter

CARDIOEMBOLISM

Atrial fibrillation: Causes 75,000 strokes/yr. Anticoagulate w/ warfarin INR (2-3) w/in 2 wk of stroke/TIA. Warfarin superior to ASA in pts w/ afib & recent stroke/TIA.

ACTIVE Trial (NEJM 2009;360:2066): ASA vs. ASA/clopidogrel. Latter had ↓‘d composite risk of stroke, MI, death from vascular event, embolism but ↑risk of major bleeding (including ICH). Stroke risk: ASA 3.3% vs. ASA/clopidogrel 2.4%. Major hemorrhage: ASA 1.3% vs. ASA/clopidogrel 2%. Number needed to treat to avoid one stroke was 111 pts. Cost $202,464 to prevent a single stroke/yr (NEJM 2009;361:13). All pts received ASA at dose of 75-100 mg/days, but only ASA 325 mg shown to ↓risk of stroke in afib (Circulation 1991;84:527).

CHF: Causes stasis & increased risk for thromboembolism. Use of warfarin in CHF controversial, warfarin sometimes used in pts w/ very low EF (<20%), most guidelines don’t routinely recommend it unless pt has DVT/PE, mobile LV thrombus, or afib. Main trials (no RCT w/ conclusive evidence yet): WASH: No difference between ASA & Warfarin (AHJ 2004;148:157). WATCH: No difference, ended early due to poor recruitment, underpowered (J Card Fail 2004;10:101). WARCEF: Ongoing study, but underpowered to detect stroke as primary endpoint. Combining WATCH & WARCEF might give statistical power. For pts w/ CHF & recent TIA/stroke either warfarin (goal INR 2-3) or antiplatelets.

LV thrombus: Warfarin (goal INR 2-3) for 3-12 mo if acute stroke/TIA, +ASA if CAD.

OTHER CARDIAC ABNORMALITIES

Atrial septal abnormalities: PFO: Fetal anomaly, allows communication between atria. ASA: redundant tissue in the region of the fossa ovalis, acts as a nidus for thrombus formation. Association between cryptogenic strokes in pts ≥ 55 yr & PFO ± ASA in one study. In pts <55 yr, PFO + ASA > ASA > PFO significantly a/w stroke. One study showed association w/

PFO/cryptogenic strokes & older pts (NEJM 2007; 357:2262).

Rx: Four main modalities: Antiplatelet, anticoag, surgical closure, percutaneous closure. PICSS found no difference between aspirin & warfarin (Circulation 2002;105:2625) but was a very limited substudy; probably did not study the proper population at risk (many lacunar strokes).

Guidelines: Atrial anomalies w/ ischemic stroke: Antiplatelets (use warfarin if pt is high risk or has concomitant DVT or PE). PFO closure: Considered in pts who fail medical therapy (i.e., get recurrent cryptogenic strokes). Clinical trials of medical vs. closure therapy ongoing.

Valvular heart dz: Rheumatic mitral valve dz: Warfarin (INR 2-3) recommended. If pt has recurrent embolism despite adequate warfarin, add ASA. Prosthetic heart valve: Modern mechanical valve & ischemic stroke/TIA: Warfarin (INR 2.5-3.5); consider adding ASA if pt has another stroke despite adequate warfarin treatment. Bioprosthetic heart valve w/ ischemic stroke, consider warfarin w/ INR goal 2-3. All other valvular dz: Antiplatelet agents.

HYPERCOAGULABLE STATES

Intro: Possible association w/ ischemic stroke/cerebral venous thrombosis in pts <50 yr. Most have conflicting data, strongest association w/ antiphospholipid antibody syndrome. If testing abnl, repeat at f/u (as can be abnormal acutely). Most guidelines recommend testing in pts <50 yr w/ venous thrombosis, no recs for acute ischemic stroke. Rx: Controversial, usu for venous thromboembolism: warfarin; for arterial thrombus (ischemic stroke) ASA v. Warfarin (except for Antiphospholipid Ab syndrome → warfarin).

Antiphospholipid antibody syndrome: Acquired, can be a/w autoimmune dz (e.g., lupus), Sx: Recurrent pregnancy loss/thrombotic events. Dx: Clinical event + 1 lab abnl: (1) antibodies against: cardiolipin & β-2 glycoprotein I, or (2) Lupus anticoagulant (misnomer, not a test just for lupus pts, not an anticoagulant!). If lab test abnl, recheck in 12 wk. Rx: Anticoagulation for life (INR 2-3).

Prothrombin G20210A gene mutation: ↑ prothrombin synthesized by liver, mostly Caucasians.

Factor V leiden: Factor V mutation → resistant to degradation (by activated protein C). Screen w/ activated protein C resistance.

Protein C, protein S, or antithrombin III deficiencies: Very uncommon. Dx

difficult due to false +‘s, esp acutely after stroke. All 3 ↓‘d in acute thrombosis/surgery, or hepatic dysfn (i.e., ↓‘d production), heparin ↓‘s antithrombin, warfarin/OCPs decrease protein C/S.

RISK FACTORS FOR STROKE

HTN: ↓ BP → 40% ↓ in stroke risk; BP goal < 140/90 or for DM/chronic kidney dz <130/80.

Diabetes: HgA1c goal ≤7%. BP < 130/80 w/ ACE-I or ARBs (which decreases progression of renal dz). LDL ≤ 70 mg/dL. Glucose control never shown to prevent macrovascular events (stroke, MI); only microvascular ones (neuropathy).

Lipids: First goal LDL, then triglycerides, then HDL. h/o stroke → target LDL < 100 mg/dL (for DM or multiple risk factors, LDL ≤ 70). Rx: Statin in atherosclerotic stroke. Goal triglycerides < 150 (TG 150-200 Rx: Lifestyle modification; TG 200-499 Rx: Lifestyle ± fibrate or nicotinic acid; TG ≥ 500 Rx: Fibrate or nicotinic acid). Goal HDL: >40 (Rx only after LDL & TG goals achieved, meds: fibrates/nicotinic acid). Statins reduce stroke risk in both pts w/ & w/o CAD.

Lipoprotein(a): An LDL, ↓‘d by nicotinic acid, is risk factor for stroke (Stroke 2007;38:1959).

Hyperhomocysteinemia: A/w 2× ↑ risk, but no evidence that ↓‘ing serum Hcy ↓‘s stroke rate. Given low risk, if levels > 10 μmol/L give folate 1 m daily (if nl level not achieved, add vit B_{12} & B_6). Vitamins in Stroke Prevention (VISP) Trial (JAMA 2004;291:565).

Cigarette smoking: Doubles stroke risk. Risk ↓‘s after quitting & disappears after 5 yr.

EtOH: Light drinking (1-2 drinks/day): ↓‘s risk (perhaps due to increase in HDL, decrease in platelet aggregation, & lower serum fibrinogen). Heavy drinking (>5 drinks/day): ↑ risk (due to alcohol-induced HTN, afib, decrease in cerebral perfusion, & coagulopathies).

Obesity: Losing weight not shown to reduce stroke risk, but obesity contributes to other risk factors for stroke including diabetes, dyslipidemia, HTN.

Physical activity: Moderately/highly active people have a reduced risk of stroke (30 min of daily moderate intensity exercise recommended).

DISSECTIONS

Intro: 35-50 yr; ICA dissection 3× more common than vert, extracranial >

intracranial. Unlike atherosclerosis, dissections usu affect distal segments of extracranial arteries. Carotid dissection: 2-3 cm distal to bulb, irregular stenosis, doesn't usu extend intracranially (passes through tight foramina often preventing extension). Vert dissection: Most often in freely moveable areas: at C1/C2 (as the artery wraps around the cervical vertebrae) & between origin & entrance into intervertebral foramina (can extend intracranially).

Etiologies: Trauma: Almost any form of trauma can cause it, e.g., MVA, vigorous coughing, & chiropractic manipulation (estimation of 1 stroke per 20,000 spinal manipulation). Genetic: Ehlers-Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, polycystic kidney disease, homocytinemia, α-1 antitrypsin. Other: Smoking, HTN, OCPs, possibly infections (especially URI, where infection causes arterial wall damage).

Clinical features: ICA dissection: Triad: neck/face/head pain. Partial Horner's in <50% (symp fibers run along ICA, ptosis/miosis but no anhidrosis—those fibers run along ECA). Cerebral/retinal ischemia. Lower CN palsy (especially XII & VI, which run near ICA) in ˜12%. Vert dissection: HA/pain back of neck, then post. circ. ischemia (e.g., dizziness, dysarthria).

Dx: Imaging: "Flame-like" appearance, tapered vessel, crescent shape around lumen. Doppler (Se > 90%): High resistance flow in distal artery. MRA w/ fat suppression, or CTA.

Rx: Asx dissections: ASA. Intradural dissections: Anticoag risks pseudoaneurysm formation, SAH. Sx dissection (extradural): Warfarin INR 2-3 (w/ heparin/LMWH bridge) for 3-6 mo until stenosis improves (on imaging) then switch to antiplt. Beyond 6 mo if pt still w/ sxs, otherwise switch to ASA (no benefit for prolonged anticoag if no symptoms). F/U monitoring at 3 then 6 mo w/ Doppler U/S, MRA, or CTA. Surgery/neuro-intervention: Considered if pt w/ sxs despite adequate anticoag.

Neuro-intervention: Angioplasty & stenting, vessel occlusion by embolization, vessel coiling or ligations, & bypass procedures.

Prognosis: Worse px: Intracranial dissections (a/w more severe sxs & bleeds). 72%-100% dissections recanalize. Recurrence rate: 1%/yr (risks lasts up to a decade), higher in first month 2%. No evidence that ASA & anticoag prevents dissections.

INTRACEREBRAL HEMORRHAGE

Intro: 10%-15% of first ever strokes are ICH (35% mortality at 30 day → half occur in first 2 days). Only 20% of pts w/ ICH are expected to be functionally independent at 6 mo. Classically, sudden focal neuro deficit, that slowly

progresses, ± HA/Vomiting. Volume of ICH & GCS on admission best predictors of 30 day mortality (ICH score).

Etiologies: HTN: Deep hemorrhage. In basal ganglia, pons, cerebellum, or deep hemispheric white matter. Other: Vascular malformation, anuerysm, trauma, coagulopathy, cocaine, vasculitis, neoplasm, sinus thrombosis, CAA (see below).

ICH score: (1) GCS: 3-4 = 2 points, 5-12 = 1 point, 13-15 = 0 points. (2) ICH volume (mL): ≥30 = 1, <30 = 0. (3) IVH: Yes = 1, No = 0. (4) Age: ≥80 = 1, <80 = 0 (5) Infranterntorial: Yes = 1, No = 0. 30 day mortality: (5+, 4, 3, 2, 1, 0) → (100, 97, 72, 26, 13, 0)%.

Volume estimation: ICH Volume: measured (ABC)/2 → A = longest diameter, B = diameter perpendicular to A, C = no. of slices × thickness of 10 mm slices (if 5 mm, divide C by 2).

Clinical features & dx of ICH: 50% basal ganglia, 33% hemisphere, 16% brainstem/cerebellum. Peak deterioration/swelling on day 3-7, but delayed edema can occur. Autonomic instability can occur (↑ RR, ↓ or ↓ HR, ↑ glucose). Labs: CBC, BMP, CXR, coags, tox screen.

Cerebral Amyloid Angiopathy (CAA):

Amyloid deposits in blood vessels, incidence increases w/ age, sporadic or a/w Alzheimer disease.

***Clinical features*:** Spontaneous lobar ICH (amyloid deposits favor cortical vessels). Microhemorrhages on gradient echo MRI. Transient neuro sxs (“amyloid spells”): brief spells of weakness/numbness 2/2 cortical irritation from microbleed (spreading depression or focal sz), dx: microbleed in area that explains spell. Inflammation: subacute cognitive decline/sz, diffuse WM T2 hyperintensity. Dementia: Due to diffuse ischemia, can be related to AD.

- *Dx*: Definitive CAA via autopsy only, probable CAA if ≥2 microbleed in cortex/gray-white junction on gradient echo.

- *Rx*: Avoid anticoag; antiplts on if strong indication (in general elderly population: 7-10× ↑ symptomatic ICH w/ anticoag even if INR is <3; 2× ↑ w/ antiplts) (*Stroke* 1995;26:1471).

Inflammatory CAA: Immunosuppression.

Neuroimaging:

CT: CTA r/o underlying vascular lesion. Subarachnoid blood = aneurysm. Temporal hemorrhage = trauma. Fluid-fluid levels in hematoma = coagulopathy (e.g., warfarin). Head CT for any changes in exam & CT day after admission (day 2).

MRI: Consider imaging to rule out underlying mass, if suspect amyloid angiopathy. Hyperacute bleed: Center → iso to hypointense on T2; rim → hypointense T1. Subacute: Hyper on T2/T1. Chronic: Hypo on T2/T1.

Rx:

Blood pressure: Overaggressively ↓ing BP may drop cerebral perfusion pressure. Unclear what BP goal should be (guidelines SBP < 180; in practice many rec SBP < 140) (Stroke 2007;38:2001). BP meds to use: Labetalol, Nicardipine, Esmolol.

Seizures: Occur early in 4.2% of pts & 8.1% w/in 30 days (Epilepsia 2002;43:175). Lobar ICH significantly ↑ed risk (especially if extends to cortical ribbon). Prophylactic Rx: Unproven benefit, no proof that it effects mortality/morbidity, consider in large cortical ICH.

Glucose: Elevated glucose a/w increased mortality; Goal 80-140.

Temperature: Fever worsens outcome, seek out sources, treat w/ acetaminophen. Persistent fever (>24 h) a/w poor prognosis & ventricular extension.

DVT/PE prophylaxis: At admit, intermittent pneumatic compressions. One study showed no ↑ risk for bleed on day 2 of ICH onset (w/ 5,000 units of heparin I id); likely LMWH is just as safe. Pts w/ DVT/PE, probably should get IVC filter.

Surgery: Supratentorial ICH: STICH trial → surgical clot evacuation no effect on mortality (one subgroup showed a trend to better outcome but not statistically significant: lobar clots w/in 1 cm of surface & GSC ≥ 9). Cerebellar hemorrhage (not included in STICH): >3 cm w/ deterioration or brain stem/fourth ventricle compression fair better w/ surgery. Minimally invasive surgery (e.g., endoscopic aspiration): Info limited, need more trials.

ICP: See “Neuro ICU” section.

Warfarin: Rate ICH on warfarin = 0.3%-0.6%/yr. Risk doubles for every 0.5

above INR 4.5. Warfarin-related ICH Rx: Goal INR < 1.4 (PT/INR q4h × 24 h). Vit K 10 mg IV (takes 6 h to normalize INR) & FFP (10-20 mL/kg, ˜4-6 U, risk of vol overload, give furosemide in CHF pts).

Restarting warfarin: Risk of stroke in afib 5%/yr, in pts w/ previous stroke 12%. Probably can restart in 7-10 days after ICH (individualize per pt). One decision analysis concluded that survivors of prior lobar ICH should not be restarted on warfarin (even if high risk pt for thromboembolic stroke; Stroke 2003;34:1710). One retrospective trial (which did not separate lobar ICH from others): (Arch Neurol 2008;65:1313). Concluded that restarting warfarin had low risk of recurrence of ICH. But incidence of thromboembolic event & ICH similar in warfarin & control group.

Other drug-induced coagulopathies

- Heparin: Rx: Protamine → 1 mg/100 U of heparin over last 3 h; q1h PTT × 4 then q4. If heparin stopped 30-60 min ago give 0.5-0.75, if 60-120 min give 0.375-0.5 mg, if >120 min then give 0.25-0.375).
- Enoxaparin: Rx: Protamine → 1 mg/1 mg of enoxaparin; Recheck PTT in 2-4 h, if still elevated consider giving an additional 0.5 mg of protamine.
- ASA/clopidogrel: No evidence for plt transfusion, restart ASA ˜ 1 wk after ICH. Transfuse plts if count < 100,000.

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME (RCVS)

Aka Call-Fleming syndrome. Problem w/ cerebrovascular tone. F > M; typical 20-50 yr.

P/w: Thunderclap HA (sudden, acute, severe) but sxs variable. Associations: Migrainous vasospasm: Pt w/ h/o migraines; Postpartum angiopathy; Drugs: Vasoactive meds (cocaine, amphetamine, ephedrine, triptans, SSRI); post CEA, neurosurg, trauma, hypercalcemia, IVIg.

Dx: CT: R/o SAH, follow up w/ LP (for CT negative SAH). LP: R/o other causes such as encephalitis, vasculitis (Nl or near nl in RCVS). MRA or CTA (gold standard conventional angio): Beading; Resolution of vasoconstriction in 3 mon f/u scan (can f/u w/ transcranial Doppler). MRI: Infarcts (especially watershed zones), ICH (presumably from reperfusion injury), SAH (nonaneurysmal, overlying cortical surface).

Ddx: Primary angiitis of CNS (i.e., CNS vasculitis): HA more indolent, slowly progressive, CSF abnl in majority of pts (CSF lymphocytosis). SAH: R/o w/ CT, then LP. Arterial dissection: R/o w/ vessel imaging. Other causes

of thunderclap HA: CVST, ICH, meningitis/encephalitis.

Rx/prognosis: Nimodipine or verapamil (first line, used for vasospasm). High dose steroids (unproven benefit). Avoid vasopressor meds. Stroke is a major determinant of morbidity.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Basics: Syndrome causing edema (usu in posterior WM), most commonly caused by relative HTN, often reversible. F > M. Usu acute process.

Clinical features: HA: Moderate to severe, constant; AMS: Confusion → coma; szs (usu GTCs); Visual sxs: Hemianopia, visual hallucinations (can have other focal sxs). Pathogenesis: Autoregulation failure: ↑ BP → cerebrovascular autoregulation to fail → breakdown of BBB → vasogenic edema → often posterior circulation possibly due to less sympathetic innervation of those vessels, so less able to handle BP change. Ischemia: Another theory, autoregulation failure → vasoconstriction → ischemia. Endothelial dysfunction: Cytotoxic meds/eclampsia causes damage to vessel wall → vasogenic edema.

Etiologies: HTN: Usu caused by rapid ↑ of BP (& not by chronically elevated BP). Eclampsia: Often after birth has occurred. Cytotoxic meds: Occurs at any point, levels may not be toxic, e.g.: cyclosporine, tacrolimus, sirolimus, cisplatin, bevacizumab, interferon.

Less common etiologies: Renal/liver disease. TTP. Electrolytes (hypercalcemia, hypomagnesemia). Hemolytic uremic syndrome (HUS). Vasculitis.

Dx: MR: Multiple vascular territories, symmetric white matter edema (sometimes affects gray matter), parietooccipital, cerebellum/brainstem often involved, edema: ADC hyperintense + DWI: hypo/iso, f/u MR → resolution of edema.

Ddx: Watershed infarcts, cerebral venous thrombosis, encephalitis, vasculitis.

Rx: HTN: ↓ BP 25% in first 4 h to dBP of <100. Sz: AED, can taper when MR nl (˜2 wk). Eclampsia: Deliver baby/placenta, Mag for szs, treat ↑ BP. Cytotoxic meds: D/c or ↓ dose.

CEREBRAL REPERFUSION SYNDROME

Intro: Incidence ˜3%. HA, sz, neuro sx after CEA, carotid angioplasty/stenting (or EC-IC bypass, dural AVF embo). Hours-days after CEA (or other reperfusion, up to 1 mo later).

Path: Usu affects post circulation (2/2 ↓ sympathetic innervation). May be 2/2: ↓ autoregulation/baro-receptor dysfxn 2/2 surgery. Hyperperfusion → transudation of fluid into parenchyma → edema.

Si/sx: HA. AMS: Confusion → coma. Seizures: Focal motor Sz. Visual sxs. Possible ICH/SAH.

Dx: MR: (post-op) WM edema, focal infarct, edema or hemorrhage. TCD: MCA diameter unchanged w/ autoregulation; shows > 100% ipsi/l flow velocity of MCA, normalization of hyperperfusion = clinical improvement. Rule out: Occlusion or thrombosis of carotid w/ vascular image (U/S, CTA, or MRA).

Rx: HTN: Labetalol (no direct effect on CBF); Clonidine (↓ CBF); Avoid vasodilators/Ca channel blockers → cerebrovasodilation → worsening hyperperfusion. Szs: AED if clinical or EEG Sz. Prognosis: Good recovery for most if Rx before secondary injury.

Prevention: → risk if surgery done w/in month of infarct, or recent contralateral CEA (w/in 3 mo). BP control helps w/ prevention. Pretreatment w/ edaravone (limits endothelial cell injury) decreased incidence of hyperperfusion after CEA (Neurosurgery 2004;55:1060).

TRAUMATIC BLEEDS

Acute subdural hematoma (SDH): Trauma may be minor in elderly, caused by tearing of bridging veins (occasional a. rupture), sxs due to brain compression from blood. Lucid → comatose after injury. CT: Crescent shaped hyperdense. MR: T2 hypointense. Rx: Likely better outcome if surgery sooner. Options: burr hole v. craniotomy. Observation for small hematoma (<10 mm thickness, no herniation shift < 5 mm), repeat CT in 6-8 h, then serially.

Chronic SDH: Trauma: Trivial or forgotten. Days-weeks of HA, AMS, encephalopathy. CT: Clot iso → hypodense (in about 1/mo). MR: Hyper (weeks) → hypointense (months) on T1. Rx: Small SDH: Observation. Large SDH (≥10 mm thick, ≥5 mm shift) or sx: surgery. Burr hole w/ catheter placement × several days until clot drained. Craniotomy if rebleed after burr.

Epidural hemorrhage: Middle meningeal a. tear 2/2 skull fx. Trauma causing LOC → lucid interval → coma. CT: Lens shaped clot. Rx: Surgery for > 30 mL bleed, coma, or neuro sxs.

In all above cases: Reverse anticoagulation like ICH if pt on warfarin.

Neurocritical Care

COMA & DISORDERS OF CONSCIOUSNESS

Coma: A state of unarousable unresponsiveness.

Vegetative state: Unawareness of self or environment, but w/ preservation of sleep/wake cycles & complete or partial preservation of hypothalamic & brainstem autonomic functions.

Persistent vegetative state (PVS): >1 mo in vegetative state.

Permanent vegetative state: 3 mo after nontraumatic brain injury, 1 yr after TBI.

Minimally conscious state (MCS): Severely impaired consciousness in which minimal but definite behavioral evidence of self-awareness or environmental awareness is demonstrated.

Locked-in syndrome: State of de-efferentation w/ quadriplegia & loss of lower cranial nerve function but preservation of sensation, cognition, & eye mvmts.

Catatonia: A state of unresponsiveness predicated on a psychiatric disorder w/ disturbance of motor behavior but maintenance of consciousness. Stuporous & hyperexcitable forms of catatonia exist, w/ stuporous form potentially being mistaken for coma. Behavioral disturbances include mutism, posturing, waxy flexibility, & catalepsy.

Coma Scales: Multiple coma scales exist; Glasgow Coma Scale (GCS) most used:

- Eye opening: 4—spontaneous, 3—to voice, 2—to pain, 1—none.
- Motor: 6—follows commands, 5—localizes to pain, 4—withdraws to pain, 3—decorticate flexion, 2—decerebrate extension, 1—no motor response.
- Verbal: 5—oriented, 4—confused, 3—inappropriate words, 2—incomprehensible sounds, 1—no verbal response.

Pathophysiology, Ddx, & clinical manifestations

Neuroanatomic localization: Dysfn of brainstem reticular activating system, thalamic relay nuclei, and/or b/l diffuse dysfn of cerebral hemispheres. In coma of unknown etiology, subsequently determined causes: diffuse and/or

metabolic brain dysfn > supratentorial lesion > infratentorial lesion > psychiatric “coma” (conversion Rxn, depression, catatonic stupor).

Etiologies of coma (Plum & Posner’s Diagnosis of Stupor & Coma 2007)

Structural causes (compressive/destructive): Hemispheres (EDH, SDH, SAH, ICH, stroke, HIE, tumor, abscess, meningitis, encephalitis, vasculitis, leukoencephalopathy, prion dz, PML); Diencephalon (basal ganglia ICH, stroke, tumor, abscess, pituitary tumor, pineal tumor, encephalitis, fatal familial insomnia, paraneoplastic syndrome); Brainstem (cerebellar stroke, ICH, tumor, abscess; brainstem stroke, ICH, tumor, or infxn).

Diffuse, multifocal, or metabolic causes: Hypoxia, ischemia, hypoglycemia, vitamin co-factor deficiency: thiamine, niacin, pyridoxine, B_{12}, folate; endogenous metabolic products (hepatic coma, uremic coma, CO_2 narcosis, exocrine pancreatic encephalopathy, myxedema-thyrotoxicosis, hypo- or hyperparathyroidism, adrenal dz); meds/poisons (sedatives, acidic agents, psychotropic drugs, medication overdose), sepsis, hypo- or hyper-natremia, acidosis or alkalosis, hypo- or hyper-Mg, hypo- or hyper-Ca, hypophos, temp dysregulation (hypothermia or heat stroke), seizure or post-ictal state, diffuse axonal injury.

Clinical Features of Coma, PVS, MCS, & Locked-in Syndrome (*Neu* 2002;58:349)

	Coma	**PVS**	**MCS**	**Locke Syndrome**
Consciousness	None	None	Partial	Full
Sleep/wake	Absent	Present	Present	Present
Motor responses	Reflex & postural	Postures or w/d to noxious stim; occ nonpur-poseful mvmt	Localizes; reaches for & holds objects; automatic mvmts, e.g., scratching	Quadri
Auditory responses	None	Startle; briefly orients to	Localizes to sound location;	Preserv

		sound	inconsistent following of verbal commands	
Visual function	None	Startle; brief visual fixation	Sustained visual fixation & visual pursuit	Preserv
Communication	None	None	Contingent vocalization; inconsistent but intelligible verbalization or gesture	Aphon anarthric; blinking & vertical eye mvmts usua intact
Emotion	None	May have reflexive crying or smiling	Contingent crying or smiling	Preserv

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Initial management & evaluation of coma & impaired consciousness:

ABCs, 1 g/kg IV dextrose, 1 mg/kg IV thiamine, 0.01 mg/kg IV naloxone

Comprehensive metabolic panel, CBC w/ diff, coags, ABG/VBG, serum & urine tox screen, serum osms, EKG; consider TFTs, adrenal function tests, UA/UCx, Bld Cxs

Head CT and/or brain MRI; consider LP, EEG

Additional laboratory & imaging investigations based on clinical suspicion for specific etiology

Natural history & prognosis of coma, PVS & MCS: Coma prognosis varies widely depending on underlying cause. Post-TBI coma better outcomes than post-anoxia coma. Prolonged coma rare; most progress to PVS w/in 1 mo. Both PVS & MCS can exist as permanent or transitional states. Likelihood of significant fxnl improvement ↓‘s over time for both PVS & MCS. PVS life expectancy typically 2-5 yr; rarely > 10 yr. Limited data on MCS outcomes, but MCS pts may have better chance of functional recovery than PVS pts, & pts w/ MCS from TBI more likely to improve than those w/ MCS from other

etiologies (J Head Trauma Rehabil 1997;12:36). MRI has prognostic value in determining which early post-TBI PVS pts (6-8 wk) will recover vs. develop permanent vegetative state → corpus callosum & dorsolateral brainstem injuries are predictive of nonrecovery (Lancet 1998;351:1763). FDG-PET studies of PVS pts demonstrate ↓ global cerebral metabolism to 30%-50% of nl (J Neurosurg Anesthesiol 1999;11:17), but low metabolic activity does not accurately predict outcome. EEG has not been validated as a prognostic tool in PVS or MCS. Functional MRI has demonstrated regions of preserved brain function in a PVS pt (Science 2006;313:1402) and willful modulation of brain activity in PVS and MCS pts (NEJM 2010;362:579). Thalamic deep brain stimulation has improved responsiveness in a pt w/ MCS (Nature 2007;448:522).

BRAIN DEATH

Definition of brain death: Total & irreversible cessation of all spontaneous & reflexive brain functions. Brain death is clinically determined by coma, absence of brain stem reflexes, & apnea. Ancillary testing not necessary in adults, but may be used for determination of brain death when clinical testing is limited or questionable (NEJM 2001;344:1215).

Preparation for brain death assessment: Notify local organ bank. (1) Involve pt's nurse & if appropriate, religious officials and/or medical ethics services before discussing plans for brain death assessment w/ family. (2) Discontinue sedatives or hypnotics. (3) Confirm that the following clinical criteria are met: Known & irreversible cause of neurologic injury; clinical or neuroradiographic evidence of CNS catastrophe consistent w/ brain death; if cardiac arrest is the etiology, consider observing >6 h then re-examining; no severe acid/base, electrolyte, endocrinologic disturbances or hyperammonemia; no drug/EtOH intoxication (if barbiturates present, must be <10 μg/mL); if significant doses of CNS depressants have been administered recently, use ancillary testing; no neuromuscular blockade (if pt recently received neuromuscular blocking agents, must confirm reversal w/ train-of-four stimulation); if severe facial trauma, prior pupillary abnormalities, toxic levels of sedative drugs, or severe chronic CO_2 retention limit the clinical assessment of brain death, use ancillary testing.

Clinical findings consistent w/ brain death: Facial myokymias; spontaneous spinal mvmts of limbs (not decerebrate/decorticate posturing) (Neurology 1984;34:1089); respiratory-like mvmts: Shoulder elevation/adduction, back arching, intercostal expansion w/o significant tidal vol; sweating, blushing, tachycardia; normal osmolar control mechanisms → absence of diabetes insipidus; presence of DTRs, triple flexion, or Babinski sign.

Clinical findings that preclude brain death: Decerebrate or decorticate posturing of the limbs; pinpoint pupils → must rule out narcotic overdose; spontaneous breathing mvmts.

Clinical criteria for brain death (clinical measures/findings c/w brain death):

Coma: No eye opening, verbal response, or purposeful mvmt. No purposeful withdrawal to noxious stimi w/ supraorbital pressure & nail-bed pressure in all four extremities.

Absence of brainstem reflexes: Pupils: Fixed pupils, even w/ bright light & magnifying glass; ocular mvmts: No oculocephalic reflex → only test if C-spine integrity has been ensured; no oculovestibular reflex (absent caloric stimulation response) → confirm integrity of tympanic membrane & absence of significant blood/cerumen in external auditory canal, elevate head-of-bed to 30 degrees & irrigate external auditory canal w/ 30-50 mL of ice water; observe for ocular response (1 min); repeat on c/l side after at >5 min delay. Facial motor responses: No corneal reflex to touch w/ cotton swab. No facial grimace to deep pressure on nailbeds, supraorbital ridge, or temporomandibular

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joint. Pharyngeal & tracheal reflexes: No gag w/ stimulation of posterior pharynx. No cough to bronchial suctioning.

Apnea testing: Prerequisites & preparation: Core temp ≥ 36.5°C (96.8°F). SBP > 90 → if pt requiring pressors or experiencing arrhythmias, consider ancillary testing instead of proceeding w/ apnea test. Euvolemia → if diabetes insipidus present, need positive fluid balance over prior 6 h. Adjust ventilator settings to achieve arterial pH 7.35-7.45 & PCO_2 35-45 mm Hg ≥ 20 min prior to apnea testing (or to pt's baseline, if known CO_2 retainer). Pre-oxygenate w/ 100% FiO_2 for 5 min to PaO_2 > 200 mm Hg. Procedure: Disconnect pt from ventilator. Administer 100% O_2 at 8-10 L/min via endotracheal tube or tracheostomy to level of carina immediately after disconnecting vent. Observe for respiratory mvmts for ˜8 min → abdominal or chest excursions. After 8 min period elapses, check ABG to measure O_2, PCO_2, & pH. Reconnect pt to ventilator after ABG is drawn. If during 8 min period off of ventilator, pt develops cyanosis, SBP < 90 mm Hg, significant O_2 desaturation, or cardiac arrhythmia → discontinue apnea testing, draw STAT ABG & reconnect ventilator. Positive apnea test (consistent w/ brain death): No respiratory mvmts. ABG criteria: PCO_2 > 60 mm Hg or PCO_2 increase ≥20 mm Hg from baseline. Apnea test considered positive if stopped early as long as no respiratory mvmts are observed & ABG criteria are met.

Negative apnea test: Respiratory mvmts observed OR ABG criteria not met after sufficient time elapsed. Indeterminate apnea test: Apnea test performed, w/ no respiratory mvmts observed but ABG criteria not met → may repeat test for longer time period if clinically stable, or proceed to ancillary testing.

Ancillary Testing to Confirm Brain Death

Diagnostic Test	Findings Consistent w/ Brain Death
EEG	Core temp must be ≥36.5°C (96.8°F). No EEG activity for ≥30 min. No change in EEG record w/ auditory, visual, or noxious stimulation EEG interpretation must be confirmed by attending neurologist & noted in pt's medical record.
4-Vessel angiogram	No contrast filling of cerebral vasculature in either anterior or posterior circulation. Contrast filling of ICAs should stop abruptly at petrous segment where ICA becomes intracranial. Delayed filling of superior sagittal sinus may be seen due to patency of external carotid circulation.
SPECT w/ Tech 99	No uptake of isotope in brain parenchyma → study must be interpreted by attending nuclear medicine physician. Isotope uptake w/in meninges & skull vessels may be seen due to perfusion from external carotids.
TCDs	Perform TCD CBF velocity measurements in b/l intracranial cerebral vasculature & extracranial vasculature (CCAs, ICAs, cervical portions of vertebral arteries). Must observe small systolic peaks in early systole w/o diastolic flow or w/ reverberating flow → suggests high vascular resistance from increased ICP & absence of tissue blood flow. TCDs must be performed 2×, 30 min apart.

Documentation of brain death in medical record: Date & time of death (for ancillary testing, use time of interpretation), name of physician declaring brain death, etiology & irreversibility of neurologic injury, absence of eye opening or verbal response. Absence of brain stem reflexes, absence of motor response to noxious stimuli, details of apnea test → time of test initiation, pre-apnea & post-apnea pH & PCO_2, use of ancillary testing, reason for indication, & interpreting physician's name, results of repeat neurologic examinations, if performed, time & reason for contacting medical examiner, if appropriate.

HYPOXIC-ISCHEMIC INJURY AFTER CARDIAC ARREST

<10% survival for out-of-hospital cardiac arrest after CPR. (NEJM 2004;351:632).

<20% survival to d/c for in-hospital cardiac arrest after CPR. (Resuscitation 2003;58:297). ↑ Duration of anoxia prior to CPR & ↓ duration CPR → ↓ outcome (Crit Care Med 1995;23:18).

Prognosis after cardiac arrest (Neurology 2006;67:203)

Neurologic examination: Absence of pupillary & corneal responses has strong predictive value w/in 1-3 days post-arrest. Eye opening & spont eye mvmts may occur early w/o indicating good outcome; best predictive value after 3 days. Motor response is stronger predictor than overall GCS score & is most specific for poor outcome after 3 days. Single sz & intermittent focal myoclonus do NOT predict poor outcome, but diffuse myoclonus strongly a/w in-hospital death & poor outcome even if brainstem reflexes intact (Neurology 2006;66:62).

MRI: Absence of diffusion restriction on DWI/ADC a/w better neurologic outcome (Mayo Clin Proc 2007;82:828). Reduction in whole-brain median ADC may predict poor outcome (Radiology 2009;252:173). Common DWI/ADC abnormalities include cortical ribbon, watershed infarct, thalamus, basal ganglia.

EEG: Generalized suppression ≤ 20 μV, burst suppression w/ generalized epileptiform activity, or generalized periodic complexes on isoelectric background strongly a/w poor outcome, but prognostic accuracy remains limited pending further studies.

Alpha coma pattern is NOT invariably a/w poor outcome (Neurology 1988; 38:773). Postanoxic status epilepticus is NOT invariably a/w poor outcome

after therapeutic hypothermia (Neurology 2009;72:744).

SSEPs: More accurate prognostic tool than EEG b/c less confounded by medications & metabolic encephalopathy. B/l absence of N20 w/ median nerve stim strongly predicts poor outcome. Insufficient data for prognostic value of BAERs & VEPs.

Biochemical markers: Neuron-specific enolase > 33 µg/L at day 1-3 a/w poor outcome. Serum astroglial S100 does not have prognostic value.

ICP & brain oxygen monitoring: Insufficient evidence for prognostic value.

Prognosis After Cardiac Arrest Using Neurologic Examination
(*JAMA* 1985;253:1420)

Time After Arrest	Virtually No Chance of Regaining Independence	Best Chance of Regaining Independence
Initial exam	No pupillary light reflex	Pupillary light reflex present Decorticate or decerebrate posturing Conjugate roving or orienting eye mvmts
Day 1	Motor response no better than decorticate posturing Spontaneous eye mvmts neither orienting nor roving conjugate	Motor response withdrawal or better Eye opening spontaneously or to noise
Day 3	Motor response no better than decorticate posturing	Motor response withdrawal or better NL spontaneous eye mvmts
1 wk	Not following commands Spontaneous eye mvmts neither orienting nor roving conjugate	Motor response obeying commands
2 wk	Abnormal oculocephalic	Normal

response	oculocephalic response
No improvement in eye opening	

THERAPEUTIC HYPOTHERMIA FOR COMA AFTER CARDIAC ARREST

Mechanisms of action: Reduces cerebral metabolic rate & oxygen demand. Reduces cerebral edema & ICP by preserving BBB integrity. Reduces excitotoxic neuronal injury. Minimizes free radical release. Suppresses inflammation.

Supporting data: Study protocols vary, but mortality & neurologic recovery benefits demonstrated by multiple randomized trials (NEJM 2002;346:549; NEJM 2002;346:557). Data exist mostly for out-of-hospital, VF/VT cardiac arrest; limited data for PEA, asystolic arrest, or in-hospital arrest → therapeutic cooling for these types of cardiac arrest may be applied at the discretion of the clinician (Circulation 2003;108:118). Therapeutic cooling NOT proven to be beneficial for coma after primary respiratory arrest w/o concomitant cardiac arrest. Hyperthermia is detrimental—odds ratio for unfavorable outcome is >2 for each 1°C increase in temp after arrest (Arch Int Med 2001;161:2007).

Basic principles & approach to therapeutic hypothermia: Initiate cooling rapidly. Multiple cooling methods may be required to meet temp goal 32°C-34°C (89°F -93°F). Total cooling period 24 h, begins when cooling is initiated, NOT when target temp is reached. Shivering generates heat & contributes to neuronal injury by increasing cerebral metabolism → sedation & paralysis may be necessary for duration of cooling.

Preparation for hypothermia: Laboratory evaluation: Complete metabolic panel, CBC, PT/PTT, fibrinogen, d-dimer. Place arterial line for BP monitoring. Temp monitor for continuous assessment of core temp → bladder temp probe, or pulmonary artery temp probe if oliguric (bladder temp probe requires presence of urine in bladder).

Inclusion criteria: Comatose w/in 6 h of cardiac arrest. Hemodynamically stable w/o high pressor requirement after CPR.

Relative exclusion criteria (hypothermia may carry ↑ risk): Major head trauma → rule out ICH by head CT prior to cooling if clinical suspicion for head trauma at time of arrest. Recent major surgery (w/in 14 days). Systemic infxn/sepsis → hypothermia interferes w/ immune function. Other etiology

for coma → drug/EtOH, pre-existing coma prior to arrest. Active bleeding → hypothermia ↓ clotting factor activity. Admin of thrombolytic, antiplatelet, or anticoagulation meds for cardiac condition is NOT a contraindication to hypothermia.

Therapeutic hypothermia protocol (may vary by institution)

- 1. External cooling w/ cooling blankets & ice: Obtain two cooling blankets & cables (one machine) to "sandwich" the pt → place sheets b/n blankets & pt to protect skin. Use additional cooling methods as needed to bring pt to goal temp. Pack ice in groin, sides of chest, axillae, and/or side of neck. Infuse cold saline via peripheral line or femoral venous catheter → 30 cc/kg of 4°C normal saline over 30 min. Do NOT infuse cold saline via jugular or subclavian catheter, as safety of cooling via these methods has not been studied. Avoid packing ice on top of chest → may impair ventilation. Paralyze w/ cisatracurium → 150 µg/kg bolus then continuous infusion of 2 µg/kg/min. Sedate w/ propofol → bolus (optional) 0.3-0.5 mg/kg followed by continuous infusion of 1mg/kg/h while pt is paralyzed or sedate w/ midazolam → bolus (optional) 0.05 mg/kg followed by continuous infusion of 0.125 mg/kg/h. Once at goal temp can d/c ice bags, use cooling blankets to maintain.
- 2. External cooling w/ cooling vest devices: Set target temp goal on device. Medicate for shivering w/ sedating & paralyzing agents. Consider secondary temp monitor → record pt temp on cooling vest device, secondary temp source & follow water temp of the cooling device → water temp indicates work device must perform to keep pt at target body temp.
- 3. Monitoring & supportive therapy during hypothermia: Monitor vitals closely. No indication for BIS or train-of-four monitoring during hypothermia; EEG used at clinician's discretion. MAP > 90 mm Hg to maximize cerebral perfusion → potentially additive neuroprotective effects of high perfusion pressure w/ hypothermia. MAP goal lowered at discretion of clinician, depending on cardiac effects of high afterload or coronary vasoconstriction. If serious cardiac dysrhythmias, hemodynamic instability or bleeding during cooling, stop cooling process, & actively rewarm pt. Osborn waves (positive deflection b/n QRS complex & ST segment) or bradycardia may develop during cooling → no indication for specific therapy. Check bcx at 12 & 24 h after initiation of cooling → hypothermia may mask systemic response to infxn. Check electrolytes, CBC, & glucose at 12 & 24 h → hypothermia may cause hypokalemia, especially during concurrent

insulin administration; rewarming may cause hyperkalemia due to K^+ efflux from intracellular compartment. Hyperglycemia & increases in serum amylase & lipase may occur during cooling. Goal CO_2 35-45 mm Hg → analyze all ABGs at pt's body temp. Examine skin for burns q2h if using cold blankets.

- 4. Basic principles of rewarming: Do NOT rewarm faster than 0.5°C/h. Shunting of cardiac output to reopening peripheral vascular beds may cause hypotension. Monitor closely for hypotension, hyperkalemia. Aim for normothermia once rewarming phase is completed. Maintain paralytic & sedative therapy until temp of 36°C (96.8°F) is reached

  → first discontinue paralytic, then sedative once pt demonstrates motor activity or once train of 4 is achieved on monitor. Rewarming after cooling blankets ± ice: Remove cooling blankets (& ice if still in use).

- 5. Rewarming after cooling vest use: Program device for controlled rewarming at a rate not to exceed 0.5°C/h over 6-8 h → dial in the desired warming rate on the machine, then keep device in place & program for target temp of 37°C (98.6°F) for the next 48 h (72 h total).

TRAUMATIC BRAIN INJURY

Classification: Mild TBI: GCS 13-15 (see GCS definition at start of chapter). Moderate TBI: GCS 9-12. Severe TBI: GCS 3-8.

Epidemiology & risk factors: 1.5 million cases of TBI per year in the United States; 230,000 hospital admissions; 50,000 mortalities; 80,000 w/ long-term disabilities. High risk groups: children, adolescent/young adult males, & elderly. Mechanisms of injury: MVA (no. 1 cause in age < 65), falls (no. 1 cause age > 65), occupational accidents, assaults, sports-related trauma.

Pathophysiology: Primary injury occurs at time of impact, secondary injury develops after impact. Morbidity/mortality from secondary injury may exceed that of primary injury. Primary injury: Blunt contact forces: direct injury to underlying tissue → coup contusion, skull fx, EDH, SDH, arterial dissection. Translational acceleration: Brain moves relative to cranium along linear axis → contracoup contusion, SDH. Rotational acceleration: Brain moves relative to cranium along nonlinear axis → concussion, DAI, SAH, IVH. Secondary injury: Can be diffuse or perilesional; develops over hours to days. Contusion/hematoma expansion, excitotoxic neurotransmitter release, altered mitochondrial metabolism, free radical & calcium-mediated injury, blood-brain barrier disruption from mechanical injury & inflammatory cytokine release, increased extracellular potassium, alterations in gene expression w/

increased production of pro-apoptotic factors.

Management of mild TBI/concussion

Concussion definition: Trauma-induced cognition Δ, ± loss of consciousness (LOC). Loss of consciousness (LOC).

Mechanism of LOC: Disruption of neuronal function in reticular activating system, due to maximal impact of rotational forces on midbrain & diencephalon (NEJM 2007;356:166).

Acute symptoms: HA, dizziness, confusion, amnesia (anterograde > retrograde), n/v, concussive convulsion (1/70 cases; Sports Med 1998;25:131). Rx: No AED required for concussive convulsion & no known increased risk of epilepsy. 0.5%-1.0% require neurosurgical intervention (J Neurosurg 2004;100:25-34; JAMA 2005;294:1519).

Concussion grading (one of several grading systems used in practice): Grade 1 → No LOC, sx < 15 min. Grade 2 → No LOC, sx > 15 min. Grade 3 → any LOC.

Chronic symptoms: Recurrent HA, light-headedness, poor attention & concentration, memory deficits, fatigue, irritability, sleep disturbances → duration of post-traumatic amnesia correlates w/ duration of LOC & severity of head injury.

Sports-related mild TBI/concussion: Must leave game for mental status check & sx eval at rest & after exertion. Medical eval reqd for Grade 2 w/ sxs > 1 h & Grade 3. Return to play after stressing w/ graduated exercises → must be asx both at rest & after exertion.

Guidelines for return to play (Neurology 1997;48:581)

Type of Concussion → Min duration of NL mental status & asymp at rest/exertion

- Grade 1 → 15 min (same day)
- Multiple Grade 1, Grade 2, Grade 3 (if LOC seconds) → 1 wk
- Multiple Grade 2, Grade 3 (if LOC minutes) → 2 wk
- Multiple Grade 3 → ≥ 1 mo
- Any swelling, contusion, or other intracranial pathology on CT → end season

Imaging guidelines for mild TBI/concussion

- Canadian CT head rule (CCHR) (GCS 13-15, age ≥16) (Lancet 2001;357:1391): High risk: GCS < 15 2 h post-trauma, suspected open or depressed skull fx, ≥2 episodes of emesis, age ≥65; Medium risk: Retrograde amnesia for events >30 min prior to trauma, dangerous mechanism of injury (i.e., MVA, fall from height >5 stairs).
- New Orleans Criteria (NOC) (GCS 15) (NEJM 2000;343:100): HA, emesis, age > 60, intox, persistent anterograde amnesia, physical evidence of trauma above clavicles, sz.
- NOC & CCHR both Se ˜100% for pts who require neurosurgical intervention. NOC more sensitive (98%) for neurocranial CT abnormalities than CCHR (83%). CCHR more specific (39%) than NOC (6%) for detecting CT abnormalities (JAMA 2005;294:1519). CT generally indicated if pt intoxicated, on anticoagulation, or cannot be reliably observed after discharge. TBI imaging guidelines not clearly established in children.

Imaging findings: CT: 10% of mild TBI pts will have abnormal CT (SAH, intraparenchymal lesion, skull fx, SDH, EDH); 8% for GCS 15, 16% for GCS 14, 25% for GCS 13 (JAMA 2005;294:1519). MRI: Typically not indicated, but higher sensitivity for traumatic microhemorrhage & diffuse axonal injury (DAI).

Post-concussion syndrome: Incidence uncertain—may be as high as 50%. Presence of HA, dizziness or nausea at time of TBI may correlate w/ long-term sequelae (JNNP 2002;73:727). Duration of symptoms varies widely & may last up to 1 yr. Diagnostic criteria (ICD-10): Sx onset ≤4 wk after concussion, & sx in ≥3 of 6: (1) HA, dizziness, fatigue, noise intolerance, (2) irritability, depression, anxiety, emotional lability, (3) subjective concentration, memory, or intellectual difficulties w/o neuropsychological e/o marked impairment, (4) ↓'d EtOH tolerance, (5) insomnia, (6) preoccupation w/ above sx & fear of brain damage, w/ hypochondriacal concern & adoption of sick role.

Second impact syndrome: Diffuse cerebral edema → neurologic deterioration from repeated minor head injuries. Incidence & risk factors uncertain (Neurology 1998;50:677).

Initial management of moderate to severe TBI

Rapid trauma-to-hospital time & transfer to neurotrauma center ↓ mortality (J Trauma 1987;27:365; Lancet 2005;366:1538).

ABCs: Secure airway & ensure adequate oxygenation; hypoxia at time of admission a/w worse outcome (J Neurotrauma 2007;24:287). If hypotensive, resuscitate aggressively w/ crystalloids; worse outcomes w/ albumin (NEJM 2007;357:874); r/o internal hemorrhage & spinal cord trauma & spinal cord trauma (TBI alone rarely causes HoTN unless brain dead). If HTN do not ↓ BP unless SBP ≥180 → avoid agents that dilate cerebral vasculature (nitroprusside, hydralazine, CCBs).

Trauma survey: TBI a/w extracranial injury in 35% of cases (J Trauma 1989;29:1193). C-spine immobilization, assess for fxs, visceral injury. Signs of skull fx: (1) Raccoon eyes: Periorbital bruising/bogginess → anterior skull fx or temporal bone fx. (2) Battle sign: Bruising/bogginess in temporal/posterior auricular region; typically takes >12 h to appear → temporal bone fx. (3) CSF rhinorrhea: Test watery discharge from nose for glucose (mucus has no glucose) and/or β-2 transferrin → cribiform plate injury. (4) CSF otorrhea, hemotympanum → temporal bone fx. (5) Cranial nerve palsies: I (anosmia from cribiform plate injury), III, IV, VI (diplopia, strabismus from orbital fx, cavernous sinus injury, or stretching/compression of nerve against skull base), VII, VIII (facial palsy, hearing loss from fx of petrous portion of temporal bone). (6) Carotid-cavernous fistula: Pulsating exophthalmos, retro-orbital bruit → occurs in 8% of traumatic middle fossa fxs (J Trauma 2007;63:1014).

Approach to neuroimaging

- Head CT: Initial imaging of choice b/c speed; good sensitivity for contusions, skull fxs, extra-axial hematomas but poor sensitivity for DAI.
- Head/neck CTA: Consider for r/o traumatic arterial dissection (a/w up to 17% of traumatic C-spine injuries) or traumatic pseudoaneurysms (especially in pts w/ penetrating head injury).
- CTV: Consider if displaced skull fx adjacent to venous sinus.
- MRI: More sensitive than CT for microhemorrhages & DAI but should be delayed until subacute period given risks of pt transport & intracranial HTN w/ prolonged supine position; request gradient echo or susceptibility-weighted sequencing for microhemorrhage detection; consider diffusion tensor imaging if available for assessment of DAI (AJNR 2004;25:370).

Radiologic findings

- 1. Coup/contracoup contusions: Incidence: 25%-35% of severe TBI pts,

5%-10% of moderate TBI pts. Anatomic localization: Superficial gray matter, especially in orbitofrontal & anterior, inferolateral temporal regions due to proximity to floors of anterior & middle cranial fossae, respectively. Often hemorrhagic b/c of high vascularity of cortex. Contusion/hematoma expansion seen in up to 50% of cases & is a/w large size of initial lesion, presence of SDH or EDH, age, & PTT (J Neurosurg 2002;96:109; Neurosurgery 2007;61:222). Expansion typically occurs within 6-9 h after trauma (J Neurotrauma 2008;25:629) → consider early repeat CT for clinical deterioration, elevated ICP, or if above risk factors present.

- 2. DAI: Reported incidence rates vary depending on imaging modality used. Nonhemorrhagic DAI → hyperintensity on DWI or FLAIR. Hemorrhagic DAI → tiny hyperdensity on CT or hypointensity on gradient echo/susceptibility-weighted MRI. Decreased fractional anisotropy on diffusion tensor imaging. Anatomic localization: Regions vulnerable to DAI (in order of increasing severity of injury) are corona radiata (especially gray-white junction), corpus callosum (especially splenium), & dorsolateral midbrain/rostral pons. Corpus callosum lesions may be a/w intraventricular hemorrhage due to disruption of subependymal venous plexus along ventricular surface of corpus callosum (AJNR 1988;9:1129). Low threshold for early repeat CT in pts w/ evidence of diffuse injury on initial CT → ˜1 in 6 will develop new focal lesion on repeat CT (Neurosurgery 2000;46:70).
- 3. Epidural hematoma: a/w skull fx; arterial (90%), venous (10%).

- 4. Subdural hematoma: Bridging cortical veins vulnerable to shearing injury by linear acceleration forces; higher incidence of SDH in falls than in MVAs b/c more rapid acceleration/deceleration in falls (Radiology 1994;191:1).
- 5. Subarachnoid hemorrhage: Typically superficial cortical, not in basal cisterns; unlike benign SAH in mild TBI, SAH in severe TBI a/w poor prognosis → likely b/c of a/w severe mechanical injury, not risk of vasospasm (Neurosurgery 2002;50;261).
- 6. Intracerebral hematoma: Differs from hemorrhagic contusion in that hematomas are deeper & are not necessarily a/w interspersed/surrounding edema; may be caused by shearing injury of intraparenchymal arteries/veins/capillaries at the time of injury, or may appear as late as 2 wk after TBI due to coagulopathy, necrosis of blood vessel wall, hyperperfusion injury from impaired cerebrovascular

autoregulation, or release of tamponade effect after evacuation of a extra-axial hematoma (Neurological & Neurosurgical Intensive Care 2004;Lippincott:Philadelphia, PA).

- 7. Pneumocephalus: a/w skull fx.
- 8. Duret hemorrhage: Delayed, secondary hemorrhage in ventral or paramedian brainstem 2/2 descending transtentorial herniation a/w shearing injury of perforating arteries.

ICU Management of Severe TBI

Intracranial pressure

Indications for ICP monitoring: Abnormal CT or NL CT w/ two or more of the following: **(1)** age > 40, **(2)** motor posturing, **(3)** SBP < 90.

Impact of ICP on outcome: Intracranial HTN occurs in up to 77% of severe TBI pts; presence & duration of elevated ICP correlates w/ worse outcome (*J Neurotrauma* 2007;24:S1; *Neurocrit Care* 2006;4:8).

Tx of intracranial HTN: See "Acute Intracranial Hypertension" chapter.

Decompressive craniectomy: Data inconclusive; subject of ongoing studies.

Barbiturate coma: High morbidity when administered prophylactically to reduce ICP, but effective at treating refractory intracranial HTN; consider trial of short-acting agent (thiopental) prior to initiating tx w/ long-acting agent (pentobarb, phenobarb).

Hypothermia: Cooling to 33°C for 48 h starting 8 h after TBI not effective in improving outcomes (*NEJM* 2001;344:556), but cooling to 32°C-34°C improves survival & functional outcome when used to treat refractory intracranial HTN (*Int Care Med* 2002;28:1563).

Hemodynamics

Impact of MAP/CPP on outcome: Duration of hypotension is independent predictor of mortality (*J Neurosurg Anesthesiol* 1994;6:4). CPP > 70 reduces secondary ischemic insults but does not improve neurologic outcome & increases risk of ARDS by 5× (*Crit Care Med* 1999;27:2086).

Alterations in cerebrovascular autoregulation are common & predict worse outcome (*J Neurosurg* 2006;104:731).

CPP management: CPP goal > 60, unless clearly defined territory of cerebral hypoperfusion, in which case higher CPP may be warranted.

CPP elevation w/ pressors may only improve contusional CBF in pts w/ baseline hypoperfusion of contusional tissue vs. paradoxical decrease in contusional CBF in pts w/ normal contusional CBF (*Neurosurgery* 2007;60:115).

Pulmonary dynamics

Impact of ventilation/oxygenation on outcome: Duration of hypoxia is an independent predictor of mortality (*J Neurosurg Anesthesiol* 1994;6:4). Prophylactic hypocapnea a/w worse outcome (*J Neurosurg* 1991;75:731).

Ventilation: Aim for normocapnea ($PaCO_2$ 35-40 mm Hg). Hyperventilation only indicated as temporizing measure for acute rise in ICP.

Oxygenation: $SpO_2 \geq 95\%$. Unpredictable relationship b/n PEEP & ICP → assess at bedside on individualized basis.

Medical therapies

Steroids: NOT effective ("CRASH" Trial—*Lancet* 2004;364:1321).

Anti-epileptic drugs: Clinical szs occur in up to 20% of severe TBI pts during first 7 days, w/ ˜50% of szs occurring w/in 24 h. 15%-18% of pts w/ moderate/severe TBI have subclinical seizures on continuous EEG monitoring (*J Neurosurg* 1999;91:750). AEDs may be indicated for prevention of early post-traumatic szs (<7 days) (*J Neurotrauma* 2007;24:S83).

17% of severe TBI pts will sz w/in 2 yr (*Arch Phys Med Rehabil* 2003;84:365).

No evidence that prophylactic AEDs prevent late post-traumatic szs, but may be a role for longerterm prophylactic AEDs in penetrating brain injury & skull fx.

Glycemic control: Hyperglycemia a/w worse outcomes (*J Trauma* 2005;58:47), but no clear outcome benefit w/ intensive insulin therapy (*Neurocritical Care* 2008;9:159).

TBI pts may be especially intolerant of hypoglycemia b/c of altered neuronal metabolism (*Crit Care Med* 2006;34:850).

Infxn control: Aggressive fever reduction & abx tx of aspiration PNA, UTI etc. → fever a/w higher ICP, more severe neurologic impairment, prolonged ICU stay (*Int Care Med* 2002;28:1555). Most CSF leaks resolve spontaneously in 7-10 days & prophylactic abx generally not recommended b/c select for multidrug resistant organisms.

Blood transfusion strategy: No mortality difference b/n liberal & conservative transfusion strategies (*Neurocrit Care* 2006;5:4).

Sodium management: Goal Na 135 to 150. Tailor tx to etiology (i.e., SIADH, cerebral salt wasting, diabetes insipidus).

Nutrition: Resting metabolic expenditure may be 1.5-2× NL in severe TBI pts w/ GCS 4-5 (*Neurosurgery* 1984;15:307) → feedings should target increased caloric requirement & include 2 g/kg/day protein. Early tube feeds promote immunocompetence & likely facilitate neurologic recovery (*Neurotrauma* 2005; Thieme: New York, NY). Enteral preferable to peripheral nutrition.

Prognosis: ˜30% mortality in severe TBI; 16% severe neurologic deficits; 3% PVS. Age, GCS, pupil response, hypoxia, hypotension, & CT findings correlate w/ outcome (J Neurotrauma 2007;24:329). Marshall head CT classification system demonstrates that compression of mesencephalic cisterns & presence of midline shift >5 mm on initial CT a/w increased mortality rate (J Neurosurg 1991;75:S14). Microstructural white matter alterations are present in chronic mild, moderate, & severe TBI pts & correlate w/ severity of TBI (Brain 2007;130:2508). Parenchymal volume loss over time also correlates w/ severity of TBI (Neurology 2008;70:771; Neuroimage 2009;44:1). Mechanical disruption of axons may be partially reversible by early hypothermia in animal models (Exp Neurol 1999;159:319).

DAI a/w high rate of coma & poor outcome, but diffusion tensor imaging

studies indicate that microstructural reorganization & restoration of axonal integrity may occur in chronic phase of TBI (Brain 2008;131:559). Comprehensive neurorehabilitation improves functional outcomes, w/ 85% of recovery occurring w/in first 6 mo (Lancet Neurol 2008;7:728).

CRANIECTOMY

Indications: Reverse mass effect & brain tissue shifts, decrease intracranial pressure, & improve cerebral perfusion pressure. Craniectomy lowers ICP by 15%, opening dura lowers ICP by 70%. Considered for cerebral mass lesions, intracerebral hemorrhage, subarachnoid hemorrhage, malignant cerebral edema from stroke, hemispheric encephalitis.

Technique: Removal of skull & incision of dural layer covering the brain for upward expansion of swollen brain tissue through skull opening, rather than downward herniation which would compress brainstem; evacuation of brain hematoma; resection of mass lesion.

Malignant edema after MCA infarct

Epidemiology: 10% of strokes develop malignant cerebral edema (Stroke 1985;16:282).

Clinical presentation: NIHSS score >15 for right, >20 for left hemispheric infarctions.

Forced gaze deviation, visual field cut, hemiplegia, aphasia, or neglect. 78% mortality rate due to temporal lobe herniation w/ brainstem compression/torque (Arch Neurol 1996;53:309).

Imaging predictors: Head CT: large hypodensity >50% MCA territory most important predictor of malignant edema, herniation & death (Am J Neuroradiol 1994;15:9); septum pellucidum midline shift >5 mm. Brain MRI: volume of infarct >80 cm^3 on DWI (Stroke 2003;34:1892). CTA/MRA: large vessel occlusions (ICA, proximal MCA).

Clinical predictors: Age: <50 yr. Early onset ↓'d consciousness. n/v <24 h. SBP >180 mm Hg <12 h. Elevated white blood cell count. Heart failure (Stroke 2001;32:2117).

Evidence: RCTs: HAMLET, DESTINY, DECIMAL 93 pts, <55 yr Rx <48 h for large MCA infarct w/ decompressive hemicrani. 1-yr favorable outcome (mRS 0-4): 75% craniectomy pts, 24% control group; mRS 3 or less: 43% craniectomy, 21% control group. 1-yr survival: 78% hemicraniectomy, 29% control group. Benefit offset if there was delay to surgery >3 days.

Edema after cerebellar infarcts

Neurologic emergency: Swelling can cause hydrocephalus due to compression of fourth ventricle, brain stem compression by upward transtentorial or tonsillar herniation.

Clinical presentation: Unsteady gait, n/v, HA, dizziness, diplopia, dysarthria, anisocoria.

Rx: (1) Medical: mannitol, hypertonic saline, hyperventilation (for acute herniation syndromes). (2) Surgery: suboccipital craniectomy w/ possible resection of infarcted brain & ventriculostomy. Maintain ventriculostomy post-op until clear evidence of no sig hematoma or continued mass effect/edema. Suboccipital craniectomy is life-saving if medical Rx unable to prevent progression of swelling or clinical deterioration. Should be performed prior to clinical decompensation; do not wait for medical therapy to fail in a pt w/ a large stroke & clear progression of fourth ventricular compression; hydrocephalus can occur acutely, & lead to rapid, fatal deterioration.

Considerations: time from symptom onset, size of infarct, pt’s age, potential for neurologic recovery. Most pts recover w/ relatively good quality of life.

Intracerebral hemorrhage

Indications: Cerebellar hemorrhages >3 cm w/ clinical deterioration, brainstem compression, or hydrocephalus (Stroke 2007;38:2001). Cerebral hematoma evacuation controversial: considered for supratentorial lobar clots w/in 1 cm of cortical surface.

Relative contraindications: Advanced age, serious medical comorbidities, stable clinical condition, remote onset of hemorrhage, bleed in dominant hemisphere.

STICH trial: International Surgical Trial in Intracerebral Hemorrhage (Lancet 2005; 365:387). No statistically significant difference in favorable outcome at 6 mo for pts randomized to hematoma evacuation at <72 h compared to medically managed pts.

Subdural hematoma: Bleeding b/n dura & arachnoid layers.

Prognosis: Mortality rate 40%-60%. Advanced age, lower GCS. Clinical prognostic factors: contusions, subarachnoid or intraventricular hemorrhage. Radiologic prognostic factors: hematoma thickness, volume, midline shift, patency of basal cisterns, contusions, SAH or IVH.

Surgery: Craniectomy has better outcomes than burr hole evacuation (Neurosurgery 2006;58:S2-S16). Rx w/in 2-4 h of neurologic decline a/w lower mortality, 30% if early surgery vs. 80% if delayed.

Indications: Acute SDH & coma (GCS score <9) on arrival. Clot thickness >10 mm or midline shift >5 mm, regardless of GCS score. Decrease in GCS score by two or more points from time of trauma to presentation. Anisocoria or dilated/fixed pupils. ICP >20 mm Hg.

Epidural hematoma: Bleeding b/n dura & skull.

Prognosis: 10% mortality. Radiologic prognostic factors: hematoma volume, midline shift, brain swelling.

Indications: Hematoma volume >30 cm^3, regardless of GCS score. Midline shift >10 mm. Acute hematoma, coma (GCS < 9) w/ pupillary abnormalities. Early signs of herniation. Elevated intracranial pressure.

Postoperative care: (1) Swallowing precautions, incentive spirometry, crystalloid fluids. (2) Prevention of intracranial pressure elevation. (3) Airway management: risk of airway collapse due to prolonged recovery of consciousness, especially in cases of brain retraction during surgery. (4) Refractory nausea, vomiting after posterior fossa surgery more common in women: Ondansetron 1-4 mg IV or promethazine 12.5-25 mg IV. (5) Unrest, anxiety, discomfort due to endotracheal tube: Dexmedetomidine, an a-2 adrenergic agonist, ↓s anxiety w/o causing resp depression; approved for use only for first 2 postoperative days.

Standard Postoperative Craniotomy Orders

Codeine	60 mg SC/IM, q4h prn
Cefazolin	500-1,000 mg IV, q4h
Dexamethasone	4 mg IV, q4h
Phenytoin	100 mg IV, q8h
Subcutaneous heparin	5,000 U, q12h

Complications: Meningitis, abscess, hemorrhage, stroke, cerebral edema, sz, air embolism.

MECHANICAL VENTILATION IN NEUROLOGIC PATIENTS

Mechanical ventilation in specific conditions: (Suarez, J. ed. Critical Care Neurology and Neurosurgery. New Jersey: Humana, 2004)

Depressed level of consciousness: Prevent aspiration, promote optimal gas

exchange, start w/ controlled modes, & as drive recovers transition to assist modes.

Elevated ICP: For short duration (4-6 h) can use hyperventilation to lower $PaCO_2$ to 30-35 mm Hg, ↓ 1-2 mL/min CBF/↓ 1 mm Hg $PaCO_2$; avoid worsening ICP elevation

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P.45

during intubation; avoid succinylcholine; propofol, lidocaine, or thiopental may lower ICP, but risk of hypotension; use etomidate if low BP; caution ischemia, rebound elevation in ICP if hyperventilating for extended duration.

Central respiratory center lesions: Controlled modes of ventilation initially to manage ↓ drive. (Examples: Cheyne-Stokes respirations in bihemispheric lesions, metabolic encephalopathies, or pontine lesions; Hypoventilation, apnea or Ondine's curse in lateral medullary lesions; Apneustic or ataxic respirations in pontine lesions; Hyperventilation in pontomesencephalic lesions.)

Spinal cord injury: Phrenic nerve paralysis, intercostals & abd weakness; caution with jaw lift, endotracheal intubation; may need tracheotomy in severe injuries; increased aspiration risk from ileus; risk of delayed apnea in high cervical injuries. Hypersensitivity to depolarizing blockade agents, seen esp. with denervating disease, extreme muscle disuse; avoid usage >48 h given risk severe hyperkalemia → cardiac arrest. Alternatives—nondepolarizing agents.

Neuromuscular ventilatory failure: (1) Acute polyneuropathy: Autonomic instability → ↓ BP with sedation (barbiturates, benzos, narcotics), ↑ K^+ w/ succinylcholine; use nondepolarizing blockade, topical anesthetics (short acting benzos, atropine), blind nasal endotracheal intubation; SIMV & PS; bedside cardiac meds for resuscitation prn. (2) NMJ dz: Exaggerated response to nondepolarizing agents e.g., vecuronium; unpredictable response to succinylcholine. (3) Myopathies: AVOID succinylcholine given risk for severe hyperkalemia → cardiac arrest; risk of malignant hyperthermia.

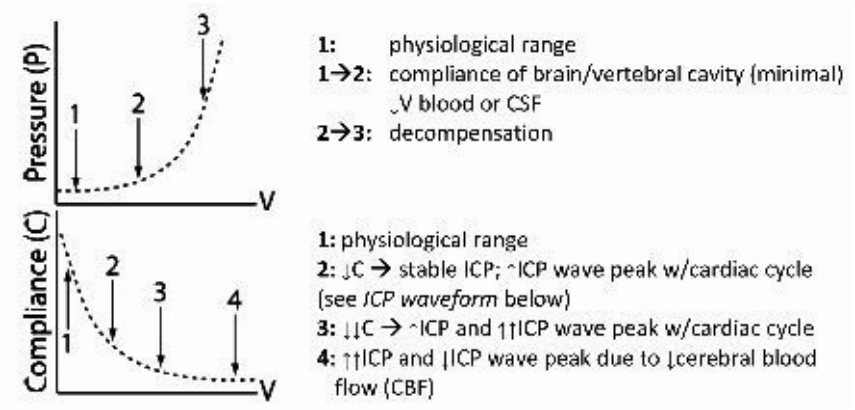
Recovery in neurogenic respiratory failure: Ventilatory drive & chemosensitivity recover first → wean from controlled to assist mode (SIMV or PS); can be hypercapneic at night when have ↓ed level of consciousness, so use controlled mode at night. Respiratory muscle strength recovers next → use PS mode, ensure adequate inspiratory pressure, or else ↑ RR.

Acute Intracranial Hypertension

Definitions: ICP > 15 mm Hg (20 cm H_2O) for >10 min (limit is lower in children).

CEREBRAL DYNAMICS

Monro-Kellie doctrine (simplified): Incompressible brain (˜1,300 mL), CSF (˜65 mL), and blood (˜110 mL) encased in relatively noncompliant skull and vertebral canal. Therefore ↑ volume (V) any component → ↓ V of another or ↑ ICP.



Cerebral Perfusion Pressure (CPP)

CPP = MAP - ICP MAP ≈ (2DBP + SBP)/3

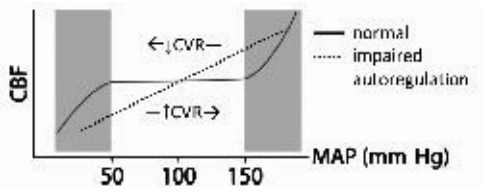
↑ ICP or ↓ MAP or both → ↓ CPP

nl CPP 80 mm Hg; CPP goal 60-70 mm Hg (ideal target debated; higher if chronic HTN); < 50 mm Hg → ischemia

Cerebral Blood Flow (CBF)

CBF = CPP/CVR

Autoregulation: MAP 50-150 mm Hg → stable CBF due to Δcerebral vascular resistance (CVR)



CBF ∝ PCO_2

Hypercarbia → ↓ CBF = ↓ CVR (vasodilation)

when PCO_2 20-80 mm Hg → ↑ ICP

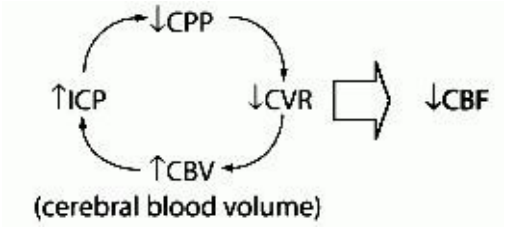
Hypocarbia/hyperventilation → ↓ ICP (but ↑ risk of ischemia)

CBF ∝ 1/PO_2 when PO_2 <50 mm Hg — No effect on CBF w/in physiological range

CBF ∝ cerebral metabolic rate of O_2 ($CMRO_2$) — E.g.: Sz → ↑ $CMRO_2$ → ↓ CBF

Impaired autoregulation

1. Vasodilatory cascade

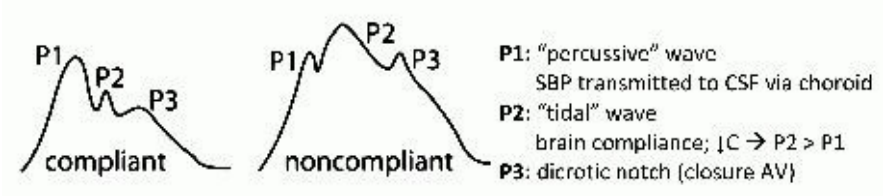


2. Acute brain injury (stroke, TBI, etc.) locally impairs autoregulation

3. Drugs (see "Etiologies of Acute Intracranial HTN" below)

4. Curve shifts to right w/ chronic systemic HTN

ICP waveform = modified arterial pressure wave (timed to cardiac cycle)



Slower ICP Waves (Lundberg Waves)

A waves or "plateau" waves (see figure) — **Arrhythmic; amp 50-100 mm Hg; last 5-20 min**

"Mirror" reductions in CPP (figure below)

Always assoc w/intracranial pathology,

sometimes w/signs herniation

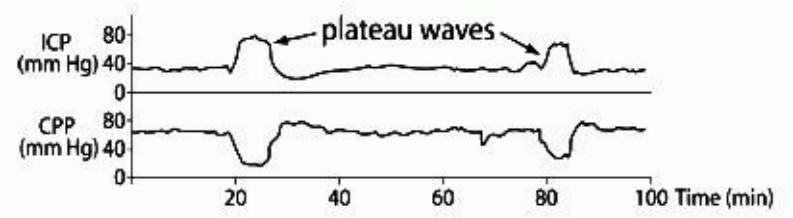
?due to vasodilatory cascade

B waves **Rhythmic; q30s-2min; amp 5-20 mm Hg, last 1-5 min**

?due to vasomotor instability at limits of autoregulation

C waves **Rhythmic; q4-8min; amp ≤ 20 mm Hg**

Occur normally ?due to interaction cardiac/resp cycles



P.47

ETIOLOGIES OF ACUTE INTRACRANIAL HYPERTENSION

Etiologies of Acute Intracranial HTN

Cytotoxic edema (↑ intracellular fluid)	Ischemic stroke, anoxic injury, cerebral contusion, fulminant hepatic failure, lead intoxication, Reye syndrome
Vasogenic edema (↑ extracellular fluid)	Hypertensive encephalopathy, RPLS, tumor, abscess, cyst, encephalitis, high-altitude sickness, eclampsia
Transependymal edema (hydrocephalus)	Blockade of CSF outflow pathway (tumor, IVH, etc.), blockade CSF resorption (SAH, crypto, etc.), IIH
Osmotic edema	Hyponatremia, overcorrection of hyperglycemia, hyperosmolar therapy rebound
Venous obstruction	Venous sinus/jugular thrombosis

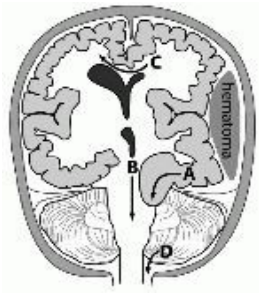
Intra-axial mass	Tumor, abscess, ICH
Extra-axial mass	Subdural/epidural hematoma, depressed skull fx, empyema, tension pneumocephalus
↑ CBV via vasodilation or reduced venous drainage	Hypercarbia, anoxia, hyperpyrexia, Sz, severe anemia, AVM/AVF, Trendelenberg, airway obstruction, pain, cough/"bucking the vent," Valsalva, high PEEP
Drugs	Vasodilators (esp. nitroprusside, hydralazine), valproate toxicity, volatile sedatives (halothane, isoflurane, NO), succinylcholine

TBI commonly assoc w/ ↑ ICP, often via multiple mechanisms (see TBI section)

CLINICAL MANIFESTATIONS OF INTRACRANIAL HYPERTENSION

Clinical Manifestations

HA ± N/V	Esp. when supine; worse w/cough, Valsalva/BM
↑ MS	Correlates w/degree of midline shift
Reflex HTN	Sometimes assoc w/bradycardia, irregular respirations (*Cushing triad*), indicating herniation imminent or occurring
Visual Sx	Visual obscurations Diplopia w/ CN IV palsy (false localizing sign) Upgaze paralysis w/ dorsal midbrain dysfxn Papilledema can take days to develop
Herniation syndromes	**A) Uncal** (lat transtentorial)**:** Ipsi CN III palsy ("blown" pupil) + contra hemiplegia/posturing (Kernohan notch phenomenon) temporal lobe mass → medial temporal lobe under



tent. cerebelli

B) Central transtentorial: Coma + b/l small pupils → decorticate → decerebrate posturing + rostral → caudal loss brainstem reflexes diffuse cerebral edema → ↓ displacement diencephalon

C) Subfalcine: Coma + contra. weakness → posturing esp leg ± ACA stroke frontal/parietal mass → cingulate gyrus under falx

D) Cerebellar (↑ or ↓)**:** Cerebellar Si/Sx + medullary dysfxn → coma + b/l posturing

WORKUP FOR ACUTE INTRACRANIAL HYPERTENSION

Emergent noncontrast CT: Cerebral edema, loss basal cisterns, hydrocephalus, mass effect, midline shift, SAH. 60% of pts w/TBI and abnl CT have ↑ ICP. Normal CT does not exclude ↑ ICP: 13% TBI + nl CT have ↑ ICP. This increases to 60% if ≥2 risk factors: age > 40, SBP < 90, decerebrate/decorticate posturing; only 4% w/ one risk factor (J Neurotrauma 2000;17:479).

MRI: Better resolution of edema and underlying lesions. Do not delay CT for MRI. Prolonged supine position → ↑ ICP.

ICP MONITORING

Invasive technique; Risks: infection >> hemorrhage/neurological injury. Indications for intracranial pressure monitoring: (1) Suspicion of ↑ ICP or risk of developing ↑ ICP. (2) GCS ≤ 8 (comatose) or intubated/sedated. For TBI: mod-severe brain injury and

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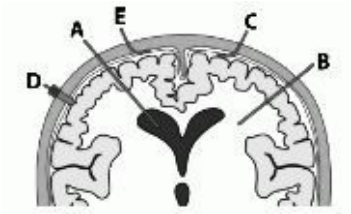
GCS ≤ 8. Allows titration of therapy to ICP → in most cases where ICP-lowering Rx is given, ICP monitoring is indicated.



ICP Monitoring Devices (in Order of Accuracy/Reliability; See

Figure Above)

Intraventricular catheters (A)	"Gold standard" device
	Allows treatment of ↑ ICP via CSF removal
	Can be rezeroed to minimize baseline drift; inexpensive
	High risk infxn (ventriculitis, see below); low risk ICH (1.4%)
	Abx PPx (Naf/Vanc) often given while in place (although limited data)
	Vent compression → difficult positioning
	Bedside transducer at level of foramen of Monro (ext aud meatus)
Intraparenchymal pressure transducers (B)	Catheter or fiber optic transducer inserted into brain tissue
	Very low infection rate (1%)
	Easily placed
	Can be advanced → ventricle for CSF removal (catheter only)
	Can also measure brain T, compliance
	Baseline drift significant after 4-5 days; expensive
Subdural transducer (C)	Non-fluid-coupled transducer inserted into subdural space
	Easily placed
	Baseline drift significant after 4-5 days and less accurate than above
Subarachnoid bolts (D)	Hollow screw inserted via burr hole in communication w/ SA space
	Low infection risk
	Prone to error (screw displacement, clogging, underestimate ICP)

	Largely replaced by above devices
Epidural transducers (E)	Transducer external to dura Low infection rate Prone to error (malfunction, displacement, baseline drift 5-10 mm Hg w/ few days use) 2/2 interposition of dura, ***rarely used

Ventriculitis: Incidence 5%-14%; rises rapidly after 5 days (NEJM 1984;210:553). Neuro ICU insertion, previous insertion, drainage CSF, steroids not assoc w/ ↑ risk infxn. Abx-coated catheter may ↓ infection rate 9.4% → 1.3% (J Neurosurg 2003;98:725-730). Lumbar access not recommended for monitoring/CSF drainage due to risk herniation. Noninvasive monitoring far less reliable and generally qualitative only. TCD US: ↓ CPP → ↑ diastolic velocity and pulsatility; estimates ICP w/in 10-15 mm Hg; can miss mild-mod ↑ ICP. Tympanic membrane displacement: unreliable and rarely used. Invasive adjuncts to ICP monitoring: jugular venous O_2 sat ($SJVO_2$), brain tissue O_2 ($PBTO_2$) and CO_2 ($PBTCO_2$), brain pH and temp, cerebral microdialysis (combined are called “multimodal” monitoring).

TREATMENT OF ACUTE INTRACRANIAL HYPERTENSION

Goals: Maintain ICP < 20-25 mm Hg. Maintain CPP > 60-70 mm Hg by titrating MAP (ideal CPP target debated). Avoid factors that aggravate/precipitate ↑ ICP.

General Prophylactic Measures

Avoid hypercarbia and anoxia	May ↑ CBF and CBV. Paralyze for intubation to reduce risk of straining/coughing.
Avoid prophylactic hyperventilation	Unsustained effect and may contribute to cerebral ischemia.
Avoid hyponatremia	Risk osmotic edema; use **isotonic fluids** (NS, LR).
Maintain	Hypoglycemia a/w poor outcome in neuro pts.

normoglycemia	
Maintain normothermia	↑ T → ↑ $CMRO_2$, a/w poor outcome in neuro pts. Goal T < 101°F w/ acetaminophen. Active cooling if necessary.
Avoid hypotension/ hypovolemia	Autoregulation intact: vasodilation and ↑ CBV → ↑ ICP. Impaired autoregulation: ↓ MAP → ↓ CPP.
Sedation/analgesia	Agitation and pain can increase $CMRO_2$ → ↑ CBF and CBV.
Head of bed to 30°	Facilitates venous drainage and ↓ CBV. Can paradoxically ↑ ICP via ↓ MAP → vasodilation. Best to adjust HOB to ICP monitor.
Avoid head turning	Compression of IJ can reduce venous drainage
PEEP for pts on mechanical ventilation	Low PEEP (5-10 mm Hg) may prevent alveolar recruitment/ derecruitment injury; unlikely to worsen CPP; higher PEEP can impair venous return and possibly increase ICP.
Early sz PPx for TBI indications less clear for other dz processes	Sz → ↑ $CMRO_2$ and ICP (including nonconvulsive status). Beyond 1 wk not beneficial in pts who have not seized. IV fosphenytoin (15-20 mg/kg load; 3-5 mg/kg/day maintenance titrated to corrected level of 20 µg/mL). Levetiracetam 500 mg q8h alternative.

Adapted from *Semin Neurol* 2008;28:690.

Acute Interventions

Intervention	Rationale	Adverse Effects
Hyperventilation	↑ CBF and CBV Target PCO_2 30 mm Hg	Risk cerebral ischemia

	No longer used routinely	Effects limited to 3-4 h Rebound vasodilation may occur (wean slowly)
Osmotherapy (see below)	Osmotic and vasoconstrictive effects ↓ edema and CBV	See below
Resection of mass/ craniotomy/ craniectomy	↓ mass effect STICH trial: early surgical Rx *supratentorial* ICH not better than medical Rx (*Lancet* 2005;365:387). See "*Craniotomy*"	Surgical morbidity
CSF drainage	↓ CSF volume	Infection, ICH
Pressors	Adjunct optimization of CPP (↑ MAP → ↑ CPP) Fluids first then NE → dopa/PE For CPP > 110, ↓ MAP w/ labetolol or nicardipine	May cause ↓ local CBF No controlled studies Use should not be prolonged
Propofol	↓ $CMRO_2$ and CBF Short half-life	Hypotension, propofol infusion synd, hypertriglyceridemia
Barbiturates	↓ $CMRO_2$ and CBF Phenobarbital load 5-20 mg/kg, then 1-4 mg/kg/h	Hypotension, multiorgan dysfunction, long half-life Rarely used
Hypothermia	↑ $CMRO_2$ and CBF	Infection, usually

See "*Cooling*"		requires heavy sedation and MV No mortality benefit for TBI w/ ↑ ICP (*NEJM* 2001;344:556)
Steroids	↓ vasogenic edema a/w tumor (only indication) Dexamethasone 10 mg load; 4 mg q6h initial maintenance	Hyperglycemia, infection, stress ulcers, critical illness myopathy No benefit beyond neoplasms (e.g., CRASH trial *Lancet* 2005;365:1957)
Neuromuscular blockade	Avoids ↑ ICP due to Valsalva	Loss of neuro exam, requires MV, ↑ critical illness myopathy

Adapted from *Semin Neurol* 2008;28:690.

Osmotherapy: ↓ brain water by creating osmotic gradient across intact BBB. Risk paradoxical ↑ edema where BBB disrupted (Crit Care Med 2006;34:3029). Place central line for administration and CVP monitoring. Overall I/O goal even to slight positive w/ isotonic crystalloid/colloid/blood; CVP > 5. Some centers use 1.5%-3% hypertonic saline as maintenance fluid (no adequate studies). Mannitol and hypertonic saline considered equivalent agents; no clear data on superiority.

Hyperosmolar Agents

20% Mannitol 1,100 mOsm/L	**1-5 min:** Reflex vasoconstriction (↑ plasma V → T CBF → ↑ CVR → ↓ ICP); requires intact autoregulation; **15-30 min:** Osmotic effects. **Other:** Improves blood rheology (decreases viscosity), ↓ CSF formation, free radical scavenging. Dose-dependent effect peaks 20-60 min; duration 4-6 h. **Dosing:** Bolus

	1-1.5 g/kg 20% mannitol load; then 0.25-1 g/kg q2-6h (ggt not recommended). Check osmolar gap q6h and titrate to osm gap 10; hold for >10. ***Osm gap = measured Sr osm - calc Sr osm = [mannitol]. Calc Sr osm = 2Na + glc/180 + BUN/2.8.*** Can be given via peripheral IV. Rebound ↑ ICP may occur in 0.5-2 h (repeat bolus or second intervention). **Adverse effects:** transient hypotension, profound diuresis → renal failure, ↓ Na, ↓ K, ↓ Mg, ↓ PO_4, rebound cerebral edema w/prolonged use (accumulation in brain; taper over days). Must replace fluid loss w/isotonic crystalloid. Minimal data for mortality benefit (*Cochrane Rev* 2007; 1:CD001049).
23.4% hypertonic saline 8,008 mOsm/L	**1-5 min:** Reflex vasoconstriction; **15-30 min:** Osmotic effects. **Other:** ↑ deformability RBCs, ↓ adhesion PMNs → anti-inflammatory. ↓ permeability across BBB vs. mannitol. Concentration varies by center; 23.4% most commonly used. **Dosing:** Bolus 30 mL/20 min (ggt not recommended); repeat q6h. Titrate to Na 150-160, serum osm 310-320 (directly measure each q6h). Must be given by central line. **Adverse effects:** Transient hypotension, electrolyte disturbance, volume overload, renal failure, dilutional coagulopathy, hyperchloremic met acidosis, rebound edema as for mannitol (taper over days). Central pontine myelinolysis not reported w/hypertonic saline for → ICP, but caution warranted in hyponatremic pts. Often used in combination w/mannitol: effects at least partially additive and counteracts mannitol-induced ↓ Na. Better choice than mannitol in hypovolemic, hypotensive pts or w/renal failure.
3% hypertonic saline 1,026 mOsm/L	Used for maintenance eunatremic/correction hyponatremia in place of water restriction (hypovolemia → ↓ CPP). Delivered as continuous ggt. Can be given via peripheral IV (max rate 30 mL/h).

Glycerol, sorbitol, urea used rarely.

Treatment protocol: Several different protocols may be equally efficacious; multiple steps may be taken at once, or advanced steps may be taken to “buy time” for definitive Rx; assumes all general PPx measures (above) are taken.

Stepwise Treatment Protocol

1. Surgical decompression	First consideration Removal of lesion, craniectomy, or CSF drainage
2. Sedation	To a motionless, quiet state (RASS 0 or -1)
3. Osmotherapy	Mannitol followed by 23.4% saline if necessary Correct hyponatremia w/ 3% saline if 23.4% saline not used
4. CSF drainage	EVD; simultaneous ICP monitoring
5. CPP optimization	Pressors if CPP < 60-70; MAP reduction if CPP >110
6. Hyperventilation	Target pCO_2 30 mm Hg (25-30 in severe refractory cases)
7. Barbiturates	Goal coma w/preserved pupil reactivity; cont. EEG helpful (limited benefit beyond burst suppression)
8. Hypothermia	Goal core temp 32°C-36°C; aim for control of ICP, not necessarily specific target temperature

Adapted from *J Intensive Care Med* 2002;17:55.

Interventional Neurology

CEREBRAL ANGIOGRAPHY

Indications: Gold standard for characterizing neurovascular anatomy & pathologies, e.g., aneurysms, arteriovenous malformations (AVMs), extra- & intracranial stenosis, other dzs of cerebral & spinal vasculature.

Endovascular devices: Extra- & intracranial uses. E.g.: catheters, microcatheters, coils, guidewires, microwires, liquid embolic agents, clot retriever, stents, angioplasty balloons.

Preprocedural care

- Pt evaluation: Procedure indications: diagnostic or therapeutic. Noninvasive vascular studies: CTA, MRA, TCDs. Clinical status: level of arousal, cognition, neurological deficits. Vitals: temperature, blood pressure, ICP, EVD settings/output. PMH, meds (aspirin, heparin, coumadin, antibiotics), allergies (esp to prior contrast exposure), renal dz & DM mellitus (risk for nephrotoxicity).
- Pt education: Explain procedure. Instruct to remain still (avoid motion artifact).
- Informed consent: ˜2% risk of groin hematoma, retroperitoneal bleed, infxn, vessel rupture, dissection, vasospasm, stroke, paralysis, blindness, contrast allergy, kidney damage, radiation complications, death.
- Preparation: NPO 8 h prior to procedure. Discontinue metformin 24 h before procedure. Resume only 2 days after procedure. In pts w/ abnl renal function, consider IV bicarbonate 1 h prior to procedure, Mucomyst 600 mg, two doses q4h before & after procedure. Start heparin gtt (goal activated clotting time [ACT] 200-250) after sheath insertion for stenting/coiling cases.

Procedure techniques: Conscious sedation & local anesthesia given before catheters placed. For most angiography the arterial or venous system accessed safely via the femoral artery or vein distal to inguinal ligament. Catheter navigated into aorta & up into cervical vessels under fluoroscopy. Contrast administered & x-rays taken to examine the vessels in the head or spine. Typically, both carotid arteries & both vertebral arteries are studied.

Postprocedural care: (1) Manual groin compression: firm pressure 3 min for each increment in size of groin sheath (i.e., 5 French sheath = 15 min). (2)

Serial neuro exams q 1h. (3) STAT head CT for any exam change. (4) BP monitoring, goal based on procedure performed. (5) Instruct pt keep legs straight for 6 h. (6) Continue antico-agulation (heparin drip) × 24 h after stent placement or aneurysm coiling. (7) Resume antiplatelets (aspirin 81 mg & clopidogrel 75 mg) after stent placement or aneurysm coiling; maintain on aspirin lifetime; clopidogrel for 1.5-12 mo. (8) Pull sheath once INR < 1.3 to ↓ risk of hematoma. (9) Upon d/c, pt should avoid heavy lifting or exercise × 10 days, avoid swimming ×5 days.

Follow-up Angiogram

Stenting	6-mo, 12-mo, 5 yr postprocedure
Aneurysm embolization	3-mo, 12-mo, 3 yr postprocedure
AVM embolization	3-mo, 6-mo, annually postprocedure

NEUROVASCULAR DISEASES

ACUTE ISCHEMIC STROKE

Angiographic signs: (1) Intraluminal thrombus: filling defect in lumen of opacified vessel; most common sites extracranial ICA & MCA. (2) Vessel occlusion: tapered narrowing or sharp termination of contrast column. (3) Slow antegrade flow w/ delayed arterial emptying. (4) Slow retrograde filling through pial collateral vessels. (5) Non perfused areas.

TICI score: (TICI: “Thrombolysis in cerebral ischemia,” J Vasc Interv Radiol 2003; 14:S493). TICI 3: complete recanalization. TICI 2: partial recanalization. TICI 1: complete occlusion.

Endovascular therapies

- IA thrombolysis: a/w ↑ recanalization rates for ICA, MCA stem, BA occlusions. Total dose ˜1/3 IV dose (b/c given locally). Can be used in postsurgical pts unlike IV thrombolysis.
- IV + IA thrombolysis: Multimodal Rx shown to result in better recanalization & higher rates of functional independence.

- IA thrombectomy or IA thromboaspiration: Achieved w/ microcatheter or microwire clot maceration, angioplasty, stent deployment, & clot-retrieval or microsnare devices. Used alone or as adjunct to IA

thrombolysis. Offers possibility of faster recanalization, ↑ recanalization rates, ↓ total thrombolytic dose, & ultimately improved outcome.

Contraindications: (1) Pregnancy, (2) serum glucose <50 mg/dL, (3) excessive tortuosity of vessels precluding device delivery/deployment, (4) known hemorrhagic diathesis, (5) oral anticoagulation Rx w/ INR > 3.0 (6), heparin w/in 48 h & PTT >2 times normal, (7) platelet count < 30,000/µL, (8) h/o severe allergy to contrast media, (9) sustained SBP > 185 mm Hg or DBP >110 mm Hg if pt received IV rt-PA, (10) CT showing sig. mass effect w/ midline shift, (11) >50% stenosis of the artery proximal to the target vessel, (12) life expectancy <3 mo.

MAJOR ENDOVASCULAR STROKE THERAPY TRIALS

"PROACTII": IA thrombolysis (JAMA 1999;282:2003): Sx duration: <6 h. Median NIHSS: 17. Angiographic occlusion (TIMI 0 or 1): M1 or M2 MCA segments. Rx groups: IA r-pro-UK (9 mg over 2 h) + low-dose IV heparin vs. low-dose IV heparin alone. Median time to Rx: 5.3 h. Outcomes: Recanalization (TIMI 2-3): Rx 66% (71/108), control 18% (19/108). 90 days NIHSS decreased >50%: Rx 50%, control 44%. 90 days mRS <2: Rx 40%, control 25%. Mortality: r-pro-UK 25%, control 27%. Complications: 9% (11/121); neurologic, anaphylaxis, bleeding. SICH: 10.9% r-pro-UK, 3.1% control group. Caveats: ↑ ICH rate c/w trials of IV thrombolysis (2/2 ↑ baseline stroke severity).

"IMS-1": IV + IA thrombolysis (Stroke 2004;3:904): Sx duration: <3 h. Median NIHSS: 18. Angiographic occlusion (TIMI 0 or 1): MCA, ACA, PCA, BA. Rx: IV rt-PA max 60 mg → if no recanalization → IA rt-PA + IV heparin. Time to Rx: <5 h. Outcomes: Recanalization (TIMI 2 + 3): 56% (35/62) IV + IA rt-PA. 90 days NIHSS <2: 31%. 90 days mRS 0-2: 43%. 90 days mortality: Rx 16%, NINDS placebo 24%; not statistically significant. Complications: 14%; hematomas, pseudoaneurysms, vessel perforations. SICH <36 h: 6.3%. Caveats: IV Rx was started later in IMS-1 than in NINDS-treated pts.

"Multi-MERCI": IV thrombolysis + IA thrombectomy ± IA Thrombolysis (Stroke 2008;39:1205): Sx duration: <8 h. Median NIHSS: 19. Occlusion (TIMI 0 or 1): ICA, MCA, VA, BA. Rx: IV rt-PA w/o recanalization or ineligible for IV rt-PA ↑ max 6 device passes ↑ if no recanalization ↑ IA rt-PA max 24 mg. Outcomes: Recanalization (TIMI 2 + 3): 54.9% (90/164) IV rt-PA + device; 68.3% (112/164) IV/IA rt-PA+device. NIHSS improved > 10 pts 24 h: 26%. 90 days mRS of <2:36%. 90 days mortality: 34%. Complications: 5.5% (9/164); decline NIHSS, death, groin hematoma. SICH: 9.8%. Caveats: Treated pts did not have improved outcome compared w/ PROACT II

historical controls. Conclusion: Mechanical thrombectomy post-IV thrombolysis as safe as mechanical thrombectomy alone.

PENUMBRA: IV thrombolysis + IA thromboaspiration (Stroke 2009;40:2761): Sx duration: <8 h.Mean NIHSS: 17.3. Occlusion (TIMI 0 or 1): ICA, MCA, BA. Rx: IV rt-PA w/o recanalization or outside 3 h window → device. Outcomes: Recanalization (TIMI 2 + 3): 81.6%. NIHSS improved >4 pts 30 days: 45%. 90 days mRS of <2: 25%. 90 days mortality: 32.8%. Procedural complications: 3.2%, none device related; groin hematoma, SAH. SICH: 11.2%.

Abbreviations: PROACT: Prolyse in acute cerebral thromboembolism; IMS: Interventional Mgt of Stroke; IA: intra-arterial; ICA: internal carotid artery, MCA: middle cerebral artery, VA: vertebral artery, BA: basilar artery; SAH: subarachnoid hemorrhage; NINDS: National Institute of Neurological Diseases & Stroke; SICH: symptomatic intracerebral hemorrhage.

Impact of revascularization on clinical outcomes: Trial, mRS < 2 (%), mortality (%) for recanalized vs. nonrecanalized pts.

- IMS 1-2: (46,11) vs. (7,35)
- MERCI: (46,32) vs. (10,54)
- Multi-MERCI: (49,25) vs. (10,52)
- Penumbra: (29,29) vs. (9,48)

Pt selection: (1) w/in therapeutic time window: initiation of IA Rx w/in 8 h sx onset for anterior circulation strokes; no consensus guidelines on time interval for post circulation strokes (Stroke 2008;39:1205). (2) No e/o ICH. (3) Large-vessel occlusion (ICA, ACA, MCA, PCA, VA, BA), however no RCTs for ICA occlusions (AJNR 2009;30:859). (4) NIHSS > 10 (Stroke 2004;35:904). (5) Infarct size <33% of MCA territory on head CT (Stroke 2005;36:66). (6) MR perfusion-diffusion mismatch >20% (Neurology 2001;57:1205; Ann Neurol 2006;60:508). (7) Clinical-diffusion mismatch if presenting w/in 12-24 h of symptom onset; (AJNR 2009;30:1024-1027). (8) Abnl hemostasis (INR > 1,7, PTT > 45 s, platelets <100 K) not contraindication for mechanical thrombectomy (Stroke 2009;40:516).

INTRACRANIAL ARTERY STENOSIS: ENDOVASCULAR THERAPIES

Angioplasty: No RCTs. Risks: stroke 8%, death 3% (Cochrane Database 2006;3: CD004133). Complications: elastic recoil of artery, dissection, vessel

collapse, high restenosis rates.

Intracranial stenting

SSYLVIA trial (Stroke 2004;35:1388): Evaluated NEUROLINK stent in 61 pts w/ TIA or stroke & >50% intracranial vessel stenosis. Successful stent deployment: 95%; 30 days stroke or death rate: 6.6%; 1 yr ipsilateral stroke rate: 13%; 6 mo restenosis of >50%: 32%, higher than those w/ extracranial carotid stenting.

Wingspan phase I study (Stroke 2007;38:1531): Evaluated Wingspan stent in 45 pts w/ recurrent cerebral ischemia on medical therapy & >50% intracranial vessel stenosis. Successful stent deployment: 98%; 30 days stroke or death rate: 4.5%; 6-mo ipsilateral stroke rate: 7%; 6-mo restenosis rate: 7.5%.

Wingspan postmarketing registry (Neurology 2008;70:1518): 129 pts treated w/ Wingspan stent for >70% intracranial vessel stenosis. Successful stent deployment: 97%; 30 days stroke or death rate: 9.6%; 6-mo restenosis rate: 25%.

Guidelines: Intracranial stenting still investigational for symptomatic intracranial large artery atherosclerosis. Perform only when part of a clinical trial or prospective registry protocol.

CAROTID ARTERY STENOSIS

See chapter “Vascular Neurology” for medical Rx options. CAS = carotid artery stenting.

Clinical considerations for neuro-intervention: Distal & intracranial carotid lesions accessible w/angioplasty ± stenting; CEA limited to cervical ICA. ↓ morbidity from coexisting CAD than w/ CEA. High-risk pts for CEA also include those who have undergone radiation therapy, neck exploration, or tracheostomy. If recent stroke, procedure may be done several wks later to ↓ chances of bleeding from anticoagulation regimen used in stenting.

Rx: (1) Aspirin 325 mg & clopidogrel 75 mg at least 1 wk prior to procedure. (2) Heparin during procedure to prevent clot from developing on the catheters or stent. (3) Performed under local anesthesia & conscious sedation. (4) Under direct fluoroscopic visualization, guide catheter placed in affected carotid artery, & small guide wire is passed beyond stenosis. (5) Built-in distal protection device used to collect any debris from angioplasty. (6) Stent deployed over guidewire, followed by possible angioplasty to secure stent in place. (7) Heparin stopped 24 h postprocedure, then groin sheath is removed. (8) Antiplatelets continued postprocedure.

Complications: (1) ↑ HR, ↑ BP:˜65% pts; 2/2 pressure on carotid body. (2)

Hyperperfusion syndrome: Cerebral vasculature loses nl autoregulation → cerebral edema; BP must be strictly regulated. (3) ICA dissection: ˜ 15% w/ angioplasty. (4) Embolic stroke: ˜ 10% w/ angioplasty. (5) Restenosis or in-stent thrombosis: up to 6% in metaanalyses, commonly from fibromuscular dysplasia; may not be amenable to emergency surgical correction. (6) Stent fracture: As high as 29% in small retrospective studies (Radiology 1996;201(3):627).

Guidelines: Systematic review of RCTs favored CEA for 30 days stroke/death risk, while long-term outcomes similar. CAS should be considered for symptomatic severe stenosis (>70%) in pts considered high-risk for CEA or who have difficult surgical access to stenosis, radiation-induced stenosis, restenosis after CEA. Interventionalists should have CAS periprocedural morbidity/mortality rates <4%-6% (Stroke 2006;37:577).

Clinical trials

SPACE trial (Neurology 2008;7:893-902): Randomized 1,183 pts to CAS or CEA, excluded high-risk pts (refractory HTN, poor prognosis). Stenosis > 70%. 30 days & 2 yr risk for stroke/death similar in both groups; about 7% & 9%, respectively. Statistically, CAS noninferiority to CEA not demonstrated.

EVA-3S trial (NEJM 2006;355:1660): Randomized 527 pts to CAS or CEA, excluded high-risk pts (unstable angina, uncontrolled DM or HTN, recurrent carotid stenosis). Stenosis > 70%. 30 days stroke/death rate: CAS 9.6%, CEA 3.9%. Criticized for lack of operator experience for CAS, optional use distal protection devices.

SAPPHIRE trial (NEJM 2008;358:1572): Randomized 334 pts w/ either symptomatic (>50%) OR asymptomatic (>80%) carotid stenosis considered HIGH risk for CEA. High risk pts: severe cardiac or pulmonary dz, contralateral carotid occlusion, prior neck surgery or irradiation, recurrent stenosis after CEA, age >80. 1-yr stroke/MI/death rate: CAS 12.2%, CEA 20.1%; 3 yr f/u: no sig. difference for major endpoints. Large no. of pts w/ recurrent carotid stenosis: bias favoring CAS, due to greater complication rates from repeat CEA & better outcomes w/ CAS for restenosis from intimal hyperplasia (lower embolization risk than w/ atherosclerosis).

CEREBRAL ANEURYSMS

Epidemiology: 2% of adults + asymptomatic aneurysms, of which 25% have multiple aneurysms. Aneurysmal SAH:˜16/100,000; represents <1% all deaths; 10% die before hospital; 85% in ant circulation, mostly circle of Willis at arterial jxns.

Pathophysiology: Saccular (berry) aneurysms: acquired not congenital, thin-walled protrusion from artery due to very thin medial vessel wall layer. Fusiform aneurysms: dilatation of entire vessel circumference, commonly due to athero. Mycotic aneurysms: develop from septic emboli due to infective endocarditis.

Risk factors: (1) HTN, smoking, EtOH, estrogen deficiency (menopause), PCKD. (2) Morphological: turbulent blood flow, hemodynamic stress, high-flow state; cause structural damage to internal elastic lamina. (3) Connective tissue dzs: Ehlers-Danlos syndrome, less likely Marfan syndrome. (4) Familial: higher incidence among first-degree relatives than general population; tend to rupture at a smaller size, younger age than sporadic aneurysms.

Presentation: HA, visual Ds, CN palsies. Strokes 2/2 emboli formed in aneurysm.

Grading scales

- Hunt Hess grading system for SAH (J Neurosurg 1968;28:14): 5 grades: (1) No sx or mild HA + slight nuchal rigidity. (2) Severe HA, stiff neck, no neuro deficit except CN palsy. (3) Drowsy or confused, mild focal neurologic deficit. (4) Stuporous, moderate, or severe hemiparesis. (5) Coma, decerebrate posturing.
- Fisher CT grading system for SAH (Neurosurgery 1980;6:1): Four groups, based on appearance of blood on CT scan: (1) No blood detected. (2) Diffuse deposition or thin layer w/ all vertical layers (in interhemispheric fissure, insular cistern, ambient cistern) <1 mm thick. (3) Localized clot and/or vertical layers 1 mm or more in thickness. (4) Intracerebral or intraventricular clot w/ diffuse or no subarachnoid blood.

Imaging: (1) CTA: Se 92% for aneurysms <3 mm, Se >99% for 4-10 mm; (AJNR 2008;29:594). (2) Conventional angiogram: if high clinical suspicion for aneurysm, may not have been seen on noninvasive studies.

Rxs: (1) Neurosurgical clipping: Utilize microsurgical techniques for placement of a clip across aneurysm neck. Brain retraction may worsen neurological deficits, temporary arterial occlusion, intraoperative hemorrhage (J Neurosurg 2002;96:515). (2) Endovascular coiling: Platinum (Guglielmi) detachable coils inserted into aneurysm lumen. Technically challenging for aneurysms w/ broad necks, low neck-dome ratio, size >20 mm (giant). Obliteration rate >80%, though clipping can be performed later if aneurysm not completely obliterated.

Unruptured aneurysms

Rx guidelines: Symptomatic intradural aneurysms of all sizes; Aneurysms of all sizes in pts w/ history of another aneurysm rupture; Asymptomatic aneurysms >10 mm.

ISUIA: International Study of Unruptured Intracranial Aneurysms

- Clipping: 30 days death/poor neuro outcome 13.7%, 1 yr 12.6% (w/o h/o aneurysm ruptures).
- Co'iling: 30 days death rate or poor neurological outcome 9.3%, 1 yr 9.8%.

Risk factors for adverse outcomes (Lancet 2003;362:103): (1) Site: rate of rupture highest for posterior circulation, intermediate for anterior circulation, lowest for carotid cavernous aneurysms. (2) Size: low rate of rupture if <7 mm, no history of any aneurysm rupture. (3) Growth: aneurysms either grow over a short period of time, then either rupture or stabilize & harden; increased risk of further growth/rupture if >10 mm. (4) Aneurysms near AVM have ↑ likelihood of growth/rupture, should be repaired prior to treating AVM. (5) Aneurysms distal to symptomatic ICA stenosis at risk for rupture post-CEA due to hemodynamic changes if >7 mm or history of another ruptured aneurysm. (6) Antithrombotic Rx: may increase rupture risk.

Follow-up: (1) Newly dx'd aneurysms: re-image at 6 mo. (2) Known aneurysms: q1yr CTA or MRA for 2 yr, then q2-5yr if stable.

Ruptured aneurysms

ISAT: International Subarachnoid Aneurysm Rx Trial (Lancet 2002;360:1267): Randomized 2,143 pts to surgical clipping or endovascular coiling (88% w/ HH grade <3,90% of aneurysms <10 mm, 95% anterior circulation). 1-yr dependence/mortality rate: 23.5% w/ coiling, 30.9% w/ clipping. Seizure risk significantly lower after coiling: relative risk 0.52. 1 yr rebleeding rate: 2.5% w/ coiling, 1% w/ clipping.

Risk factors for adverse outcomes: Clipping: smoking, HTN, multiple aneurysms w/ initial SAH. Coiling: young, large lumen size, aneurysm >10 mm, incomplete initial occlusion.

Early Rx: <72 h, HH grade <3: Prevention of rebleeding. Allow for management of vasospasm w/ "Triple H" (HTN, hypervolemia, hemodilution); (Neurology 2000;55:1656). Mortality rate up to 8%. Clipping more challenging due to cerebral edema, clot around aneurysm, risk of

ischemia (J Neurosurg 1995;83:394).

Follow-up: Clipping: CTA (↓artifacts from clip c/w MRA) 3 & 6 mo (Stroke 2005; 36:2394). Coiling: Visualize coil mass after embolization. Digital subtraction angiography at 3 mo. MRA (↑ artifacts from coil vs. CTA) at 6 & 12 mo (AJNR 2000; 21:1523).

ARTERIOVENOUS MALFORMATIONS

Epidemiology: Incidence: 0.1%; account for 1%-2% strokes, 9% of SAH. 90% supratentorial.

Pathophysiology: Direct arterial-venous connections w/o capillary network b/n; congenital. May be a/w hereditary hemorrhagic telangiectasia or Osler-Weber-Rendu syndrome. Gliotic brain tissue forms w/in AVM. High flow may form afferent/efferent pedicle aneurysms. May ↓ regional brain perfusion 2/2 stealing of flow from surrounding parenchyma.

Presentation: Typically presents at age 10-40. (1) Intracranial hemorrhage: 40%-80%: Average annual rate for untreated AVMs 2.8-4.6%. Hemorrhage as initial clinical presentation strongest predictor of recurrent hemorrhage, 7% annually (Neurology 2006;66:1350). Risk factors: older age, exclusive deep venous drainage, deep location; all three risk factors increase hemorrhage rate to 34% annually (Stroke 2004;35(3):660-663; Stroke 2006;37:1243). Children not at any higher risk for recurrent hemorrhage compared to adults. Annual mortality < 1%. (2) Seizures: 10%-30% (3) Headaches.

Imaging: CT/CTA: Identifies hemorrhage, but low Se for detecting AVM if nidus compressed by hematoma.MRI/MRA: Very sensitive in locating AVM nidus & associated draining veins. Useful especially post-Rx for assessing decrease in nidal volume. Angiography: Gold standard for dx, planning of Rx, & f/u: Accurately assess nidus configuration, location of arterial feeders, draining veins; analyzes flow state based on contrast transit time.

Rxs: (1) Surgery: Mainstay of Rx, 5% risk of morbidly/mortality. (2) Radiosurgery: if high-risk for surgery. (3) Endovascular embolization: usu adjunct to surgery or radiosurgery: uses microparticles & cyanoacrylates. Only afferent (arterial) pedicles to nidus embolized, avoid venous drainage. <5% cure rate. Partial embo → pedicle pressure → risk of hemorrhage (J Neurosurg 1987 Jul;67(1):17). Adjunct to surgery (grade 3 lesions): limit blood loss. Prior to radiosurgery: reduce nidus size. Low risk of disabling complications (Stroke 2002;33:1816).

Unruptured AVMs: Rx a/w worse outcome than no Rx: high rates of ICH (Neurology 2004;62:A101). ARUBA (“A randomized trial of unruptured brain AVMs”): in progress; studying natural hx of unruptured AVMs, medical

Rx vs. combination of Rx modalities. Considerations: (1) Age: treat children & young adults. (2) Surgical risk: Spetzler-Martin grading scale (consistently an accurate predictor of outcomes) (J Neurosurg 1986;65:476): Points assigned for size: in cm [0-3, 3-6, >6] → [1,2,3] points location: (Noneloquent, Eloquent [regions of crucial cortical fxn, deep nuclei, brainstem] → [0,1] points; Deep venous drainage: [absent, present] → [0,1] points). High-grade lesions (score >3) difficult to resect safely. (3) Gender: females may pose increased surgical risk. (4) Lifetime risk (%) of hemorrhage calculator: 105—pt age in yr (Neurosurgery 2000; 46:1024).

AVM-associated aneurysms: Feeding artery aneurysms: if <7 mm, consider clipping or coiling. Intra-nidal (w/in AVM nidus): obliterated during Rx. Manage those not feeding AVM based on guidelines for aneurysms in pts w/o AVM (NEJM 2007;356:2704).

SPINE DISEASES

VERTEBRAL FRACTURES

Etiology: (1) Trauma: flexion-compression fx, axial-compression fx, rotational fx. (2) Osteoporotic fracture: occur in 20% people >70 yo. True incidence likely underestimated—many are painless, discovered incidentally. Risk of new fx in vertebra adjacent to incident fx ↑ 5-25-fold from baseline. Risk factors: F > M, postmenopausal, white race, low bone density. (3) Daily steroid use. (4) Pathologic fracture: from metastatic dz or vertebral neoplasm. (5) Infection: osteomyelitis, Pott dz (tuberculosis spondylitis). (6) Osteomalacia.

Presentation: Pain, weakness, numbness, tingling.

Imaging: Plain film: difficult to detect hairline/nondisplaced fxs. CT: detects bony fxs & extent. MR: extent of damage to cord. Bone scan: detects additional lesions (in CA setting).

Vertebroplasty: Described in 1987. Technique: augmentation of vertebral body w/ bone cement (polymethylmethacrylate). Indications: stabilization of painful vertebral fractures. Contraindications: Host features: evidence of ongoing systemic or localized spine infection, bleeding disorders; Fracture features: significant burst component, neurologic compromise, posterior vertebral body wall fracture, poor visualization/access of fracture. Benefits: decreased pain (usually w/in 3 days). Complications: cement leakage → cord/nerve root compression or PE. Extravasation more likely in setting of metastases or hemangiomas.

Percutaneous vertebroplasty vs. optimal pain medication Rx (VERTOS Trial)

(AJNR Am J Neuroradiol 2007;28:555). First randomized prospective long-term study comparing vertebroplasty vs. optimal medical mgt. Day 1: vertebroplasty → ↓ pain. Wk 2: vertebroplasty → ↓ analgesic use (pain comparable in both groups). Blinded, randomized, placebo-controlled trials have compared vertebroplasty vs. sham procedures & have shown that both groups have equivalent improvement in pain at 1 mo (NEJM 2009;361:569) & 6 mo (NEJM 2009;361:557). Further studies are investigating benefits of vertebroplasty at longer time points & subgroups of pts that benefit from vertebroplasty over placebo.

Kyphoplasty: Consider 6 wk after conservative management. Technique: Percutaneous placement of inflatable bone tamp into a fractured vertebral body → bone tamp is inflated → elevates depressed vertebral body end plate & creates cavity w/in vertebral body. Indications: painful osteoporotic or osteolytic fractures; not used for metastatic lesions. Contraindications: similar to vertebroplasty. Benefits: ↓ pain (usually w/in 2 wk); restore vertebral body height; Improved spinal balance. Complications: cement leakage leading to spinal cord/nerve root compression.

Fracture reduction evaluation (FREE Trial) (Lancet 2009;373:1016): First large randomized long-term study comparing kyphoplasty vs. nonsurgical management. Kyphoplasty resulted in improvement in quality of life, disability, & back pain at 1 mo, but no difference at 1 yr. Ongoing RCTs are directly comparing vertebroplasty vs. kyphoplasty.

LUMBAR DISC HERNIATION

Definitions: Localized displacement of disk material (nucleus, cartilage, fragmented bone, annulus) beyond intervertebral disc space.

Stages: Disc degeneration. Prolapse: annulus bulges. Extrusion: annulus ruptured but expelled nucleus attached to rest of disc. Sequestration: disc tissue expelled, detached.

Presentation: Cervical: pain in neck, shoulders, arms; arm weakness. Thoracic: pain radiating into chest. Lumbar: pain in back, buttocks and/or legs; pain worse w/ sitting & improves w/ walking, positive straight leg raise, sciatica, leg weakness. Concerning symptoms: fever, history of IVDU, trauma, bowel/bladder symptoms.

Imaging: MRI, CT myelogram.

Percutaneous discectomy (nucleoplasty): Technique: percutaneous needle placement into symptomatic disc → application of radiofrequency energy → destroys tissue → removal of tissue → decompression of disc contents → retraction of disc bulge → relieves pressure from nerve root. Indications:

chronicdiscogenic back pain; prospective clinical trails show reduction in pain & disability in carefully selected populations for lumbar disc dz (Acta Neurochir (Wien) 2008;150:1257; Spine J 2007;7:88) & cervical disc dz (Eur Spine J 2008;17:1664). Consider in small (<6 mm) contained disc herniations, w/ a disc height of ≥50% & w/ annular integrity. Contraindications: myelopathic signs; back pain from other sources (e.g., bony arthritis, spinal fracture, tumor); Disc extrusion. Benefits: relief of pain; decreased need for analgesics; does not preclude further surgery. Complications: infection; bleeding; nerve damage; worsened pain; recurrence of herniation.

Seizures and Other Spells

SEIZURES AND SIMILAR SPELLS

Seizure: Sudden behavior Δ 2/2 abnl, excess excitation of cortical neurons.

Provoked: +attributable cause (e.g., systemic illness, direct neuro insult).

Unprovoked: Occurs w/o acute illness, 2/2 persistent brain abnlity/dz.

Acute symptomatic: Synonymous w/ “provoked” sz.

Aura: First part of sz, often the only part remembered by pt; a simple partial sz (SPS) that sometimes progresses to complex partial or secondarily generalized sz.

Postictal period: The period from end of sz until return to baseline.

Psychogenic (pseudosz): Resemble szs but w/o electrographic correlate.

Epilepsy: ≥2 unprovoked szs (or: a tendency toward recurrent unprovoked szs).

Epilepsy syndrome: Specific form of epilepsy; implies specific cause, si/sx, prognosis.

Status epilepticus (SE): Over 30 min: Continuous sz or >1 sz w/o full return to baseline b/n.

Epidemiology of epilepsy (NEJM 2008;359(2):166): 45 million cases worldwide; USA ˜7/1,000; 70% focal, 30% generalized. Causes (in adults): 60% unk; 40% w/ known causes: Stroke 9%, TBI 9%, EtOH 6%, neurodegen 4%, static encephalopathy 3.5%, brain tumor 3%, infxn 2%.

DIFFERENTIAL DIAGNOSIS OF SEIZURES

Ddx: TIA; transient global amnesia (TGA); panic attacks & other anxiety manifestations, migraine; narcolepsy/other sleep d/os; tremor, nonepileptic myoclonus, dystonia/other movement d/os; pseudoszs, malingering, breath holding spells; stereotypies in cognitively impaired individuals.

Sleep disorders: If events occur mostly in sleep (parasomnias & sleep-related mvmt d/os): REM behavioral d/o: Partial arousals from REM w/ complex/aggressive behaviors; Sleepwalking—partial arousal from non-REM sleep; Sleep terrors—Distinguish sleep d/o vs. sz (e.g., nocturnal frontal lobe epilepsy) w/ VEEG (gold standard) or Frontal Lobe Epilepsy & Parasomnias (FLEP) scale (Se 100%, Sp 90%) (Arch Neurol 2006;63: 705-709).

Transient ischemic attack (TIA): Si/sx usually (−), but can be (+) (e.g., jerking, rigidity, hallucinations, visual illusions). Limb shaking TIAs: A/w preocclusive dz in ICA or MCA, usually orthostatic. Todd's paralysis (transient weakness after sz) can mimic TIA/stroke.

TGA: Dx criteria: Witnessed; acute onset antegrade amnesia; no Δ consciousness or loss of self-awareness; cog. impairment limited to amnesia; no recent head trauma or sz; duration of sx <24 h; no other neuro sx other than dizziness, vertigo, HA. Epidemiology: Mid-age/elderly. Etiology/prognosis: Usu benign, not recurrent. Atypical or a/w vascular risk factors → consider stroke w/u. Etiology: ? (Theories: hippocampal TIA, migraine, venous congestion.) Can have small (reversible) DWI-bright lesions on MRI.

Migraine aura (e.g., visual illusions/hallucinations, AMS w/ basilar migraine) can mimic CPS; aura onset usually more gradual & duration less. HA after CPS can mimic migraine.

Pseudoseizures (aka psychogenic nonepileptic sz, PNES): See below.

Syncope: Including "convulsive syncope": See below.

SYNCOPE

*This section adapted from Pocket Medicine, 3rd edition.

Clinical Features Helpful for Distinguishing Sz Vs. Syncope

Feature	Tonic-Clonic Sz	Vasovagal (Neurocardiogenic) Syncope
Injury	Common	Occasional
Incontinence	Common	Rare
Premonitory sx	Short or none	Longer
Postictal confusion	Common, long	Rare, short
HA	Common	Rare

Focal deficit	Occasional	Rare
Related to posture	No	Yes
Skin color	Cyanotic	Pale

P.58

Etiologies: (1) Vasovagal/neurocardiogenic: (20%) mechanism: ↑ sympathetic tone → vigorous LV contraction → mechanoreceptors in LV trigger ↑ vagal tone → ↓ HR, ↓ BP. Related d/os: Carotid sinus hypersensitivity (in 39% of elderly); Caused by cough, swallowing, defecation, micturition. Convulsive mvmts (convulsive syncope) more likely if head remains elevated. (2) Orthostatic hypotension (10%): Hypovolemia, diuretics, deconditioning; vasodilators (esp w/ neg chronotropes); autonomic neuropathy (DM, EtOH, amyloid, renal failure, POTS, Shy-Drager). (3) Cardiovascular: Arrhythmia (15%: Bradyarrhythmias: SSS, high grade AV block, neg chronotropes, PPM malfunction; Tachyarrhythmias: VT, SVT, (syncope rare unless structural heart dz or WPW); mechanical [5%: Endocardial: AS, MS, PS, prosthetic valve thrombosis, myxoma; Myocardial: pump dysfn from MI; outflow obstruction from HCM (usually VT)].

Workup (etiology remains undetermined in ˜35% cases)

History: (1) activity/posture before event; (2) triggers: exertion (AS, HCM, PHT), positional Δ (orthostasis), stressors (blood, pain, emotional distress, fatigue), prolonged standing, warm setting, n/v, cough, urination, defecation (vasovagal), head turning or shaving (carotid sinus hypersens.); arm exercise (subclavian steal); (3) prodrome: (e.g., sweating, n/v, blurry vision): cardiac <5 secs, vasovagal >5 secs; (4) ass. sx: Chest pain, palp.

PMH: Prior syncope, cardiac dz; no known CV dz → 5% cardiac, 25% vasovagal; known CV dz → 20% cardiac, 10% vasovagal.

Meds: Vasodilators, alpha-blockers, nitrates, ACEi/ARB, hydralazine, phenothiazines, diuretics, BBs, CCBs; proarrhythmics; psychoactives (antipsych., TCA, barbit., benzos, EtOH).

FHx: Cardiomyopathy, sudden cardiac death.

Exam: (1) VS ([check mark] orthostasis: supine to standing → >20 mm Hg ↓ SBP, > 10 mm Hg ↓ DBP, or > 10-20 bpm ↑ HR); BP in both arms, (2) CV: HF (↑ JVP, S3, displ PMI); murmurs, LVH (S4, LV heave), (3) Vascular:

asymm. pulses, carotid bruits, ?carotid sinus massage.

EKG: (abnl in 50%, finds cause in 10%): Sinus bradycardia, sinus pauses, AVB, BBB, SVT, VT; ischemic Δ (new or old); atrial or vent. hypertrophy. Markers of arrhythmia: ectopy, ↑ QT, preexcitation, Brugada pattern, θ-wave, arrhythmogenic RV dysplasia (ARVD).

Other diagnostic studies: (1) echo: r/o structural heart dz, (2) exercise stress test: esp w/ exertional syncope, catecholamine-induced arrhythmia, (3) tilt table (provokes vasovagal syncope): (+) in 50% w/ recurrent unexplained syncope; Se 26%-80%, Sp > 90%, (4) cardiac MRI: to r/o ARVD if suggestive EKG, echo (RV dysfxn), or (+) FHx of SCD.

High risk features: (1) FHx: Cardiomyopathy, sudden cardiac death; (2) Age > 60, CAD, CMP, valvular dz, congenital heart dz, arrhythmias; (3) Syncope c/w cardiac dz (lack of prodrome, exertional, resultant trauma); (4) Abnl cardiac exam or EKG.

Treatment: (1) Arrhythmia, cardiac mechanical: treat underlying d/o; (2) Vasovagal: ? midodrine, fludrocortisone, disopyramide, anticholinesterases, theophylline, ?16 oz H_2O before at risk situations (Circulation 2003;108:2660); (3) No proven benefit w/ beta-blockers (Circulation 2006;113;1164) or PPM (JAMA 2003;289:2224); (4) ? SSRI (e.g., Paxil); (5) Orthostatic syncope: Fluids; if chronic: advise to rise slowly; compressive stockings, midodrine, fludrocortisone (florinef), high Na diet.

Prognosis of syncope (Ann Emerg Med 1997;29:459; NEJM 2002;347:878). 22% overall recurrence rate. Cardiac: 2× ↑ mortality, 20%-40% 1-yr SCD rate; median survival ˜6 yr. Unexplained: 1.3× ↑ mortality; noncardiac or unexplained w/ nl EKG, no h/o VT, no HF, age < 45 → low recurrence & <5% 1-yr SCD. Vasovagal: No increase in mortality, MI, stroke.

PSEUDOSEIZURES (PSYCHOGENIC NONEPILEPTIC SZS, PNES)

Definition: Spells resembling epileptic szs but w/o electrographic correlate. Psychological origin; usually somatoform (conversion d/o > somatization d/o >> factitious, malingering). 10%-30% of patients w/ PNES also have epileptic szs.

HPI suggestive of PNES: Multiple nl/nonspecific EEGs, resistance to multiple AEDs, strange triggers (stress, pain, specific mvmts, sounds, lights), antecedent sexual trauma, occur only around others (e.g., doctor's office), florid ROS, vague somatic sx c/w somatization, coexisting poorly defined dx (e.g., fibromyalgia, chronic pain, fatigue), depression, anxiety, inappropriate affect/lack of concern ("la belle indifference"), inducibility by suggestion.

Semiology suggestive of PNES: Side-to-side head shaking, b/l asynchronous

mvmts (e.g., bicycling), crying, moaning, stuttering, back arching, pelvic thrusting, ?stuffed animals ("teddy bear sign"), eye closing, prolonged spells (10-30 min), maintained consciousness despite generalized motor involvement; waxing & waning pattern rather than clear beginning/mid/end.

P.59

Features against PNES: Arise during verified sleep, injuries sustained during spells, tongue laceration (especially sides of tongue), incontinence, postictal confusion.

Dx: Often difficult by history/exam alone; requires LTM/VEEG. Provocation (e.g., suggestion, hyperventilation, photic stim, saline injection) useful, but ethically controversial.

Rx: Pt education, psychiatric mgt (psychotherapy, Rx of associated psych conditions).

Prognosis: Sx > 10 yr → >50% cont. to have PNES w/ sig disability. Better outcomes: Young onset, early dx, less dramatic features, no other somatoform c/o; limp or catatonic features (vs. thrashing). In children w/ PNES: Suspect ongoing sexual abuse, serious mood d/o.

PROVOKED SEIZURES: ETIOLOGIES

Etiology of Provoked Seizures

Primary neurologic d/os	Systemic d/os
Acute/subacute neurologic insult: Head trauma, meningitis/encephalitis, brain abscess, stroke, SAH, HIV encephalopathy, cerebral anoxia, hypertensive encephalopathy/PRES, eclampsia, neurosurgery	*Metabolic*: Hypoglycemia, hyperglycemia, hyperosmolar state, hyponatremia, hypocalcemia, hypomagnesemia, uremia, hepatic encephalopathy, porphyria, hyperthyroidism
Structural abnlities: Mass lesions, vascular malformations	*Drugs*: Overdose, withdrawal (EtOH, sedatives); others (see below)
Hyperthermia	*Sleep deprivation*
High fever: In children	

Drugs that Commonly Cause Seizures or ↓ Sz Threshold

Anticholinesterases	Cyclosporine, FK506

(organophosphates, physostigmine)	Hypoglycemic medications
Antidepressants (e.g., welbutrin)	Isoniazid
Analgesics (e.g., meperidine, tramadol)	General anesthetics (e.g., enflurane)
Antibiotics (e.g., FQs, TMP/SMX)	Methylxanthines (theophylline, aminophylline)
Antihistamines	Narcotics (fentanyl, meperidine, pentazocine, propoxyphene, tramadol)
Antipsychotics (phenothiazenes, butyrophenones, clozapine)	Penicillins (esp w/ renal failure)
Chemotherapy drugs (etoposide, ifosfamide, cisplatinum)	Phenylcyclidine, stimulants (amphetamines, cocaine, ephedrine, MDMA (ecstasy), phenylpropanolamine, terbutaline)
? Beta-blockers (propranolol, oxprenolol)	
Local anesthetics (bupivacaine, lidocaine, procaine, etidocaine)	

WORKUP OF FIRST SEIZURE

NOTE: For SE or impending status (sz >5 min or multiple sz w/o return to baseline) → proceed to the SE algorithm.

Clinical eval: HPI: Preceding illness/fever, trauma; aura, ictal & postictal phenomena (e.g., confusion, depression, aphasia, embarrassment, exhaustion, sleep, fear, HA, amnesia, nausea, pain, perceptual distortions, psychosis, thirst, weakness).

PMH/ROS: Early history (prenatal, birth, perinatal), febrile sz, milestones (motor, language), birthmarks/other congenital anomalies, myoclonic jerks, photosensitivity, prior szs, FHx sz, stroke, head trauma, CNS infxns, diurnal variation, relation to menses, triggers (e.g., emotion, exercise, loud music, flashing lights, television, fever, menses, sleep deprivation, coughing), injuries during sz, number of sz ED visits past yr, prior AEDs & why d/c'd, prior studies (EEG, LTM, CT, MRI, PET, SPECT). Gen exam: Skin exam for neuroectodermal d/os (e.g., NFT, tuberous sclerosis). Neuro exam: Focal abnlities (suggestive of underlying cause).

Tests: (1) Labs: chem7, LFTs, serum & urine tox screen, AED levels, UA, ESR, CRP, CXR. (2) Imaging: CT before LP if focal deficits, r/o space occupying lesion or acute hemorrhage. MRI preferable if nonurgent. (3) LP if: suspect meningitis/encephalitis; all HIV + pts; elderly; focal deficits. (4) MRI ± gado (r/o structural causes, e.g., tumor, stroke, infxn, AVM) (5) EEG w/in

24-48 h, or emergently if persistent MSΔ. (6) Prolactin level: ?utility. Does ↑ after GTCs & some focal szs, e.g., CPS of TL origin; can help distinguish GTC vs. psychogenic sz (if pretest prob GTC > 50%, then PPV > 90%, but low sens.) rise attenuated after repeated szs. Cannot distinguish sz vs. syncope (may rise after syncope, too). Draw 10-20 min & 6 h after event. + result: (level @ 20 min)/(level @ 6 h) > 2.

CLASSIFICATION: SEIZURE TYPE & EPILEPSY SYNDROMES

General principles: Prognosis & optimal Rx depends on characterization of sz type & epilepsy synd. Appropriate level of detail in characterization varies w/ clinical situation.

1. Simplified clinical epilepsy classification based on a few key distinctions (Mayo Clinic Proc 1996;71:405): Focal → lesional vs. nonlesional; if lesional: TL vs. non-TL. Generalized: Symptomatic vs. idiopathic; specific synd. or dz.

2. Current Official ILAE epilepsy classification system (1989).

3. New (2001) scheme by ILAE Task Force on Classification & Terminology. Not officially adopted yet (Epilepsia 2001:42:796-803). Characterizes epilepsy along five "axes."

Axis 1. Ictal phenomenology—describe sz using terms in tables A1. (1-2).

Axis 2. Sz type (& localization). Adapted from current ILAE sz classification (1981).

Axis 3. Epilepsy syndrome (see next section for details about common syndromes).

Axis 4. Etiology (specific dz causing the epilepsy, if identifiable).

Axis 5. Degree of disability (e.g., based on WHO ICIDH-2 criteria)—optional.

Detailed info on epilepsy syndromes on ILAE web site: http://www.ilae-epilepsy.org Next subsections = aids for characterizing/localizing/classifying, organized around these Axes.

AXIS I: ICTAL PHENOMENOLOGY

Descriptive Terminology for Seizures (Table A1.1)

Predominant	Subtype	Examples

Feature		
Motor	Elementary	Tonic (epileptic spasm, postural, versive, dystonic), myoclonic (negative myoclonic, clonic, Jacksonian), tonic-clonic, atonic, astatic
	Automatism	Oralimentary, mimetic, manual, gestural, hyperkinetic, hypokinetic, dyphasic, dyspraxic, gelastic, dacrystic, vocal, verbal (see next table)
Nonmotor		
Sensory	Elementary	Somatosensory, visual, auditory, olfactory, gustatory, epigastric, cephalic, autonomic
	Experiential	Affective, mnemonic, hallucinatory, illusory
Dyscognitive		Perception, attention, executive function
Autonomic	Aura	Cardiovascular, GI, sweating, vasomotor
	Seizure	Cardiac arrhythmia, ictal vomiting
Somatotopy	Laterality	Unilateral, hemilateral, generalized, asymmetric, symmetric
Timing	Incidence	Regular, irregular, cluster, triggers, reactive, reflex
	State	Wakefulness, sleep, upon awakening

Duration	Self-limited, SE
Severity	Benign, severe
Prodrome	
Postictal phenomenon	Todd's phenomenon, lateralizing, nonlateralizing, impaired cognition, amnesia (antegrade, retrograde), psychosis

(Adapted from Continuum, *Epilepsy* 2007;13(4), Chapter 1.)

Common Automatisms (Table A1.2)

Oralimentary	Lip smacking, tongue mvmts, chewing, swallowing, teeth grinding
Mimetic	Acting out emotional state
Manual, pedal	Fumbling, tapping, grasping mvmts
Gestural	Movement, often in response to external stimuli
Ambulatory	Wandering, walking, running
Vocal	Single or repetitive utterances (not words)
Verbal	Single or repetitive words or sentences
Hypokinetic	Behavioral arrest, motionless limbs
Hyperkinetic	Large amplitude mvmts or proximal limbs or trunk, e.g., pedaling thrashing, rocking, pelvic thrusting
Gelastic	Bursts of laughter w/o mirth

Dacrystic	Bursts of crying w/o sadness

(Adapted from Continuum, *Epilepsy* 2007;13(4), Chapter 1.)

P.61

AXIS 2: SEIZURE TYPES

ILAE official classification (1981): Based on two dichotomies: (1) ± LOC, (2) ± altered consciousness (AMS): (1) +LOC → generalized sz. - LOC → partial (focal) sz. (2) For focal szs: +AMS → complex partial sz (CPS); -AMS → SPS.

SPS (includes sz auras): Altered perception (e.g., of body size, sounds, space, time), spontaneous experiences/sensations (Déjà-vu, Jamais-vu, psychic intuitions, out of body, racing thoughts, electric shocks, “tightness,” tingling, vertigo, lightheadedness), autonomic sx (flushing, pallor, tachycardia, sweating, incontinence), noises (grunting, crying out), labored breathing, chewing, drooling, stomping, running, pacing, shaking, eye fluttering, eye rolling, falling, hand waving, lip smacking, stiffening, dysphasia, teeth clenching/grinding, inability to move, incontinence (many of these sx more commonly occur w/ some alteration in consciousness).

CPS (aka psychomotor sz if automatisms): Awake but not (or less) responsive or interactive. Black outs, confusion; common behaviors: staring, automatisms (grimacing, chewing, lip smacking, finger snapping, repeating words/phrases, walking, running, undressing, hostility). Often preceded by SPS, which would then constitute the aura. Many of the sx listed for SPS sx also occur w/ altered consciousness.

Generalized seizures

Absence: Children >> adults; 5-10 secs; often clusters, 10-100s/day, esp w/ childhood onset; p/w staring, impaired consciousness. If >10 s, often +eye blinking, lip smacking.

GTCs (aka grand mal sz, major motor sz, convulsion): Classically: scream/shriek → abrupt LOC → arms, legs, torso stiffen (lasts <1 min) → jerking + twitching 1/2-1 min, ± tongue biting, incontinence → postictal (deep sleep, gradual wakening, ± HA lasting minutes-hours).

Clonic: Rhythmic jerking of arms, neck, face.

Myoclonic: Sudden brief muscle contractions, consciousness usually intact or untestable.

Tonic: Sudden stiffening, often a/w AMS & falling to the ground; often arise from sleep.

Atonic (aka drop attacks): Sudden loss of muscle control → collapse, often w/ injuries.

Typical Ictal Clinical & EEG Features by Seizure T (Table A2.1)

Sz Type	Duration	LC	Clinical Features	PC	Ty EEG
Simple partial	5-30 secs	−	Motor; psychic; somatosensory; special sensory; autonomic	−	Fo spikes, rhythmi be nl
Complex partial	1-3 min	+	Often follows SPS; staring; unawareness, automatisms	+	Fo rhythmi → 1 or hemispl
Secondarily GTC	1-2 min after start of generalization	+	Onset = SPS or CPS; head version; asymm tonic posture; generalized clonus	+	Fo rhythmi spreads hemispl obscure rhythmi
Primary GTC	1-2 min	+	Sudden LOC; ictal cry; tonic phase; clonic phase	+	Lo voltage rhythmi high-an then rh artifact
Typical	5-10 secs	+	Staring;	−	Ge

absence			eyelid fluttering		spike-&
Atypical absence	15-45 secs or longer	+	Staring, clonus; myoclonus; atonic; confusion	+	Ge Hz spik wave
Myoclonic	< 1-2 secs	+	Generalized rapid jerks of limbs	−	Ge polyspi wave
Tonic	5-20 secs	+	Sustained posture of limbs	±	Pa low-am activity
Atonic	5-10 secs or longer	±	Sudden loss of tone	±	Va

(PC = postictal confusion, LC = loss of consciousness. Adapted from Continuum, *Epilepsy* 2007; 13(4), Chapter 1.)

Seizure Types—New Proposed ILAE Classification (2001)—abbreviated

Self-limited types: (1) Focal: Focal sensory (elementary or experiential); focal motor (elementary clonic motor; asymmetrical tonic motor, “typical” automatisms; hyperkinetic automatisms; focal negative myoclonus; inhibitory motor); gelastic;

hemiclonic; secondarily generalized; reflex szs. (2) Generalized: Tonic-clonic, tonic, clonic, typical absence, atypical absence, myoclonic, myoclonic absence, massive b/l myoclonus, spasms, eyelid myoclonia, myoclonic atonic, negative myoclonic, atonic, reflex szs.

Continuous types: (1) Focal SE: Epilepsia partialis continua of Kojevnikov; aura continua; limbic SE (“psychomotor status”); hemiconvulsive status w/ hemiparesis. (2) Generalized SE: GTC SE, clonic SE, absence SE, tonic SE, myoclonic SE.

Lateralizing & Localizing Ictal Features (Table

A2.2)

Ictal feature	Laterality	Localization[a]
Eye deviation	c/l in FL sz c/l or i/l in OL sz	FL, OL
Early unforced head turn	i/l	TL
Late forced head turn	c/l	FL or SGTC of any origin
Focal clonus	c/l	FL
Dystonic limb	c/l	TL (→BG)
Tonic limb	c/l	FL
Motionless limb	c/l	TL, FL
Asymmetric tonic, fencing posture	c/l	FL, SMA
Figure 4 sign	c/l to ext. limb	SMA, PFG, SGCTS of any origin
Oralimentary automatisms		TL
Limb automatisms	i/l	TL
Hyperkinetic automatisms	—	FL
Pedaling, bicycling	—	FL

Speech arrest	Dom hemisphere	TL, FL
Postictal features		
Todd paralysis	c/l	FL, PL > TL
Nose wiping	i/l	TL
Aphasia	Dom hemisphere	Language areas
Confusion	—	TL > FL

[a] At the time when the sign appears.

(SMA = supplementary motor cortex; PFG = prefrontal gyrus. Adapted from Continuum, *Epilepsy* 2007;13(4), Chapter 1.)

Typical Features of Focal Seizures by Region of Onset (Table A2.3)

Temporal lobe

Mesial TL: Aura (e.g., epigastric, psychic, affective, olfactory); impaired consciousness; fixed stare; early oralimentary automatisms; limb automatisms (b/l or i/l to focus); dystonic posturing; postictal confusion & amnesia.

Lateral TL: Aura, e.g., Hallucinations (auditory, complex perceptual or experiential), language dysfxn; Late oralimentary automatisms; Late manifestations ≈ mesial TL.

Frontal lobe

Brief, often in clusters; little or no postictal confusion; rapid generalization; motor si/sx (clonic, tonic, postural); hyperkinetic complex or bizarre automatisms; sexual automatisms; frequent falls; nocturnal predominance; SE.

Occipital lobe

Elementary visual

Parietal lobe

Somatosensory auras; receptive

hallucinations, especially in c/l hemifield; blindness; sensation of eye movement; eye deviation (c/l or i/l); forced blinking; variable spread to: PL (sensory sx), TL/OL (formed visual hallucinations), mesial TL.	aphasia (dom hem); neglect (nondominant hem); variable spread to: OL (visual hallucination), mesial TL, precentral regions (motor).

(Adapted from Continuum, *Epilepsy* 2007;13(4), Chapter 1.)

AXIS 3: EPILEPSY SYNDROME

ILAE official epilepsy classification (1989): See Epilepsia 1989;20(4):389-399.

New ILAE epilepsy syndrome classification (2001). Has not yet officially replaced 1989 classification scheme. See Epilepsia 2001;42:796-803. Largely the

domain of pediatric neurology. Details of common epilepsy syndromes are covered in the next section.

AXIS 4: EPILEPSY ETIOLOGIES

Diseases commonly a/w epilepsy (not exhaustive; see Epilepsia 2001;42:796-803) (1) Progressive myoclonic epilepsies: Ceroid lipofuscinosis, sialidosis, Lafora dz, Unverricht-Lundborg dz, neuroaxonal dystrophy, MERRF, dentatorubropallidoluysian atrophy. (2) Neurocutaneous d/os: Tuberous sclerosis complex, neurofibromatosis, hypomelanosis of Ito, epidermal nevus synd., Sturge-Weber synd. (3) Cortical malformations: Isolated lissencephaly sequence, Miller-Dieker synd., X-linked lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, focal heterotopia, hemimegalencephaly, bilateral perisylvian synd., unilateral polymicrogyria, schizencephalies, focal or multifocal cortical dysplasia, microdysgenesis. (4) Other cerebral malformations: Aicardi synd., PEHO synd., acrocallosal synd. (5) Tumors: DNET, gangliocytoma, ganglioglioma, cavernous angiomas, astrocytomas, hypothalamic hamartoma (esp w/ gelastic szs). (6) Chromosomal abnlities: Partial monosomy 4P or Wolf-Hirschorn synd., trisomy 12p, inversion duplication 15 synd., ring 20 chromosome. (7) Monogenic mendelian dzs: Fragile X synd., Angelman synd, Rett synd. (8) Inherited metabolic d/os: Nonketotic hyperglycinemia, D-glyceric acidemia, propionic acidemia, sulphite-oxidase def, fructose 1-6 diphosphatase def, other organic acidurias, pyridoxine dependency aminoacidopathies (e.g., maple syrup urine dz, phenylketonuria), urea cycle d/os, d/os of carbohydrate

metabolism, d/os of biotin metabolism, d/os of folic acid & B_{12} metabolism, glucose transport protein def, Menkes dz, glycogen storage d/os, Krabbe dz, fumarase def, peroxisomal d/os, Sanfilippo synd, mitochondrial dzs [pyruvate dehydrogenase def (PDH), respiratory chain defects, MELAS]. (9) Pre/perinatal insults (anoxia/ischemia/infxn): Porencephaly, periventricular leukomalasia, microcephaly, cerebral calcifications & other lesions 2/2 Toxo, HIV, etc. (10) Postnatal infxn: Cysticercosis, HSV, bacterial meningitis. (11) Other postnatal inuries: Head injury, alcohol & drug abuse, stroke. (12) Misc: Celiac dz (epilepsy w/ occipital calcifications & celiac dz), northern epilepsy synd, Coffin-Lowry synd, Alzheimer dz, Huntington's dz, Alpers dz.

EPILEPSY SYNDROMES

Largely synonymous w/ "pediatric epilepsy," but many survive into adulthood.

Relevance: >50% epilepsy begins in childhood. Some sz types virtually unique to childhood (e.g., absences, myoclonic szs), exclusively during specific neurodevelopmental stage (e.g., infantile spasms), & often have genetic underpinning.

Epilepsy syndromes are defined by: sz type, age at onset, gender predominance, etiology [idiopathic/genetic, symptomatic, cryptogenic (cause suspected but not found), associated developmental delay, diurnal variability, precipitating factors (sleep deprivation, photic stimulation)], severity, family history, developmental prognosis & epilepsy outcome. Syndrome identification has implications for management, prognosis, research, genetics.

FOCAL (PARTIAL, LOCALIZATION RELATED)—IDIOPATHIC

BNC: Benign (idiopathic) neonatal convulsions (fifth day fits) (Epilepsia 2002;43(S3):2-10). Prev: Rare, <1% of pediatric epilepsy. Onset: Day 1-7 (most Day 5). Sz type: Brief, 1-3 min. Partial clonic, partial tonic, or subtle (e.g., apnea). May start on one side, then affect other side. Often repeated or clustering, leading to SE. EEG: Interictal nl or asynchronous rhythmic theta "theta pointu alternant," ictal rhythmic sharp or slow waves, or spikes. Rx: PB PHT, BDZ. Prognosis: Excellent. Remission after 24-48 h. Dx often after resolution & nl outcome. Some data suggests mild developmental deficits in 50% cases, ↑ risk epilepsy later. Cause: Hypotheses include Zn def., rotavirus. ↓ Freq in recent years, no case-series reported since 1990s.

BECTS: Benign Childhood Epilepsy w/ Centro-Temporal Spikes (Rolandic Epilepsy, or Benign Rolandic Epilepsy of Childhood, BREC) (Epilepsia 1998;39(S4):S32-S41). Prev: Most common childhood epilepsy, 10%-15%. Onset: 3-13 (peak 7-9) yr. Sz type: Nocturnal, u/l, tongue, lips, cheek, larynx, pharynx (anarthria), occasionally arm, preserved consciousness. May

generalize during sleep. Sensory aura common but underreported. EEG: Interictal u/l or b/l centrotemporal triphasic spikes w/ horizontal ant-post dipole, prominent sleep activation, nl background. Rx: OXC, CBZ, LTG, TPM, GZP, LEV. Prognosis: Excellent, szs remit by puberty. May be frequent initially. Consider no Rx if infrequent, nocturnal or partial only. May have learning & behavioral difficulties, in part related to frequency of interictal discharges. Atypical

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BECTS a/w language & developmental delay. Genetic etiology suspected. EEG pattern fxns as biomarker, is inherited aut dom w/ age-related penetrance.

Panayiotopoulos (Early onset) Benign Childhood Occipital Epilepsy; Panayiotopoulos syndrome (Pediatrics 2006;118:1237-1243). Prev: Reported to be common, 6%. Onset: 1-13 (peak 3-6) yr. Sz type: Long (30+ min), mainly autonomic szs/status, often from sleep: (1) feeling sick, HA, pale, vomiting, pallor, flushing, cyanosis, eye-deviation, mydriasis, cardio- & thermoregulatory sensations, incontinence, hypersalivation, ictal syncope (unresponsive, limp). Next may have (2) complex-partial features and/or (hemi)clonic convulsions, brief. EEG: Multifocal spike-&-wave, rolandic morphology, w/ occipital predominance (but absent or not occipital predominant in 33%). Rx: As in rolandic. Some need rectal DZP only. Prognosis: Better defined than Gastaut-type (see below). Benign prognosis despite autonomic status even if frequent szs. Remission <2 yr. Most have infrequent szs, 25% have only 1, 50% have <5. No ↑ risk of epilepsy in adulthood. Misdx is common, ddx includes migraine, GI (gastritis, cyclic vomiting, abdominal migraine), syncope, sleep d/o. Cardiac arrest described, but is rare.

Gastaut: (Late onset) Idiopathic Benign Childhood Occipital Epilepsy (Brain 2008;131:2264). Prev: Rare, <1%-2%. Onset: 3-16 (peak 8) yr. Sz type: Brief, seconds-2 min. Frequent, many ×/day in awake pt. Visual SPSs: Wide range (blindness, colored luminous discs, formed visual hallucinations). Eye-deviation, eyelid flutter & postictal HA 50% & vomiting 5%. EEG: High amplitude spike-&-wave occipital discharges w/ eyes closed or during sleep. Ictal: Fast, occipital spikes. Rx: As in rolandic. Prognosis: Overall, rare & less well-defined synd. w/ no typical sz type & no clearly defined clinical course. “Idiopathic” is speculative as genetic etiology is not proven. Frequency, nature, & brevity of the visual symptoms help distinguish from the visual aura of migraine. Fair prognosis—60% remit w/in few years. Migraines in 20%, FHx(+) epilepsy in 50%.

FOCAL (PARTIAL, LOCALIZATION RELATED)—FAMILIAL (AUT.

DOM.)

BNFC: Benign Neonatal Familial Convulsions (Ann Neurol 1991;29:469-473). Prev: Unknown; rare. Onset: Day 2-7, but can be up to 3 mo. Sz type: Focal tonic & clonic, “officially” still categorized as generalized (new classification not adopted yet). EEG: Interictal EEG nl. Ictal: Generalized flattening → generalized spike-&-wave or focal discharges. Rx: PB. Prognosis: Spont remission by 2-3 mo. Nl neuro exam. Aut dom defect in voltage gated potassium channel KCNQ1, 2, 3 w/ incomplete penetrance. Later childhood epilepsy 11%-16%.

Benign infantile (non-)familial szs (J Child Neurol 2002;17:696-699). Prev: Rare, < 1%. Onset: <2 yr. Sz type: Behavioral arrest w/ staring → focal clonic, focal tonic, or secondarily GTC. May cluster. EEG: Interictal nl, ictal w/focal discharges, may generalize. Rx: VPA, CBZ, PB. Prognosis: Sporadic, in some cases familial. Good response to Rx, good neuro outcome. Some are a/w familial paroxysmal choreoathetosis.

ADNFLE: Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (Brain 1999;122:1017). Prev: Rare. Onset: 0-50 yr (85% <25, mean 12, median 8). Sz type: Frequent (multiple/night), very stereotyped, brief, sudden onset & end, during non-REM sleep stage II: arousal w/ complex, bizarre motor/other behaviors & automatisms including (dys-)tonic posturing & hypermotor activity (e.g., leg pedaling); no postictal phase, may have daytime szs. Often (partially) preserved awareness. EEG: Routine EEG is nl, rarely frontal epileptiform or nonspecific abnlities. Ictal inpatient video-EEG: rapid rhythmic frontal epileptiform abnlities. Rx: CBZ, OXC, LTG, TPM. Prognosis: Challenging electroclinical dx. Aut dom w/ high degree of penetrance. Different mutations in several genes 20q13.2, 1p21 (nicotinic acetylcholine receptor → Δ in presynaptic NT release), but all w/ similar phenotype. Sleep deprivation & stress worsen/precipitate szs. Behavioral problems common until sz control. Overlap w/ paroxysmal nocturnal dystonia.

ADLTE, FMTLE: Familial Temporal Lobe Epilepsy (Epilepsia 2009;50(S5):52-54, & 55-57). Prev: Rare, <1%. Onset: 1-60 yr, peak 15-19. Sz types: SPS &/or CPS. Mesial: Psychic (déjà vu) & autonomic. Lateral: Auditory auras, may be triggered by noises. Secondary generalization more common in mesial form. EEG: Interictal: Nl or w/ focal slow waves or epileptiform abnlities over temporal regions. Rx: CBZ, OXC, LTG, TPM. Prognosis/comments: Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTE): Nl conventional MRI, good response to AEDs, & overall benign outcome. Same phenotype shared by sporadic & familial cases w/ complex inheritance. Mutations in LGI1 gene, function unknown. Familial Mesial

Temporal Lobe Epilepsy (FMTLE): More heterogeneous phenotypes w/ mild to severe epilepsy & variable assn w/ hippocampal sclerosis & febrile szs. Genetics unclear.

FOCAL (PARTIAL, LOCALIZATION RELATED)—(PROBABLY) SYMPTOMATIC

MTS: Mesial Temporal Sclerosis (Curr Opin Neurol 2004;17:161). Prev: Uncommon (1%-5%). Prev: Childhood-adolescence. Onset: CPS 1-2 min; oral, hand, verbal automatisms w/ semi-purposeful behavior & ↓ responsiveness, ± secondary generalization. Common auras: rising epigastric sensation, derealization, déjà vu. EEG: U/l or b/l ant. to midtemp. spikes, Ictal pattern: 5-9 Hz temporal sharp waves. May need depth electrodes. Rx: CBZ, TPM, LTG, LEV. Prognosis: Initial recurrent/prolonged febrile szs @ 0-4 yr as a cause or consequence of MTS. MRI w/ MTS; children have higher proportion dysplasia & low grade glioma. 60% fair control w/ AEDs, surgery (ant TL, selective amygdalohippocampectomy) w/ >75% excellent outcome. Progressive behavioral & memory dysfunction common.

Rasmussen (Chronic progressive epilepsia partialis continua of childhood) (Pediatr Neurol 2005;32:295). Prev: Rare, <1%. Onset: <10 yr. Sz type: Progressive & intractable focal szs, hemiparesis, expressive aphasia (when L hemispheric). Szs remain (multi-)focal & u/l; epilepsia partialis continua is common. EEG: Very freq focal fronto- & midtemporal epileptiform discharges w/ focal slowing → widespread slowing. Rx: Any. Prognosis: Originally “chronic viral encephalitis,” now considered “progressive autoimmune multifocal encephalopathy.” Clinical dx, MRI w/ progressive (initially peri-insular) atrophy & gliosis, neither abs to Glu-R3 nor cortical bx helpful. Natural course w/ slowly progressive hemiparesis, hemianopia, MR, & cortical atrophy. Steroids, immunoglobulins, plasmapheresis: only temporary relief. Early hemispherectomy unequivocally improves outcome.

HHE: Hemiconvulsion Hemiplegia-Epilepsy syndrome (Neurology 2008;70: 2116). Prev: Very rare, << 1%. Onset: 0-4 yr. Sz type: Initial prolonged hemiclonic szs → hemiparesis of variable duration (may be permanent). Several years later CPS from TL. EEG: Ictal pattern w/ 2-3 Hz b/l slow waves, u/l fast ictal discharges. Later EEG as in MTS. Rx: Hemiconvulsions: See status epilepticus Rx. Prognosis: Hemiclonic convulsions provoked by fever. Later uni → b/l atrophy similar but worse than MTS. Historically poor neurodevelopmental outcome but now increasingly rare w/ better Rx of prolonged febrile szs & (febrile) SE. Etiology: Idiopathic (fever) or symptomatic (trauma, vascular, infxn).

MMPEI: Malignant Migrating Partial Epilepsy of Infancy (Epilepsia 2009;50 (S5):49). Prev: Very rare, << 1%. Onset: <6 mo. Sz type: Evolves, three phases: 1. Sporadic focal szs w/ rapid secondary generalization & autonomic phenomena (weeksmonths). 2. (Months to years), near-continuous or clustering focal polymorphic szs, variable semiology depending on location. Frequent status & subclinical szs warrant prolonged inpt VEEGs. 3. Prolonged sz free intervals w/ occasional breakthrough. EEG: First phase: Multifocal spikes, migratory focal slowing. Second phase: Migrating & expanding focal discharges, complicated multifocal EEG w/ near-merger of ictal & interictal patterns. Rx: Combinations of multiple AEDs. Prognosis: Malignant epilepsy synd. Usu very AED-resistant. KGD variable success. Outcome: Severe progressive deterioration of psychomotor development, microcephaly, MR, some mortality. Based on age, can be placed b/n EME, EIEE, & IS. MRI typically neg. w/ later atrophy. Some w/ MTS. Extensive neurometabolic w/u typically neg. No identified genetic cause to date.

GENERALIZED EPILEPSIES (IDIOPATHIC)

BMEI: Benign Myoclonic Epilepsy of Infancy (Epilepsia 2006;47(S5):31) Prev: Rare, <1%. Onset: 3 mo-4 yr. Sz type: Brief generalized myoclonic, mainly head & upper body; awake, on falling asleep, or during slow wave sleep. Multiple daily in isolation or clustering, some subtle. EEG: Generalized (poly-)spike (& wave); nl interictal EEG. Rx: VPA, BDZ, LTG. Prognosis: Nl neuro outcome (though reportedly some w/ developmental delay). Reflex form is common variant w/ excessive sleep startle, photosensitivity, earlier onset, & good outcome. Other idiopathic generalized epilepsies (IGEs) may occur in adolescence.

EMAS: Epilepsy w/ Myoclonic Astatic Szs, Myoclonic Astatic Epilepsy (Doose) (J Clin Neurophysiol 2003;20:449). Prev: Uncommon, 1%-5%. Onset: 7 mo-6 yr. Sz types: Primarily generalized myoclonic, astatic, or myoclonic-astatic szs → falls; short absences, GTCs, nonconvulsive SE (NCSE); no tonic szs or tonic drop attacks during daytime. EEG: Generalized EEG patterns [(poly-)spike & wave, photosensitivity, 2-3/s rhythms], no multifocal abnlities (may have pseudofoci). Rx: VPA, ESM, BDZ, LTG, TPM, LEV. Dx criteria: (1) Szs as above. (2) Genetic predisposition (high incidence of szs & /or genetic EEG patterns in relatives 15%-40%). (3) Nl development & neurol exam prior to onset. (4) EEG as above. (5) Exclusion of SMEI, BMEI, LGS. Differences from

LGS: In Doose myoclonic predominant type, genetic basis, outcome usu better, but variable—at times fair w/ sz good control & (near-)nl cognition.

CAE: Childhood Absence Epilepsy, pykno-lepsy, petit mal (Paediatr Drugs 2001;3:379). Prev: Common, 5%-12%. Onset: School age (peak 6-7 yr). Sz types: Several to innumerable absences/day, 5-15 s. Degree of impaired consciousness highly variable. ± motor: (facial myoclonic, tonic, & atonic components alone or in combination), automatisms & autonomic si/sx. Hyperventilation provokes sz in 90% (office-dx). ± FHx IGE. EEG: (Inter-)ictal 3-4 Hz generalized (poly-)spike & wave, nl background. Rx: ESM, VPA, LTG. Prognosis: Typically neurologically nl. Not always "benign": Only 60% respond to first AED, prominent life-long (cognitive and) learning disabilities, 15% develop JME, may affect long-term psychosocial outcome.

JAE: Juvenile Absence Epilepsy (Paediatr Drugs 2001;3:379). Prev: Less common than CAE. Onset: 7-16, peak 10-12 yr. Sz types: Typical absences as above, longer, less frequent, less severe. Often can perform relatively complicated tasks but usually cannot speak. Also GTCs (awakening), & myoclonic jerks. EEG: Mildly faster than CAE: Generalized 2.5-4.5 Hz (poly-)spike & wave, but EEG does not differentiate. Rx: See "CAE." Prognosis: Overlap synd. between CAE & JME. Prognosis not as favorable, life-long d/o although absences may become less severe. EEG may show asymmetry, & partially preserved awareness may lead to false dx of CPS, & wrong Rx, e.g., CBZ will aggravate JAE.

JME: Juvenile Myoclonic Epilepsy, Impulsive Petit Mal (Janz) (Pediatr Drugs 2006;8:303). Prev: Common, 5%-11%. Onset: 8-26, peak 12-16 yr. Sz types: B/l, single or multiple myoclonic szs, predom in arms, esp on awakening. GTCs in 90%, JAE-type absences in 10%-30%. EEG: Generalized (poly-)spike-&-wave 3-6 Hz. Photosensitivity in 40%-70%. Rx: VPA, LTG, BDZ, TPM, LEV. Prognosis: Sz-precipitating factors (sleep deprivation, fatigue, alcohol, photosensitivity, stress). Genetics: See reference. Absences can appear during childhood → myoclonic jerks & GTCs in mid-teens. Life-long; milder in 3rd-4th decade but withdrawal of AEDs → recurrence. 70% control w/VPA. Avoid PHT, CBZ: aggravation.

GEFS+: Generalized Epilepsy w/ Febrile Szs Plus (Lancet Neurol 2004;3:421). Prev: Common, >5%. Sz types: Febrile szs <5 yr, others in later childhood. Marked phenotypic diversity: Typical febrile szs in early childhood. GTC, absence, myoclonic, (a)tonic, partial motor or continuing brief, generalized febrile szs follow. EEG: Nl or as in IGEs: generalized epileptiform discharges. Rx: Standard AEDs ˜ on sz type. Prognosis: Aut dom w/ incomplete penetrance 70%-80%. SCN1A, SCN2A, SCN1B, & GABRG2 gene mutations. Strong FHx w/ variable phenotypes, including partial szs ˜15%. Outcome ranges from remission at 10-12 yr to ongoing refractory epilepsy.

MAE: (Tassinari) Myoclonic Absence Epilepsy: Ictal 3 Hz myoclonus w/ arms “ratcheting” upward. Usually a/w MR. AED-resistant. (Epilepsia 2002;43(S3):27).

EMA: (Jeavons) Epilepsy w/ Myoclonic Absences: Marked ictal eyelid & more subtle facial or upper arm jerking. AD inheritance. AED-resistant (Epilepsia 2002;43 (S3):27).

MAE: Micturational Absence Epilepsy: Ictal detrusor contraction w/ urination. May be AED-resistant. Prominent social implications (Epilepsia 2002;43(S3):27).

EGTCA: Epilepsy w/ GTCs on Awakening: GTCs soon after awakening or when relaxing. Aberrant wake-sleep cycle; unstable sleep (Clin Neurophysiol 2000; 111 (S2):S103).

EGTCO: Epilepsy w/ GTCs Only: Broadly defined—includes random & nocturnal GTCs. Typically no absences & myoclonic szs (Epilepsia 2008;49:2050-62).

EPILEPTIC ENCEPHALOPATHIES

EME: Early Myoclonic Encephalopathy (Epilepsy Res 2006;70S:S58). Prev: Rare, <1%. Onset: Neonatal period. Sz types: Fragmentary (segmental, erratic) myoclonic, generalized myoclonic & partial motor; evolves into IS (transient) w/ atypical hypsarrhythmia, but may persist into late childhood. EEG: Suppression-burst: Bursts of spike & sharp waves alternate w/ periods of voltage attenuation, more clearly in sleep. Rx: Steroids, BZD, VPA, VGB, KGD. Prognosis: Malignant epilepsy syndrome. Poor neuro outcome 100%, mortality 50% <1 yr. Nonstructural, metabolic disorders common (e.g., NKH). Later atrophy & delayed myelination on MRI. Ddx: EIEE occurs in first months, tonic szs main type, EEG has longer bursts & brain malformations are common, earlier transition to IS & LGS.

EIEE: (Ohtahara) Early Infantile Epileptic Encephalopathy (Epilepsy Res 2006;70S:S58) Prev: Rare, <1%. Onset: (Early) neonatal to first months. Sz types: Tonic szs main type, occur during wake, sleep & do not typically cluster. Also partial motor, erratic focal motor szs, hemiconvulsions, GTCs. EEG: Suppression-burst (see above),

but during wake & sleep, longer bursts. Rx: Same as EME. Prognosis: Malignant epilepsy synd.: Poor outcome in most. Structural brain abnlities from encephaloclastic events, cerebral dysgenesis, even in cryptogenic cases; rarely metabolic EIEE is considered a chronic static encephalopathy.

IS: (West) Infantile Spams (Pediatr Neurol 2006;34:253). Prev: Uncommon, 1%-5%. Onset: 3-14 mo (peak 4-9). Sz types: Brief tonic or clonic spasms, typically clustering, many times daily (on arousal). Flexor (arms, neck)-and-extensor (legs), or flexor (jack-knife) or extensor. Can be subtle, e.g., head nod only. 50%-60% have szs in later life, mainly LGS. EEG: Disorganized high-voltage multifocal polymorphic slowing w/ interspersed epileptiform discharges. Initially may be during (light) sleep only. Ictal generalized high voltage slow wave w/ electro-decrement or diffuse fast beta-range activity. Rx: Steroids, VGB, TPM, vit B_6, LTG, BZD, KGD. Dx/prognosis: Triad of clusters of spasms, psychomotor arrest & deterioration & EEG w/hypsarrhythmia. >85%-95% symptomatic: Prenatal, perinatal, & postnatal insults—e.g., hypoxic ischemic injury, perinatal infections, tuberous sclerosis, cerebral malformations & dysgenesis, chromosomal (trisomy 21, del1p36), gene mutations (ARX, STK9), metabolic (untreated PKU, tetrahydrobiopterine def, Menkes), & mitochondrial (NARP mutation). Poor prognosis, rarely good outcome w/ cryptogenic etiology ˜5%.

SMEI: (Dravet) Severe Myoclonic Epilepsy of Infancy (Some related syndromes w/ different phenotypes, see ref: Brain Dev 2009;31:394). Prev: Rare, <1%. Onset: First yr or life, peak 3-8 mo. Sz types: Prolonged febrile sz (or status), next recurrent 1-2/mo generalized & alternating u/l clonic or tonic-clonic szs, often prolonged & w/fever. Later myoclonic, atypical absence, CPS, atonic, & u/l szs, NCSE. Tonic szs rare. EEG: Generalized spike-and-wave complexes, focal & multifocal spikes. Massive myoclonias = bursts of irregular spike-and-waves; erratic myoclonias = No EEG Δ. Atypical absences = generalized 2-3.5 Hz irregular spike-waves. Rx: Refractory to most AEDs. LTG & CBZ worsen. Prognosis: Malignant epilepsy synd. Hallmark: Recurrent febrile hemiclonic SE b/n 6-12 mo, w/developmental arrest after age 1 & regression & recurrent status. Early control may lead to better neuro outcome. FHx(+) (febrile) szs in 25%. MRI nl initially; later —> hippocampal sclerosis. SCN1A (& GABRG2) mutations in >70%. MRI nl & later w/ nonspecific atrophy & gliotic changes, hippocampal atrophy.

LGS: Lennox-Gastaut Syndrome (Lancet Neurol 2009;8:82) Prev: Uncommon, 1%-5%. Onset: <8 yr, peak 3-6 yr. Sz types: Tonic szs (required for dx, but not at onset; > in sleep), variable severity & semiology. Atypical absences (gradual onset & ending), (a)tonic drop-attacks (>50%; → injury), ± preceded by myoclonus, (non-) convulsive status 50%-70%, myoclonic, & others. ≥20% preceded by IS. EEG: Wake: Bursts of diffuse slow 1-2.5 Hz spike-&-wave. Sleep: Bursts of diffuse or b/l fast rhythms ≥10 Hz or “polyspikes” (generalized paroxysmal fast activity). Ictal: Tonic diffuse fast bursts, atypical absence 1-1.5 Hz spike-&-slow-waves, atonic or myoclonic diffuse spikes or polys-pike & slow waves. Rx: (1) Nonpharmacological mgt:

epilepsy surgery (callosotomy, VNS, others), KGD. (2) AEDs: LTG, TPM, FBM, RUF, VPA, BZD, ZNS, LEV (but refractory to most AEDs). (3) Steroids. (4) Comorbid psych/behavioral d/o: Neuropsych & psychiatric assessment. (5) Monitor side effects (coordination, cognition, behavior, sz aggravation). Dx/prognosis: Triad of multiple sz types, typical EEG, cognitive impairment. Tonic szs (hallmark) not present at onset, EEG not pathognomonic. Progressive developmental delay, regression, often psychosis. Causes (see IS) heterogeneous: Cerebral malformation, tuberous sclerosis, in LGS less commonly acquired destructive lesions or metabolic dzs. Genetics less important.

ESES & CSWS: Electrical SE of Sleep & Continuous Spike & Wave during Slow Wave Sleep (Clin Neurophysiol 2000; 111(S2):S94). Prev: Rare, <1%. Onset: 5-7 yr, peak 4-5 yr. Sz types: Severity & frequency of szs may worsen over time. Formerly rare, mostly nocturnal, partial motor or secondarily GTCs, may get focal &/or (apparently) generalized szs: U/l or b/l clonic szs, GTCs, absences, partial motor szs, CPS, or epileptic drop attacks. Tonic szs never occur. EEG: Interictal, wake: Generalized spike & wave, may occur in bursts & have clinical accompaniment. Focal fronto- or centrotemporal spikes. Sleep: Continuous & diffuse paroxysms occupying >85% of slow wave sleep; not necessarily rhythmic. Rx: AEDs (“spike-suppressors”) e.g., VPA, LEV, ESM; steroids, IVIG, HD BZD, MST. Prognosis: Childhood-onset epileptic encephalopathy: age-specific d/o characterized by continuous spike activity in slow wave sleep a/w cognitive, memory, language, & behavioral decline. ESES more global regression than LKS, more refractory epilepsy, EEG foci located predominantly in frontotemporal or central regions. Early & aggressive Rx (beyond sz control) aiming to “clean up” EEG discharges → improved neuropsychological outcome. Prominent language, cognitive, behavioral, motor sequelae in ˜50%.

LKS: Landau-Kleffner Syndrome (infantile acquired aphasia) (Ment Retard Dev Disabil Res Rev 2004;10:144). Prev: Rare, <1%. Onset: 3-8 yr, range 2-10, peak 5-7. Sz types: Infrequent GTC or partial motor szs, preceded more often than followed by severe receptive & expressive language regression (w/ nl hearing/audiometry). EEG: Posterotemporal, parietooccipital or multifocal spike-&-wave discharges. Sleep: As above. Note: Secondary b/l synchrony underlies ESES; apparently generalized szs may in fact be focal onset. Prognosis: Acquired epileptic auditory agnosia, fewer szs than ESES (see above), posterotemporal EEG foci. Ddx: (1) Autistic regression → loss of socialization, restricted behavioral repertoire, loss of communication & language. If EEG(+) = “autistic regression w/ epileptiform EEG”: may be

LKS variant (controversial, differences in age of onset, clinical phenotype, & EEG findings). (2) w/ derailed (atypical) BECTS, or iatrogenic aggravation (CBZ) an epileptic encephalopathy can occur. (3) Rare secondary LKS (e.g., tumor).

ANTIEPILEPTIC DRUGS (AEDs)

General Considerations: Treat underlying causes (e.g., infxn, low AED levels, intox/withdrawal). Generally reserve AEDs for pts w/ underlying structural cause or idiopathic sz + SE on presentation, focal exam (incl. transient postictal Todd's paralysis), abnl EEG after sz, or >1 idiopathic sz. Start slowly (unless repeated szs), monitor based on side effect profile. Consider side effects, gender, comorbidities, age, other meds, $, avail. routes.

Effectiveness of AEDs (Neurology 2002;58(Suppl 5): S2-S8). % pts achieving sz freedom (in general—differs w/ specific dx): First monotherapy 47%; second monotherapy 13%; third monotherapy 1%; on two drugs 3%. Total sz free 64%.

Withdrawal of AED: 1 unprovoked sz → consider if no sz × 1 yr + EEG nl; if >1 unprovoked sz, wait for at least 2 yr + nl EEG. In pediatric Epilepsy: No straightforward correlation between (ab-)normal EEG and success of AED discontinuation. "Two years" arbitrary, ample data supports early withdrawal in certain easily controlled children (e.g. Epilepsia 2008;49(S9):25-28).

Decision to treat new onset szs: Risk-benefit analysis of three factors: (1) Risk of recurrence: Strong: Remote symptomatic cause, epileptiform EEG. Moderate/weak: +FHx (first deg relative), sz during sleep, prior provoked sz, Todd's. Possible: partial szs. (Neurology 1990;40(8):1163). (2) Risks of treatment: ˜30% have some adverse event. Risk ↑ in chronic liver/kidney/immune dz, infants, elderly, pregnancy. (3) Risks/cost of sz recurrence: No driving × 3-18 mo since last sz (varies by state). Occupational hazards: Heights, power tools, sharps, care for children or elderly, psychosocial impact.

AED Trade Names & Abbreviations

Generic Name	Trade Name	Abbreviation
	First Generation ("old") AEDs	
Phenytoin	Dilantin	PHT

Carbamazepine	Tegretol, Tegretol XR, Carbatrol	CBZ
Primidone	Mysoline	PRM
Valproic acid	Depakote, Depakote ER, Depakene	VPA
Phenobarbital	Luminal, Solfoton	PB
Ethosuximide	Zarontin	ESX
Benzos (BZD): Lorazepam, diazepam, midazolam, clonazepam, clorazepate	Ativan, Valium, Versed, Klonopin, Tranxene	LZ, DZ, MZ, CLZ, CZP
Second Generation ("new") AEDs		
Felbamate	Felbatol	FBM
Lamotrigine	Lamictal	LTG
Gabapentin	Neurontin	GBP
Topiramate	Topamax	TOP
Oxcarbazepine	Trileptal	OXC
Tiagabine	Gabitril	TGB
Levetiracetam	Keppra	LEV
Zonisamide	Zonegran	ZNS
Pregabalin	Lyrica	PGB
Lacosamide	Vimpat	LCS

Rufinamide	Banzel	RUF

P.69

CHOICE OF AED: GENERAL PRINCIPLES

Special considerations when choosing an AED

Seizure type: Narrow spectrum (focal or tonic-clonic szs): CBZ, OXC, PHT, PB, PRM, GBP, PGB, TGB. Broad spectrum (focal + generalized, including myoclonic & absence): LEV, VPA, TOP, ZNS, LTG (less effective for myo), FBM.

Cost: First generation AEDs generally cheaper.

New dx: ˜50% become sz free w/ first med (→ will be on this AED chronically) → generally try first meds w/ best safety & tolerability (e.g., LEV, TOP, LTG, OXC, CBZ, GBP).

Refractory epilepsy: When adding extra AEDs consider intxns w/ other AEDs.

Some combinations to monitor closely b/c pharmacokinetic or pharmacodynamic intxns (there are many more): PB + VPA, PHT+CBZ, CBZ+LTG, VPA+LTG (↑ side effects & efficacy).

Other meds?: Consider intxns w/ other non-AED medications.

Female: Childbearing years? Taking OCPs? Bone health? Teratogenicity?

- ↑ metabolism of OCPs: CBZ, FBM, PB, PHT, PRM, TOP (>200 mg/day), ?OXC (≥900 mg/day),
- All old AEDs are class D = known teratogens to humans; recent data = VPA is highest risk (6%-11%), PB ˜6%; risk w/ others modest (2%-5%, overlaps control population). All old AEDs can → "fetal anti-convulsant syndrome": craniofacial + digital abnlities, ˜3% w/ major defects (e.g., cardiac, cleft lip/palate, microcephaly, dev delay, neural tube).
- New AEDs are class C = unknown fetal effects.

Elderly: Lower threshold for side effects, esp cognitive dysfn, tremor, gait problems. CrCl, hepatic clearance ↓ after age 65; albumin levels ↓ w/ age—need to ↓ doses of protein-bound drugs; generally use lower doses titrated more slowly.

IV formulations (when rapid titration is necessary): Exist for: PHT, VPA,

LEV, PB.

CHOICE OF AED: “EXPERT RECOMMENDATIONS”

Abbreviations: IGE = Idiopathic Generalized Epilepsy, SLRE = Symptomatic Localization Related Epilepsy (focal epilepsy).

Individualize—e.g., also consider side effects, interactions, comorbidities.

Reference: Epilepsy & Behavior, vol 7, supplement 1, 2005;1-64

AED Choice for IGE: Expert Recommendations

Monotherapy

Setting	GTC	Absence	Myoclon
Mono #1	VPA > LTG, TOP	VPA,ESX>LTG	VPA
Mono #2 after VPA	LTG>TOP,LEV>ZNS	ESX, LTG	ZNS,LEV
Mono #2 after LTG	VPA>TOP,LEV>ZNS	VPA, ESX	VPA>ZN
Mono #2 after TOP	VPA, LTG	VPA,ESX>LTG	VPA

Combination Therapy

Current AED	Consider Adding
FBM	VPA > LTG
LTG	VPA, TOP, LEV, ZNS
LEV	VPA> LTG, TOP

TOP	LTG, VPA > LEV
VPA	LTG > TOP, LEV, ZNS
ZNS	LTG, VPA > LEV
Vagus nerve stim	VPA > LTG, TOP

P.70

AED Choice for SLRE: Expert Recommendations

Initial Monotherapy

Simple partial	CBZ, OXC > LTG, LEV
Complex partial	CBZ, OXC > LEV
Secondarily generalized	CBZ, OXC > LTG, LEV

Second Monotherapy

First AED	**Consider Next**
CBZ	LTG > LEV, TOP
GBP	LTG, CBZ, OXC > LEV, TOP
LEV	LTG, CBZ, OXC > TOP
OXC	LTG > LEV, TOP
PHT	LTG > LEV, CBZ
TOP	LTG, CBZ, OXC > LEV
VPA	LTG, CBZ, OXC, LEV, TOP

Combination Therapy

Current AED	Consider Adding
CBZ	LEV > LTG, TOP, ZNS
GPN	LTG, LEV > OXC, TOP, CBZ, ZNS
LTG	LEV > TOP, OXC, CBZ, ZNS
LEV	LTG, CBZ > OXC, TOP, ZNS, VPA
OXC	LEV > LTG, TOP, VPA, ZNS
PB	LTG, LEV > OXC, CBZ, TOP
PHT	LTG, LEV > TOP, VPA
TGB	LTG > LEV, TOP, OXC, CBZ
TOP	LTG, LEV > CBZ, OXC, VPA
VPA	LEV > OXC, LTG, CBZ, TOP
ZNS	LTG, LEV, OXC, CBZ

AED Choice in Special Circumstances: Expert Recommendations

Healthy Woman who Might Become Pregnant

IGE	LTG > LEV
SLRE	LTG > LEV, OXC

Healthy Woman Trying to Become Pregnant

IGE	LTG
SLRE	LTG > LEV, OXC
Elderly Patients	
SLRE, medically stable	LTG > LEV
SLRE, medically ill	LTG > LEV, GPN
HIV (+) Patients	
IGE	LTG, LEV ˜
SLRE	LEV, LTG
Depressed Patients	
IGE	LTG > VPA
SLRE	LTG > OXC, CBZ
Renal Disease	
IGE	LTG, VPA
SLRE	LTG
Hepatic Disease	
IGE	LEV, LTG
SLRE	LEV, GPN
Emergency Department	
Unknown epilepsy syndrome	LEV, VPA > PHT, OXC, LTG, CBZ, TOP

SIDE EFFECTS, INTERACTIONS, COMORBIDITIES, & MONITORING

Influence of Comorbid Conditions on AED Choice

AEDs to Use Cautiously or Avoid

Liver dz	VPA, PHT, PB, CBZ, LTG, ZNS, FBM
Renal impairment	LEV, GBP, PB, PGB, TOP, ZNS
h/o renal stones	ZNS, TOP
Arrhythmias	CBZ, PHT
Pancreatic dz	VPA, CBZ
Hypothyroidism	CBZ,OXC, PHT
Hyponatremia (or risk for)	CBZ, OXC,
Osteopenia	PHT > CBZ, PB
Obesity	VPA, PGB (↑ 10-50 lb), ?CBZ, ?GBP (↑ 5-10 lb)
Anorexia/malnourished	FBM, TOP, ZNS
PCOS	VPA
Taking OCPs	CBZ, OXC, PHT, PB, TOP (at dose >200)
Bleeding diathesis	VPA
Blood dyscrasias	CBZ

Peripheral edema	PGB
h/o hypersensitivity rxns	AEDs w/ risk of rash (esp PHT, CBZ, LTG)
Absence szs	CBZ, OXC, TGB
Myoclonic szs	GBP, LTG, OXC, CBZ, TGB, PGB,
Generalized szs	GBP, CBZ, OXC, (may exacerbate)
Psychiatric d/o	LEV, PB
AEDs that May Help the Condition	
Mood instability	OXC, VPA, LTG, CBZ
HA	TOP, VPA, CBZ in children
Neuropathic pain	GBP, OXC, CBZ, TOP
Obesity	TOP, ZNS
PLMS	CZP, GBP, TOP, ZNS
Tremor	CZP, PBT, PRI, ELV, TOP
Insomnia	TGB

COMMONLY USED AEDS: DOSES, SIDE EFFECTS, INTERACTIONS

Table below lists general information about commonly used AEDs. Format is as follows:

- First line: Route (PO, IV, IM), starting dose (mg), increment by which to ↑(mg), typical maint dose (mg), div: schedule (e.g., qd, bid, tid, qid), metabolism (renal, liver), target serum level (mg/L = microgram/mL), half life (hours), % protein bound.

- “Peds maint” = maintenance dose for pediatric patients (weight-based).
- Vd = volume of distribution (if unknown, can approximate by Vd = IV dose/Δ conc).
- Monitoring suggestions (levels, other labs/tests). If none is given then is reasonable to follow generic suggestions below (see “Routine labs & AED level monitoring”).
- Acronyms: LLS = lupus like syndrome, TEN = toxic epidermal necrolysis, SJS = Stevens Johnson Syndrome, CSE = common side effects, SSE = serious side effects, LTE = long-term side effects.
- “Routine” labs—no formal guidelines exist. See below for reasonable suggestions.
- Interactions: “↑” or “↓”: lists drugs & conditions that commonly ↑ or ↓ the level of this AED.
- &U21E8;: lists effects of this AED on other commonly used drugs.

“Routine” labs & AED level monitoring

Levels: Generally check 1-2×/yr once stable. Check 5 half lives after dose change (usu 5-7 days).

Other tests: For most AEDs (but varies—see below for individualized suggestions):

- Before Rx starts: CBC, LFTs, chem7 (esp BUN/Cr).
- Monitoring: After 1 mo, then every 3-6 mo: CBC, LFT, chem7.

P.72

P.73

P.74

PHT PO, IV, 300, ↑ 150 q3d, 300-600, div: qd-tid, hepatic/renal 10-20, 8-40 h, 90% [Pedi: Maint 2-8 mg/kg/day bid-tid.]

Free level target range: 0.50-3.

Vd: child 1.0; adolescent 0.7-1.0; adult 1.0.

Rapid titration: *Loading dose*: *20 mg/kg*, *Bolus dose* (*mg/kg*): *Vd* × (*desired-measured PHT level*). *Wait to check level >60 min; rebolus if nec using Vd.*

Corrected level = Measured PTH level/[(*albumin* × *0.2*) + *0.1*].

CSE: n/v, ataxia, nystagmus, diplopia, lethargy, confusion, ↓ T_4.

SSE: SJS or TEN (4/100 K), bone marrow suppression, blood dyscrasias, megaloblastic anemia, liver failure (rare), LLS, arrhythmias, dystonia/ophthalmoplegia.

LTE: Gingival hyperplasia, osteomalacia, lymphadenopathy, neuropathy, hirsutism, coarse facies, mvmt d/o, cerebellar atrophy/ataxia/slurred speech

Caution: Fever can ↓ level; don't give IM—can → tissue necrosis (use FOS-PHT). Nonlinear kinetics—small dose ↑ can cause large level increase. Can mask sx of hypoglycemia in diabetic pts.

Contra: Sinus bradycardia, heart block, hypotension, low EF.

Monitoring: Routine + yrly DXA scans (lumbar spine & proximal femur). If giving IV: cardiac monitoring, BP monitoring.

Pts should take: Vit D 2,000 IU qd + Ca 1,200 mg qd
Interactions:

↑: FBM, OXC, VPA; Y (chlorpromazine, fluoxetine, fluvoxamine, imipramine, sertraline, trazadone, viloxazine); Abx (sulfa drugs, Chloramphenicol, fluconazole, isoniazid, miconazole, sulfaphenazole); chemoRx (doxifluridine, fluorouracil, tamoxifen, tegafur, tegafur-uracil); Misc (aspirin, amiodarone, allopurinol, cimetidine, chlorpheniramine, propoxyphene, diltiazem, disulfiram, omeprazole, phenylbutazone, sulfinpyrazone, tacrolimus, ticlodipine, tolbutamide, azapropazone, EtOH; uremia, hypoalbuminemia)

↓: VPA, CBZ, chronic EtOH, antacids, steroids

&U21E8; ↓ theophylline, ↓ digoxin, warfarin (↑ INR), ↓ cyclosporine, ↓ OCPs, ↓ haldol

FOS-PHT IV, IM, load 20 mg/kg, 300-600 (qd-tid), hepatic, 10-25, 12-29 h, 90%

CSE: HoTN, burning, itching

Caution: Max admin rate 150 mg/min. Porphyria

Contra: Sinus bradycardia, heart block

Other info same as PHT.

CBZ PO 200, ↑ 200 q3d, 200-400, div: tid, Hepatic; 4-12, 12-18 h, 80% [Pedi: Start 5-10 mg/kg/d bid, ↑ 5 mg/kg/d qwk, maint 15-30 mg/kg/d]

CSE: Mild leukopenia, ataxia, diplopia, lethargy, urinary retention, ↓ wt, ↓ T4

SSE: Agranulocytosis (1/20 K), aplastic anemia (1/500 K), rash (10% pts), SJS (rare), hyponatremia, pancreatitis, hepatitis, LLS, arrhythmias

Caution: Glaucoma, cardiac dz, liver dz, prostatic hypertrophy.

Contra: w/ MAOIs, h/o bone marrow suppression, allergy to TCAs

Monitoring: CBC, LFTs, chem7 at: baseline, 6 wk, 3 mo, 6 mo, then q3-6mo, yrly DXA scans (lumbar spine & proximal femur).

In Asian pts test for HLA-B*1502 before starting (higher risk of SJS)

Pts should take: VitD 2,000 IU qd + Ca 1,200 mg qd

↑: FBM, VPA; ψ (fluoxetine, fluvoxamine, nefazodone, trazodone, viloxazine); Abx (erythromycin, isoniazid, Clarithromycin, fluconazole, ketoconazole, metronidazole, ritonavir, troleandomycin); Misc (Cimetidine, danazol, propoxyphene, diltiazem, risperidone, quetiapine, ticlodipine, verapamil, grapefruit juice)

↓: PHT, PB; &U21E8; ↓ VPA, ↓OXC, ↓OCPs, warfarin (↓ INR), ↓ theophylline, ↓cyclosporine, ↓ haldol, ↓ klonopin

CBZ-XR PO 200 bid, 400-600 bid; o/w same as CBZ

VPA PO 750, ↑ 150-300 qwk, 750-1,500, div: tid, hep. >> ren., 50-100, 10-12 h, 95%

[Pedi: Maint 15-20 mg/kg/d div bid-tid. Start 5-10 mg/kg/day, ↑ 5 mg/kg/day qwk.]

If Δ'ing to VPA-ER, ↑ dose 10%-20% to achieve bioequivalence.

Rapid titration: *Loading dose 20 mg/kg. Wait to check level >60 min*.

CSE: Lethargy, ataxia, wt gain, n/v/d, tremor, hair loss, mild ↓ plts, ↓ carnitine

SSE: Liver failure (1/20 K), hyperammonemia, aplastic anemia (rare), pancreatitis (1/3 K), significant thrombocytopenia (dose-related), SJS (rare), encephalopathy (w/ or w/o ↑ NH_3), teratogenicity

LTE: PCOS, amenorrhea, hyperandrogenism in females, hair thinning

Caution: No evidence for excess operative bleeding, but some recommend stopping before surgery (can cause ↓ factor 7)

Contra: Hepatic dz, porphyria

Monitoring: CBC, LFT, lipase at: baseline, qmo × 6 mo, then q3-6mo

↑: FBM; ψ (Sertraline, chlorpromazine); Abx (Isoniazid); Misc (cimetidine, propoxyphene, salicylates)

↓: PB, LTG, CBZ, PHT *[free fraction PHT ˜VPA level*: *Free PHT % = 10% (baseline level) + (0.1 × VPA level)]*

&U21E8; ↑ PB, ↑ FBM, ↑ LTG, ↑ CBZ

VPA-IV IV load 10-20 mg/kg, or for status 20 mg/kg @ 5 mg/kg/min Called "Depacon"

PB PO 60-250, 60-250, div: qd-bid, hepatic/renal; 15-45, 24-1 10 h, 50% [Pedi: Maint 5 mg/kg/d div qd-bid.]

Vd: infant 0.9; adult 0.5.

Rapid titration: *Loading dose 20 mg/kg. Bolus dose*: *Vd* × (*desired - measured level*). *Can check level immediately after, rebolus if nec using Vd*

CSE: Fatigue, dizziness, ataxia, diplopia, n/v, sedation,

depression, confusion

SSE: IV form: resp. depression; PO: rare, include: blood dyscrasias, liver failure, rash, SJS/TEN, arthritis, laryngospasm, bronchospasm, LLS

LTE: Frozen shoulder, rickets, osteomalacia

Caution: Can be habit forming; depression, suicidal tendencies, other CNS

depressant meds; renal, pulm, or hepatic dysfxn. Psych d/os. Taper slowly.

Contra: Porphyria; EtOH intolerance; severe liver dysfxn, significant resp. dz

Monitoring: IV form: RR, BP. PO form: Routine, plus yrly DXA scans (lumbar spine & proximal femur). Pts should take: Vit D 2,000 IU qd + Ca 1,200 mg qd

↑: FBM, PHT, VPA, sulthiame; Abx (Chloramphenicol); Misc (dextro-propoxyphene, acetazolamide); &U21E8; ↓ OCPs, warfarin (↓ INR), ↓ theophylline

PB-IV Load: 20 mg/kg, max rate 2 mg/kg/min; note: takes 2-3 wk to read steady state if no load given. Other info same as PO PB.

ESX PO 500, ↑ 250 q4-7d, 1,000-2,000, div: bid; Hepatic, 40-100; 30-60 h, <5%

[Pedi: Start 5 mg/kg/d bid, ↑ 5 mg/kg/d qwk, maint 15-40 mg/kg/d]

CSE: Sedation, HA, n/v

SSE: Blood dyscrasias, erhythemia multiforme, SJS, LLS, psychosis

Caution: Sudden w/d → sz; High conc. in breast milk

Contra: Porphyria

Monitoring: Routine, plus: CBC, LFTs at: baseline, q1mo × 6 mo, then q6mo

↑: Isoniazid, VPA; &U21E8; ↓ OCPs, ↓ VPA effectiveness

CLZ PO 1.5, ↑ 1.5 q3d, 2-15, div: tid, hepatic; 20-80, 18-50 h,

85%

[Pedi: Maint 0.25-1 mg bid-qid, typically temporary Rx]

CSE: CNS: Sedation, ataxia, hyperactivity

SSE: Psychosis, resp. depression

Caution: Sudden d/c may provoke sz. Excreted in breast milk

Contra: Don’t use w/ flumazenil

↓: CBZ, PB, PHT;&U21E8; none

DZP PO 4, ↑ 1 q3d, 15, div: bid-tid, hepatic, 0.1-1; 30-36 h, 95%

[Pedi: 1-10 mg bid-qid, typically temporary]

CSE: Sedation, irritability, HA, dizziness, depression

SSE: HoTN, resp. depression, interstitial nephritis, thrombophlebitis

Caution: Sudden w/d → sz; pulm dz, psychosis. Excreted in breast milk.

Contra: Don’t use w/ flumazenil. Acute narrow angle glaucoma.

Monitoring: No routine lab monitoring needed

↑: VPA; ↓:CBZ, PB, PHT;&U21E8; none

DZP-rectal PR 0.2 mg/kg, can repeat after 4 h (brand name: Diastat) O/w same as DZP

DZP-IV IV Load: 10-20 mg @ 2 mg/min, can repeat @ 15 min

Maintenance: 0.4 mg/kg/h

O/w same as DZP

Second Generation AEDs

FBM PO 1,200, ↑ 600 qwk, 3,600, div: tid-qid, hepatic/renal, 30-80, 20 h, 25%

CSE: CNS: HA, sedation, insomnia, diplopia, agitation, anorexia, tachycardia

SSE: Aplastic anemia, liver/renal failure, pancreatitis, LLS, ↑ NH^3, SJS

Caution: Only for severe epilepsy given risk of aplastic anemia; renal dysfxn.

Conta: H/o blood dyscrasia, liver dz, +ANA.v

Monitoring: ANA at baseline; CBC, chem7, LFT at baseline, then q3-6mo

↓: PHT, PB, CBZ; ↑ none; &U21E8; ↓ OCPs, ↑ CBZ, ↑ VPA, ↑ PHT

LTG PO 25 bid, ↑ 25-50 qwk, 200-400, div: bid, hepatic/renal; 4-20, 10-60 h, 55%

[Pedi: Maint 5-15 mg/kd/d div bid (+inducer or mono), 5 mg/kg/d (+VPA); Start & ↑ (qwk) by # mg/kg/d: 0.6 (+ inducer), 0.4 (mono), 0.15 (+VPA).]

CSE: CNS: lethargy, dizziness, diplopia, HA, insomnia, tics

SSE: Rash, SJS (1/1,000; more common w/ VPA & in children; risk decreased w/ slow titration), hypersensitivity (rare), multiorgan failure (rare), liver failure (rare), renal failure (rare), aplastic anemia (rare), DIC, arthritis

Caution: Discontinue at first sign of rash. Levels ↑'d by pregnancy & OCPs

Monitoring: Routine

↑: VPA; ψ (sertraline); ↓: PHT, PB, CBZ; &U21E8; none

LTG+ VPA PO 25 qd, ↑ 25/wk; 100 bid

Other info same as LTG monotherapy

GBP PO 300, ↑ 300 qdx 3days then 600 qwk, 900-4, 800, div: tid-qid, renal, 12-20, 5 h, <10%

[Pedi: Maint 100 mg/kg/d div tid. Start 10-20 mg/kg/day, ↑ q3d.]

CSE: Fatigue, sedation, mild wt gain, tinnitus, ataxia, wt gain, behavior Δs

SSE: Rare, but include: ICH, TTP, eye hemorrhage,

psychosis

Caution: Avoid w/ Lennox Gastaut (may ↑ szs); taper if d/c'ing. Renally dose.

Monitoring: No routine lab monitoring needed.

TOP PO 25-50, ↑ 25-50 qwk; 200-400, div: bid, renal; 5-25; 20 h, 15%

[Pedi: Maint 5-9 mg/kg/d, max 12 mg/kg/day. Start 2-4 mg/kg/d div bid.]

CSE: Lethargy, ataxia, word finding problems, slow speech, poor concentration, wt loss, paresthesias, mild metabolic acidosis, agitation

SSE: Severe metabolic acidosis (3%), renal stones (1%), AV-block, acute angle closure glaucoma (rare), ↓ sweating/heatstroke (esp children), psychosis (rare)

Caution: ↑ risk of renal stones w/ acetazolamide, dichlorphenamide, ZNS, or ketogenic diet; w/ renal insuff use renal dosing; caution w/ liver dz.

Contra: Allergy.

Monitoring: Routine.

↓: CBZ, PHT; &U21E8; ↓ OCPs, ↓ digoxin

OXC PO 150-300, ↑ 150 qod, 1,200, div: bid; renal, 3-40(MHD); 8-10 h, 50%

[Start 5-10 mg/kg/d bid, ↑ 5 mg/kg/d qwk, maint 30 mg/kg/d]

CSE: Fatigue, n/v, ataxia, diplopia, somnolence, HA, ↓ T_4.

SSE: Hyponatremia (3%), SJS/TEN (1/million), anaphylaxis (rare)

Caution: Allergy to CBZ (30% crossover allergy); Crosses placenta.

- Can switch CBZ → OXC overnight at ratio of 1/1.5 (CBZ/OXC).
- MHD = 10-monohydroxyl metabolite (active

metabolite of OXC)

Monitoring: Routine, plus: Na at baseline, then 1 mo × 3 mo, then q3-6mo.

↓: CBZ; &U21E8; ↓ OCPs, ↑ PB, ↑ PHT (at doses >1,200/d), ↑ VPA

TGB 4, ↑ 4-8 qwk, 32-56, div: bid-qid, hepatic, 0.1-0.3 (?utility), 8 h, 95%

CSE: Fatigue, dizziness, ataxia, insomnia, somnolence, irritability, weakness

SSE: Rash, SJS (rare), spike-wave NCSE

Caution: Can → NCSE in pts w/ spike-wave EEG findings. ?Long-term vision problems (concern given similarity to vigabatrin; but no e/o real risk)

Monitoring: Routine.

↓: PHT, CBZ, PB; &U21E8; minimal

LEV PO 1,000, ↑ 500 qwk, 1,000, div: bid, renal, 10-45, 6-8 h, <5%

[Pedi: Maint 20-100 mg/kg/d div bid.]

Rapid titration: *Loading dose 20-30 mg/kg*.

CSE: Sedation, anxiety, irritability, generalized wkness, dizziness, depression

SSE: Psychosis (rare)

Caution: Reduce dose for impaired renal fxn. Can exacerbate psych d/os.

Monitoring: Routine.

↑: None, ↓: none, &U21E8; none

ZNS PO 50-100, ↑ 50 qwk, 200-400, div: qd-bid, renal, 10-40, 60 h, 40%

[Pedi: Maint 4-8 mg/kg/d div bid. Start: 2-4 mg/kg/d div bid.]

CSE: Somnolence, dizziness, ataxia, photosensitivity, ↓

conc., ↓ wt, n/v, HA

SSE: Aplastic anemia, renal stones (2%), SJS/TEN (rare), anhydrosis/heat stroke (rare)

Caution: Taper slowly; renal or liver dysfxn; ↑ risk of kidney stones w/ acetazolamide or TOP.

Contra: GFR < 50. Hypersensitivity to sulfonamides.

Monitoring: Routine.

↓: PHT, PB, CBZ, VPA; &U21E8; ↑ PHT

PGB 75-150, ↑ 75-100 qwk, 150-600, div: bid-tid, renal; not established; 6 h, <5%

CSE: Wt gain, diplopia, peripheral edema, fatigue, dizziness.

SSE: None known.

Caution: Avoid abrupt d/c; elderly; depression; renal dysfxn; h/o angioedema; CHF; controlled substance (schedule V)

Monitoring: Routine.

&U21E8; may ↑ effect of CNS depressants (e.g., benzos, barbiturates, EtOH)

References: Ultimate Review for the Neurology Boards, pp. 91-104; Continuum, *Epilepsy, 2007;13(4):84-85; Br J Clin Pharmacol* 2006;61:246-255; *Complete Pocket Reference for the Treatment of Epilepsy, Editors*: *M. Deray, T. Resnick, L. Alvarez, 2001; JAMA* (4):2004;291 (4): 615-620; *Neurology* 2004;62:1252-1260; *Br J Clin Pharmacol* 2006;61:246-255.

KETOGENIC DIET

J Child Neurol 2009;24:979-988 & Lancet Neurol 2004;3:415-420.

Definition: High-fat, low-carbohydrate diet based on ketogenesis, i.e., production of ketones [acetoacetate, beta-OH-butyrate (BOHB)] in the setting of FFA as a main energy source. Unclear but likely multifactorial antiepileptic mechanism.

Indications: Refractory epilepsy (medication failure, unacceptable sz frequency, medication toxicity), some specific metabolic dzs [Glucose

Transporter Def (GLUT-1), PDH]. Most often used in pediatric epilepsy.

Contraindications: Hyperlipidemia, certain metabolic dz (pyruvate carboxylase def, organic acidurias), d/o involving defect in fatty acid transport or β-oxidation, medications interfering w/ carbohydrate metabolism (corticosteroids).

Normal diet: Calories from carbohydrate (CHO) 50%, fat 30%, protein 20%. By contrast: W/ KGD 90% from fat, 10% from protein & CHO, while allowing for sufficient nutrition for growth & development w/ help of specialized nutritionist. Variations include "low glycemic index" diet, modified Atkins, polyunsaturated fatty acids, & others. Ratio of fat: (CHO + protein) = usually 3:1 to 4:1. Urine check: 3-4+ ketones ˜60-80 mmol/L, corresponds to 30-100 mg/dL (2-12 mmol/L) plasma BOHB, & goal is >40 mg/dL BOHB for best antiepileptic effect. Plasma BOHB has long laboratory turnover.

MANAGEMENT OF COMMON PROBLEMS ON KGD

Acute problems

Dehydration: Lethargy, decreased urine output, dry mucous membranes, sunken eyes, no tears. Causes: Intercurrent (GI) illness. Ketosis inhibits thirst → ↑ ketosis; acidosis may induce vomiting. Rx: Home: Sugar-free fluids (water, diluted eggnog, formula [RCF®: soy protein based plus glucose polymer powder & microlipids, KetoCal®: Cow's milk protein based, fat source is soy oil), Fruit2O ("smart water"), broth, diet ginger ale.]. Hospital: IVF (1/2 NS, other electrolytes PRN, no dextrose).

Hypoglycemia: Lethargy, but often asymptomatic. Causes: Medications interfering w/ carbohydrate metabolism, intercurrent illness (stress, sepsis, infection), caregiver non-compliance. Rx: Home: Give 1 tbsp of juice & seek medical attention if needed. Hospital: q6h dextrostix (1) if <40, & asymptomatic: document w/ lab glucose, go to q2h; (2) if <25, document, give 30 mL orange juice (OJ), continue q2h until stable > 40; (3) if symptomatic at any time, document w/ lab, give 30 mL OJ.

Vomiting: Causes: Excess ketosis or acidosis may induce vomiting. Rx: Give 1 tbsp of juice & seek medical attention if needed. Consider IVF (see above).

Acidosis: Hyperventilation vomiting, tachycardia, irritability, facial flushing, lethargy. Causes: Excess ketosis, dehydration, intercurrent illness, caregiver noncompliance. Rx: Hospitalization. If HCO_3 < 15: supplement w/ Bicitra or Polycitra (2-3 mEq/kg/day div tid or qid).

Intercurrent medications: If total adds up to <0.1 g of CHO/day: No need to recalculate. If >0.1, daily dietary total CHO allowance will need adjustment

(consult nutritionist).

Steroids: Steroids break ketosis (glucocorticoid effects), notify ketogenic diet team.

Chronic problems

Poor growth, vitamin & mineral deficiencies, bone demineralization: Ketoacidosis → ↑ Ca & PO_4 loss in urine; ↓ fluids, high fat → ↓ water soluble vitamins. Dietary deficits. Mgt: Monitor height, weight, BMI, clinical vigilance for deficiencies, measure Cu, Se, Zn, Ca, Mg, PO_4. Supplement calcium. Adjust calory & protein requirements. Ketogenic nutritionist consultation.

Hyperlipidemia, pancreatitis: High fat intake → linear ↑ of cholesterol & triglycerides. Long-term effects unknown. Unclear role for lipid lowering agents. Ketogenic nutritionist consultation.

Constipation: Common. ↓ Fluid intake, ↓ bulk intake. Mgt: Encourage fluid intake, CHO-free laxative, mineral oil, suppositories.

Urolithiasis: Hematuria, crystals, gravel, or stone passes, pain, obstruction. Common 5%-8%: ↓ urinary pH, ↓ urine flow, ↑ calciuria, calcium supplements. Mgt: Routine urine dipstick. ↑ fluid intake, alkalizing agents, lithotripsy, rarely diet discontinuation.

Cardiomyopathy: Rare, poorly understood: Low HCO_3 & high BOHB: cardiomegaly, ↑ QTc. Mgt: Pre-diet EKG. Monitor HCO3 & BOHB. Avoid selenium def (cardiomyopathy).

Hematologic: Lipid Δ in platelet membrane, Δ platelet proteins: ↑ bruising, ↑ bleeding time. Mgt: Some responsive to DDAVP. Consider presurgical evaluation.

Immunologic (controversial): Ketosis, malnutrition: ↑ infections (↓ phagocytosis, ↓ killer ↑ cell function). Controversial.

P.76

Miscellaneous: Worsening of GERD, behavioral changes, medication toxicity (TOP & other carbonic anhydrase inhibitors: ↑ acidosis but not stones), surgery (CHO-free IVF, no drops in glc, pH drop after 3 h → Rx 5-20 mEq HCO_3).

SURGICAL TREATMENTS FOR EPILEPSY

RESECTIVE EPILEPSY SURGERY

Candidacy: (1) Refractory epilepsy. (2) Reasonable chance of benefit.

Morbidity & mortality of uncontrolled szs: Accidental injuries (e.g., fxs, burns, head injuries, lacerations), cognitive ↓, depression, sudden unexplained death (depends on epilepsy severity, 1/3,000-1/200/yr), ↓ fertility, unemployment. For mesial temporal lobe epilepsy M&M of surgery generally < uncontrolled epilepsy (Neurology 2003;60(4):538).

Refractory epilepsy: Consider epilepsy surgery w/u after failing at least 2 AED regimens.

D/os amenable to epilepsy surgery (not exhaustive): Very high surgical success rates: Mesial temporal/hippocampal sclerosis; specific benign brain tumors (ganglioglioma, DNT); cavernous angiomas. Less success: Other brain tumors (low-grade glioma, meningioma), vascular lesions (AVM, stroke), neurocutaneous d/os (tuberous sclerosis, neurofibromatosis, Sturge-Weber's synd.), infections (meningitis/encephalitis, brain abscess, empyema, tuberculoma, cysticercosis lesion), trauma, nonlesional focal epilepsy.

Focal epilepsies amenable to surgery: (1) Success by lobe: TL >> FL, PL, OL. (2) In any lobe removal of well-localized structural lesion is often curative. (3) Ictal SPECT can sometimes identity sz focus if not clear from MRI, but very sensitive to technique; confirm w/ intracranial EEG. (4) Interictal FDG-PET shows hypometabolism in TL epilepsy (˜80%); sometimes eliminates need for intracranial recording if other data not definitively lateralized.

Generalized epilepsies amenable to surgery: (1) Generally cannot treat IGE resectively. Some success w/ VNS (though approved only for focal epilepsies); DBS is being tried experimentally. (2) Specific cases of generalized epilepsies more amenable to surgery: Infantile spasms (West's synd.): Many causes; amenable if PET shows large area of hypometabolism. Lennox-Gastaut's synd.: Callosotomy often palliative, decreases drop attacks & generalized convulsions; VNS also can help.

Preoperative evaluation: Routine testing: Long-term VEEG, PET, MRI, neuropsychological testing, Wada test (for memory if mesial temporal lobe epilepsy suspected,&/or for language if language areas may be involved. (1) VEEG: Usually need to record several sz to localize; interictal discharges may be better localized than ictal onsets. (2) Neuropsych testing: Helps w/ localization; compare deficits before & after surgery. (3) MRI: Coronal FLAIR & T1 w/ thin cuts for detecting hippocampal sclerosis & cortical dysplasias; gradient echo for cavernomas or posttraumatic blood; gadolinium contrast for tumor, infection. (4) PET: Detect area of decreased glucose metabolism & blood flow—often corresponds to sz focus, especially if temporal. (5) Wada test: Give intracarotid amobarbital (Amytal)—to determine dominant hemisphere, to determine whether hippocampus c/l to lesion can support memory. Not routine, sometimes helpful:

magnetoencephalography (MEG), MR spectroscopy, fMRI, cerebral angiography, SPECT, intracranial EEG. (1) MR spectroscopy: Ratio of N-acetylaspartate to choline & creatine can help distinguish nl vs. abnl tissue (e.g., gliotic scars); can help identify tumors, abscesses. (2) fMRI: Uncertain role for now, may help to localized functional areas. (3) Cerebral angiography: To characterize vascular lesions that cause epilepsy. (4) SPECT: Inject isotope during szcan scan after (isotope remains bound >1 h); area w/ more binding (hyperperfused during sz) is potential sz focus. SPECT images coregistered w/ MRI used to guide electrode placement for confirmatory intracranial EEG. Useful for surgical evaluation of nonlesional epilepsy. (5) Intracranial EEG: For more precise localization & for functional mapping (record & stimulate underlying cortex); need testable hypotheses to guide placement.

VAGUS NERVE STIMULATOR

Reference: Mayo Clin Proc 2003;78:371-378. “VNS”: Only FDA approved of many investigated forms of neurostimulation. Incompletely clarified antiepileptic mechanism (?immediate (de)synchronization of cortical electrical activity, ?long-term effects on NT levels & regional CBF). Settings: 20-30 Hz, 250-500 μs pulse width stimulus of 0.25-3.5 mA, lasting 30 s, q1.1-5 min. Magnet activation (see below) w/ higher current, longer duration & bigger pulse width. Battery life 5-12 yr. Efficacy: 25%-30% have >50% sz freq reduction w/ high levels of stim. No clear, consistent predictor of efficacy, no specific sz type responds better, trend for generalized szs. Indications: (1) medically intractable epilepsy, (2) trial of ≥3 appropriate AEDs, (3) exclusion of nonepileptic events, (4) not candidate for respective surgery. Pros: Lack of CNS adverse effects, no AED interactions, no compliance concerns, ↑ quality of life (alertness, communication

skills, mood, independence, others; in part from ↓ AEDs). Cons: Invasive, expensive, ineffective in many. Surgery: L vagus nerve (cervical): 80% afferents, less pain fibers, widespread anatomic projections, less cardiac innervation. Complications: Infection 1%-2%, hoarseness/temporary vocal cord paralysis 0.7%, hypesthesia/lower left facial paresis 0.7%, diaphragmatic paralysis (rare), asystole during lead-testing <0.1%, surgical mortality 0.0%. Adverse effects (during stim on-time, may ↓ w/ time or stimulator Δ): Voice alteration 58%, cough 38%, ear/throat pain 1%, ↑ salivation 1%, headache, dysphagia (rare). No deaths, no idiosyncratic reactions, no ↑ SUDEP. MRI compatible after turned off (call supplier if needed). Possible acute manual interventions: (1) Magnet activation: By sweeping the magnet over the pulse generator the on-demand mode is started, giving a temporary increase in

stimulation (e.g. for 60 s) w/ higher current & bigger pulse width. Goal is to stop or reduce a sz, end a cluster and/or reduce the post-ictal phase. (2) Stop stimulation: In order to acutely stop the VNS, e.g. for an electrophysiological study, keep the magnet over the pulse generator (use tape).

STATUS EPILEPTICUS

SE: Over 30 min interval: Continuous sz, or >1 sz w/o full return of consciousness/return to baseline b/n szs. Can be: focal vs. gen, convulsive vs. nonconvulsize.

“Prolonged seizure”: >5 min: Signifies failure of sz termination mechanism & risk of SE.

“Impending status”: > 10 min (treated as SE).

Clusters of szs: considered transitional state toward SE.

Generalized convulsive SE (GCSE): Convulsions are evident clinically. [Includes tonic-clonic SE (most common), tonic-SE, clonic-SE, myoclonic-SE.]

NCSE: Electrographic SE w/o clinically evident “convulsions” (but other signs are present, e.g., altered consciousness).

Refractory SE (RSE): Ongoing sz following first & second line drug Rx.

Epidemiology: GCSE: Most common neurologic emergency. In USA 50-200 K/yr. ˜ 1/3 known epilepsy, ˜1/3 new epilepsy, ˜1/3 acute neurologic disturbance (proportions vary by age). 15% of pts w/ epilepsy will have at least 1 episode of status. Most common precipitant: withdrawal of AEDs or noncompliance w/ AEDs. NCSE: Accounts for 25%-50% of all SE. In comatose ICU pts incidence ˜30%. Incidence in medical ICU: ˜0.5%; in neuro ICU: ˜10%. RSE: ˜30% of SE cases (varies greatly w/ cause: e.g., more likely w/ encephalitis, GTCs; less w/ low AED levels, drug withdrawal).

Etiology of SE: Main risk factor: prior SE (25%), but most SE occurs w/o prior sz. In first time SE, cause in order of increasing frequency (but varies by age): tumor, trauma, infection, unknown, metabolic, anoxia, EtOH/drugs, medication change, stroke. Most common type: GCSE, from evolution of primary or secondarily generalized GTCs.

Pathophysiology: Disruption of nl sz-terminating mechanisms. Includes intxns b/n neuronal injury & systemic disturbances (cause & caused by SE): Neuronal injury: excitotoxicity, ↑ met. demand, ↑ blood flow, ↑ edema/mass effect. Systemic disturbances: pulmonary edema, high output cardiac failure, contraction band necrosis, cardiac arrhythmias, aspiration PNA, fever, metabolic disturbances (glucose, K, Na, phos, pH), hypoxia, ATN,

rhabdomyolysis → ARF.

Prognosis: GCSE: M&M vary w/ age, etiology, duration. Mortality: children ˜3%; adults ˜20%. Highest mortality: anoxic injury; Lowest mortality: AED, EtOH, or benzo w/d. Mortality ↑ 20% for SE lasting >1-2 h; no obvious reln at longer durations. NCSE: Prognosis less well understood. M&M generally < GCSE, though cause is critical.

Mortality Prediction Score for SE (Neurology 2006;66:1736)

	Features	Score
Level of consciousness	Alert, somnolent, or confused stuporous or comatose	0 1
Sz type	SP or CP	0
	generalized	1
	NCSE + coma	2
Age	<65	0
	>65	2
Previous sz	Yes	0
	No	1
Total		0-6

Using cutoff >3 to predict death results in the following test statistics:

Se 81%, Sp 65%, PPV 25%, NPV 96%, accuracy 73%.

Diagnosis

GCSE: Suspect after witnessed sz w/o arousal after 5 min, or if subsequent sz. Distinguish from “sz cluster” (pt awakes between szs)—less urgent, but risk of → SE. Motor activity may ↓ after multiple szs. Pseudoszs/nonepileptic szs: Sometimes hard to distinguish from GCSE. Clues favoring GCSE: hypoxemia, ↑ CPK, acidosis; clues against GCSE: avoidance behavior.

NCSE: Clinical picture + EEG e/o nonconvulsive szs >30 min. If routine EEG unavailable, interim hairline EEG is useful (but less sensitive). Routine continuous EEG in ICU pts & required duration is controversial. 95% noncomatose pts have first sz in 24 h. In comatose pts who get szs: 80% in 24 h, ˜95% in 48 h (Clin Neurophysiol 2007 Aug; 118(8):1660-1670). Specific interictal patterns predict ↑ risk of delayed NCSE, e.g., PLEDs. Benzo trial is useful when dx in doubt about NCSE, but must have clinical + EEG improvement to be diagnostic.

Criteria for Nonconvulsive Seizure

EEG pattern = nonconvulsive sz if duration > 10 s & satisfies at least 1 of 3 primary criteria.

Primary criteria

1. Repetitive generalized or focal spikes, sharp-waves, spike-&-wave, or sharp-&-slow wave complexes at ≥3 **Hz**.

2. Same as above but frequency **<3/s** + satisfies the secondary criterion (below).

3. Sequential rhythmic, periodic, or quasiperiodic waves at ≥1 **Hz** & unequivocal *evolution* in frequency (gradually ↑ or ↓ by at least 1 Hz), 1/s, e.g., 2-3/s), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone or in sharpness w/o other change in morphology is not enough to satisfy evolution in morphology.

Secondary criterion

• Significant improvement in clinical state or appearance of previously absent nl EEG patterns (such as posterior-dominant “alpha” rhythm) following admin of rapidly acting AED (see next table: benzo trial).

* Resolution of the “epileptiform” discharges leaving diffuse slowing w/o clinical improvement & w/o appearance of previously absent nl EEG patterns would not satisfy the secondary criterion.

**From Chong & Hirsch, 2005, who modified the criteria of Young et al., 1996.*

Benzodiazepine Trial for Dx of NCSE (Clin Neurophys 2007;118:1660)

Monitoring: EEG, pulse ox, blood pressure, ECG, respiratory rate w/ dedicated nurse

Benzo trial: Sequential doses of rapidly acting short-duration BZD e.g., midazolam at 1 mg/dose. Between doses, repeated clinical & EEG assessment. Trial is stopped after any of the following: **(1)** Persistent resolution of the EEG pattern (& exam repeated). **(2)** Definite clinical improvement. **(3)** Respiratory depression, hypotension, or other adverse effect. **(4)** Maximum allowed dose is reached (e.g., 0.2 mg/kg midazolam).

Test is (+) if: resolution of ictal EEG pattern resolves **& EITHER:** improvement in the clinical state **OR:** appearance of previously absent nl EEG patterns (e.g., posterior-dominant “alpha” rhythm). *Test is equivocal if*: EEG improves but pt does not.

TREATMENT OF ADULT STATUS EPILEPTICUS

Significant M&M w/ delayed Rx. Best to use pre-established time-based algorithm.

Pediatric SE: See separate protocol & considerations in next section.

NCSE: Optimal mgt less well defined than for NCSE, b/c M&M generally less; risks/benefits of aggressive sz termination are similar. General principles: (1) Promptly establish high therapeutic AED doses. (2) Tailor to clinical course, esp level of consciousness. (3) Avoid intubation & drug induced coma if possible. (4) Otherwise follow algorithm for GCSE.

GCSE: See below for in-hospital/ED protocol. If at home w/ sz clusters, prolonged sz, impending status: Rectal diazepam gel (diastat) 0.2 mg/kg, OR

sublingual lorazepam 1 mg, OR nasal midazolam 0.1-0.2 mg/kg; Call EMS.

Treatment Algorithm for Adult SE (in Hospital Rx)

Time	Interventions/Actions
0-30 min	0 min: Initial rapid assessment: Airway, breathing, circulation
	1 min: VS
	2 min: Monitor: O_2 saturation, EKG
	2-10 min: IV access (at least 2 IVs), send labs: CBC, chem7, Ca, Mg, PO4, LFTs, AED levels, tox screen, ABG
	5-10 min: Thiamine 100 mg IV then D50 50 mL IV bolus (after thiamine)
	Prepare to intubate in case necessary
	Consider antibiotics & LP, esp if febrile or not known epileptic
	5-10 min: Lorazepam 0.1 mg/kg IV (<2 mg/min)
	10-20 min: Phenytoin (50 mg/min) or FOS-PHT (150 mg/min): 20 mg/kg IV
	—Begin PHT FOS-PHT concurrently w/ lorazepam.
	—Monitor EKG, check BP q2min
	—Use separate IVs—ativan & PHT not compatible
	—Send PHT level ˜20 min after load
	—Treat fever w/ antipyretics, cooling
30-40 min	**If szs persist**
	Phenytoin (50 mg/min) or FOS-PHT (150 mg/min): 10 mg/kg IV
	—Monitor EKG, check BP q1min
	—Send second PHT level 20 min after load
	May use valproic acid (*Depacon*) *30 mg/kg IV* (*150*

	mg/min) *or levetiracetam* (*Keppra*) *50 mg/kg IV* (*100 mg/min*) *as alternatives when fosphenytoin or phenytoin contraindicated*[*]
30-60 min	**If szs persist** 40 min: Phenobarbital (75 mg/min) 20 mg/kg over 5-10 min 50 min: INTUBATE (if not already done) Initiate EEG monitoring
50-60 min	**If szs persist** 50-60 min: Midazolam 0.2 mg/kg IV (loading dose) (preferred if BP is unstable) —Titrate dose (0.1-0.4 mg/kg/h) to stop EEG & clinical szs —IVF or pressors to support BP if needed **OR** 50-60 min: Pentobarbital, 5 mg/kg IV (loading dose) for burst suppression —Titrate (0.3-9 mg/kg/h, avg = 4 mg/kg/h) for burst suppression —IVF to support BP if needed; pressors only if IVF fails or contraindicated —Maintain at 0.5-5 mg/kg/h × h before taper, watch for recurrence **OR** 50-60 min: Propofol, 1-2 mg/kg load, 2-10 mg/kg/hr maintenance drip to stop clinical & EEG szs or maintain burst suppression on EEG Head CT if not done previously/clinically indicated
3-24 h	Correct underlying cause of SE Adjust AED doses to therapeutic effect (w/ continuous EEG guidance)

24-48 h	Taper midazolam, pentobarbital, or propofol after above is complete, while maintaining high therapeutic levels of PHT (18-30 mg/L) &/or PB (25-50 mg/L) &/or VPA (70-120 mg/L) to avoid recurrent szs

(Adapted from MGH SE treatment protocol.)

* *Epilepsia* 2009;50(3):415-421; *Neurology* 2006 25;67(2):340.

First Generation AEDs

Electroencephalography (EEG)

Electroencephalography (EEG) assesses local & global cortical fxn. Reflects synchronous activity of large neural population, mainly neurons perpendicular to scalp. Good temporal but poor spatial resolution.

Electrode placement: Electrodes are applied to the scalp, connected to an amplifier system. Standard placement: International 10-20 system, based on anatomical landmarks (Sagittal plane: Line from nasion → inion; Coronal plane: Line from one tragus to the other; Axial plane: Line: 10% above nasion → point 10% above tragus →

10% above inion; Nasion = depression at top of the nose, Inion = midline bump at base of occiput. Electrodes are then placed at 20 degree intervals b/n the different points.) Electrode labeling: Odd = left, even = right; lower numbers = midline, higher = lateral. Electrode names: Fp1/Fp2 = frontopolar, F3/F4 = midfrontal, F7/F8 = frontotemporal, C3/C4 = central sulcus, P3/P4 = parietal, O1/O2 = occipital, T3/T4 = midtemporal, T5/T6 = posterior temporal. Additional data: Additional recording from: EKG, eye mvmt electrodes, respiratory monitor.

Figure 9-1 Left: 10-20 EEG electrode placement on scalp. Right: double banana montage.

EEG montages: Synaptic current flow produces an electromagnetic potential field. Signal recorded = cortical potentials + interference (e.g., ambient 60 Hz + EKG signals). Can reduce interference by displaying difference b/n adjacent leads (or diff from average). Note: Negative potentials in first lead are displayed as upward, positive as downward deflections. Standard montages: (1) Referential: Scalp electrodes compared w/ common reference, e.g., i/l ear, midline/vertex, avg of all electrodes, or weighted sum of neighbors. In referential montages, sz focus is at the electrode w/ the largest deflection. (2) Bipolar: Adjacent electrodes in a chain are compared to each other: Anterior electrode is ahead of posterior electrode, & left is generally ahead of right. A common montage is the longitudinal bipolar (“double banana,” Fig. 9.1: Left temporal chain: Fp1 → F7 → T3 → T5 → O1; Left parasagittal chain: Fp1 → F3 → C3 → P3 → O1; Central chain: Fz → Cz → Pz; similarly for right side). In bipolar montages, EEG activity at end of chains is not easily assessed; additional montages w/ different chain constructions help assess

activity at these leads [e.g., transverse montage & the circumferential (circular) montage].

Localization of activity achieved via detecting reversal of polarity of deflections.

ESSENTIALS OF EEG INTERPRETATION

Interpretation follows structured approach that assesses background frequency, organization, symmetry, state changes, response to stimulation & activation methods, & presence of transients.

Background frequency: Predominant frequency in absence of external stim. EEG is conventionally divided into four frequency bands (Fig. 9.2).

“Normal” freq varies w/ location, state, age. For nl healthy young adult: Alpha predominates in posterior leads when awake, alert, eyes closed. Beta prominent frontally, no change w/ eye opening. Theta seen temporally, ↑ during drowsiness. Delta: Usu minor in awake EEG; a defining feature of slow-wave sleep. Diff frequencies can be superimposed.

Organization: An assessment of the frequency & amplitude of the EEG: “Well-organized” EEG = posterior dominant rhythm in the alpha frequency (usually 9-11 Hz). Amplitude—noteworthy features: focal attenuation, significant ↑ or ↓.

Symmetry: Asymmetries in frequency or amplitude can indicate underlying pathology. (Example: Frequency: prior R MCA infarct or parietal tumor ↑ delta activity in R parietal lead; Amplitude: prior craniotomy site ↑ increased amplitudes overlying the area.) For epilepsy, determining asymmetries in interictal patterns, sz onset & amplitude is critical in localization (& thus subsequent management).

Figure 9-2 Background frequency

State: EEG differs w/ state; various abnormalities often best seen in specific states. (1) Awake, eyes closed: State in which organization is assessed, due to presence of alpha rhythm in posterior leads in healthy subjects. (2) Awake, eyes open: Attenuation of alpha, w/ development of low-voltage faster activity. Eye blinks in frontal leads. Muscle artifact often present. (3) Drowsiness: Slow, pendular eye mvmts. Attenuation of occipital alpha. Increased frontocentral theta slowing. May see vertex waves (synchronous bilateral sharp waves in central leads). Can see ↑‘d epileptiform (interictal) discharges. (4) Stage 2 sleep: Appearance of sleep spindles (12-14 Hz

synchronous waves, largest in middle of spindle, greatest in central leads). Diffuse slowing in delta/theta range. Frequent vertex waves. K-complexes (high-voltage polyphasic waves often associated w/ sleep spindles; Fig. 9.3). POSTs (positive occipital sharp transients, see below) common. Increased epileptiform activity commonly present. (5) Sleep stages 3-4: Stage 3 has 20%-50% delta, ˆ/slowing of sleep spindles & vertex waves. Stage 4 is >50% delta activity, sleep spindles practically absent. (6) REM: Low-voltage fast activity, rapid eye mvmts, absent muscle artifact.

Activation procedures

(1) Physical stimulation: Eye opening & closure, sounds, names, startle responses, physical stimulation. Used to assess EEG reactivity in nl & esp. abnl states. (2) Hyperventilation (HV): Standard (nl) response to HV: no change or development of mod-high amplitude delta/theta w/ frontal predominance; EEG → baseline w/in a minute after stopping. May provoke absence szs. Also effective in provoking other generalized epilepsies. (3) Photic stimulation: Strobe light in 10 secs trains beginning 1-3 Hz, increasing up to 30 Hz. Normal response: “photic driving”: Induction of occipital-predominant rhythm at a harmonic or subharmonic of strobe flash frequency. A photomyoclonic response (stimulus-induced contraction of frontal muscles) is a nl (rare) variant. Photoparoxysmal response: Marker for generalized epilepsies (tonic-clonic, myoclonic, & absence). (4) Sleep deprivation: Effective method for activating interictal discharges (J Clin Neurophysiol 1984;1:83). May ↑ likelihood of detecting interictal discharges in pt w/ previously nl EEG.

Epileptiform transients

Spikes: Sharply contoured, distinct from background, duration 20-80 ms (Fig. 9.4a). Have a field, rise phase faster than falling, often followed by high-voltage slow wave in delta/theta range (then called “spike-wave complex”).

Figure 9-3 Sleep spindles & K-complexes

P.82

Figure 9-4a Spike

Figure 9-4b Sharp wave

Figure 9-4c Polyspike & wave

Figure 9-4d Triphasic waves: High-voltage (>70 μV) positive sharp transient, preceded & followed by negative waves of lower amplitude.

Sharp waves: Like spikes but longer (80-200 ms; Fig. 9.4b); ±subsequent slow wave.

Polyspike & wave: Multiple spikes → slow wave (Fig. 9.4c). Common in myoclonic epilepsies.

Common artifacts

Eye mvmts: Cornea is positively charged (relative to retina), so eye mvmts → potential changes in frontal leads. Eye closure/opening produces symmetric changes in FP1/FP2, while lateral eye mvmts produce opposite changes in F7/F8. Can see lateral rectus spikes in F7/F8.

Eye blink: Initial (+) in frontopolar leads 2/2 eye closure, then (−) from eye opening.

EKG: Sharp EEG potentials may result from cardiac activity—correlate EEG w/ ECG strip.

Muscle: Extremely fast spikes/transients, <20 ms in duration & often of very high amplitude, too fast to be of cerebral origin. Often prominent in frontotemporal leads, more prominent in waking state. Can be rhythmic (i.e., chewing, tremor, walking).

Machine: Stereotyped rhythmic potentials from machines (e.g., ventilator, IV drip, LVAD).

60 Hz: Rhythmic frequency at 60 Hz from nearby electrical devices or wiring, often recorded from electrodes w/ high impedance.

Electrode “pop”: Faulty electrode contact → momentary ↑ impedance. Can resemble spikes; distinguishing feature = lack of electrical field (transient restricted to single faulty electrode).

EEG IN HEALTH & DISEASE

NORMAL EEG: COMMON VARIANTS

Alpha variants: Include slow variant (post. rhythm 4.5-5 Hz, often notched, subharmonic of nl posterior alpha). Can also have fast alpha variant 16-20 Hz. Both attenuate w/ eye opening.

Mu: Negative arch-shaped rhythm, 7-11 Hz, in the central electrodes (C3/C4), over the motor strip. Can be present at rest, attenuates w/ mvmt (or thinking of mvmt) of the c/l arm.

Rhythmic temporal theta: Bursts of sharply-contoured waves, theta (5-7 Hz) range, predominately in midtemporal electrodes. Common in adults in relaxed wakefulness & drowsiness.

POSTS/Lambda waves: POSTS = positive occipital sharp transients of sleep. Nonepileptiform sharp + waves, predominantly in occipital leads during stage II sleep. Lambda: +occipital waves present when viewing scenes/complex images; attenuates w/ eye closure.

Sleep associated nl variants: Stereotyped sharply contoured transients present during drowsiness & light sleep, NOT associated w/ epilepsy. These include Wicket spikes, 14 & 6 (14/6) positive spikes, 6-Hz spike-&-wave bursts ("phantom spikes"), benign epileptiform transients of sleep ("BETS"), aka small sharp spikes (SSS).

Breach: Focal area ↑ amplitude, sharply contoured activity near skull defect (i.e., craniotomy).

ABNORMAL EEG RHYTHMS

Focal slowing & focal attenuation: Indicative of underlying focal lesion (e.g., infarct, tumor, abscess, contusion/hematoma, focal epileptic region). Delta activity indicates more severe disruption of nl cortical circuitry than theta activity. Irregular polymorphic delta activity suggests lesions of underlying WM. Focal attenuation suggests damage to cortex or ↑ distance b/n cortex & skull (i.e., from focal atrophy or a subdural hematoma).

Generalized slowing: Nonspecific indicator of diffuse disturbance of cerebral activity (i.e., toxic-metabolic encephalopathy, hypoxic-ischemic encephalopathy, encephalitis, neurodegenerative conditions). More severe encephalopathies often a/w more diffuse slow activity, greater degree of slowing, & higher amplitudes.

FIRDA: Frontal Intermittent Rhythmic Delta Activity consists of bilaterally synchronous & regular delta waves w/ a relatively constant frequency in frontal leads. Believed to result from an abnl interaction b/n the cortex & thalamus, & can indicate metabolic disturbances, subcortical frontal or diencephalic tumors, or increased ICP.

Focally increased activity: Often 2/2 skull defects, i.e., craniotomy. Can be an ictal phenomenon in epileptic encephalopathies (e.g., Lennox-Gastaut).

Excessive fast activity: A generalized increase in beta activity often results from sedative tranquilizing medications such as benzodiazepines & barbiturates.

PLEDs: Periodic Lateralized Epileptiform Discharges, consisting of repetitive discharges of high-voltage sharp waves (±slow components) occurring continually every few seconds in a periodic fashion (Fig. 9.5). PLEDs often result from acute structural lesions such as acute infarcts, HSV encephalitis, or rapidly growing tumors. They are on the continuum b/n abnl & frankly ictal, along w/ other related EEG findings such as BiPLEDS (bilaterally asynchronous PLEDs), GPEDs (generalized periodic epileptiform discharges), & others.

Figure 9-5 PLEDs

Burst suppression: Periods of marked depression of cerebral activity, visualized as flattening of the EEG background, interrupted by bursts of bilaterally synchronous high-voltage delta & theta waves, possibly w/ superimposed spikes & sharp waves. Seen in coma from CNS depressant drugs such as barbiturates, in general anesthesia, & from severe diffuse anoxic injury, where it may be associated w/ a poor prognosis.

Triphasic waves (Fig. 9.4d): Usu bilaterally synchronous, generalized, max over ant leads. Nonspecific, but commonly seen in metabolic encephalopathies (e.g., hepatic dz or uremia).

EEG CORRELATES OF NEUROLOGIC DISEASE

Herpes simplex encephalitis: Many EEG correlates described: Focal slowing, focal epileptiform discharges, szs. Temporal PLEDs are an early & classic finding.

Creutzfeldt-Jacob disease: Initially ↑‘d focal or generalized slowing in theta range. Subsequently low-to-mod amp bi- or triphasic sharp waves w/ frequency ˜1 Hz, may be a/w myoclonic jerks. Eventually degenerates into generalized low-voltage tracing.

P.84

Subacute sclerosing panencephalitis: High voltage repetitive polyspike-&sharp-&-slow-wave complexes, recurring 4-15 s, a/w rapid or slow myoclonic jerks.

EEG IN EPILEPSY

INTERICTAL EPILEPTIFORM DISCHARGES

Interictal epileptiform discharges (IEDs) include: spikes, sharp waves, spike-&-wave complexes, sharp-&-slow-wave complexes, polyspike-&-wave complexes, multiple-sharp-&-slow-wave complexes. All imply irritated region of cortex; some are a/w particular epileptic syndromes. IEDs satisfy

the following (“Not all sharply contoured transients are IEDs”): (1) Paroxysmal—high voltage c/w background & disrupt background cortical rhythm. (2) Duration 20-200 ms. (3) Often accompanied by time-locked high-amplitude slow wave. (4) Must have physiologic field in >1 electrode + voltage gradient. (5) Typically surface neg in polarity, i.e., ↑ deflection. (6) Asymmetric appearance w/ steeper slope during rise than decline w/ the decline returning past the isoelectric point (decline is greater than the rise).

Localization of sz focus: (1) Location of IEDs can reveal location of ictal focus: Consistent discharges from single electrode or pair often suggests epileptiform region is nearby, e.g., F7-T3 electrodes in left TL epilepsy. (2) Two independent foci still suggests partial epilepsy, but localization is more difficult. (3) Specific IED patterns a/w specific epilepsy syndromes, e.g., 3 Hz spike-&-wave in idiopathic generalized epilepsy (IGE), esp. childhood absence epilepsy (CAE).

EEG IN SEIZURE

EEG correlates of szs vary widely, e.g., well-defined epileptic rhythm (i.e., generalized 3 Hz spike-&-wave in absence szs); subtle Δ in background w/ development of synchronous theta activity; no electrographic Δ at all on surface EEG in medial frontal lobe sz w/ a deep origin.

Electrographic szs: Often have a common pattern of development (1) Onset: (Focal or general) that is often distinct from the preceding background; (2) Evolution: Buildup of rhythmicity, may generalize, often starting at higher frequencies that generally slow down over the course of the sz; (3) Abrupt termination; (4) Post-sz slowing.

Ictal patterns: Include: rhythmic spike-wave, sharp-wave, polyspike-&-wave, or sharp-&-slow-wave; rhythmic delta or theta activity; generalized paroxysmal fast activity.

Uninterpretable ictal EEG (e.g., 2/2 muscle artifact or lack of definite ictal EEG pattern): Surface spike requires synchronization of ˜6 cm^2 of cortex. Thus, EEG will not detect focal szs confined to small regions.

Deep & midline cortical structures (i.e., medial frontal lobes, orbitofrontal cortex, cingulate cortex, deep sulci) are inaccessible to surface EEG.

EEG IN EPILEPSY SYNDROMES

Idiopathic generalized epilepsies (IGEs)—a set of genetic epilepsy syndromes, likely due to channelopathies. Often have interictal fragments of generalized discharges w/ frontocentral predominance. (1) CAE: 3 Hz (range: 2.5-4 Hz) generalized bisynchronous spike-&-wave discharges, maximal in frontocentral leads. Bursts start at ˜4 Hz, slow to 2.5 Hz by end of sz. Can

often see occipital intermittent rhythmic delta activity in the interictal period. (2) Juvenile myoclonic epilepsy (JME): Interictal period contains nl background w/ spontaneous bursts of generalized bisynchronous epileptiform discharges w/ polyspike & polyspike-wave morphology. Frequency of discharges is faster than in absence, typically in the 3.0-5.5 Hz range.

Medial temporal lobe epilepsy (MTLE): Most common focal epilepsy in adults. Interictal EEG: Typically anterior temporal sharp waves w/ intermittent temporal slowing. ˜1/3 pts w/ b/l interictal epileptiform discharges. Ictal EEG: ≥5 Hz anterior temporal discharges that begin w/in 30 s after onset of clinical Si/Sx. Temporal intermittent rhythmic delta activity (TIRDA) is a nonepileptiform interictal EEG pattern that has a high positive predictive value for temporal lobe epilepsy (Can J Neurol Sci 1989; 16:398).

Benign childhood epilepsy w/ centrotemporal spikes (BECTS): Syndrome of primarily nocturnal stereotyped partial szs w/ u/l facial paresthesias & tonic-clonic mvmts + secondary generalization. Resolves spontaneously during adolescence. Aka “benign rolandic epilepsy.” EEG: stereotyped sharp waves in midcentral/temporal regions (C3/C4. T3/T4), often w/ frontal positivity runs of repetitive spikes during sleep (usually during SWS).

Childhood occipital epilepsy: Usually presents ages 5-7 w/ brief szs, lasting seconds; begin w/ visual Sx. ± ictal/postictal vomiting & HA. Generally excellent prognosis.

P.85

EEG: background nl, but stereotyped high-voltage occipital spike-wave complexes that disappear w/ eye opening & visual fixation. Activated during NREM sleep.

Childhood epileptic encephalopathy syndromes: Diverse group of syndromes a/w slowing or regression of development. Many have characteristic EEG signature. Examples include early infantile epileptic encephalopathy (Ohtahara’s syndrome), infantile spasms (West syndrome), Lennox-Gastaut’s syndrome, Landau-Kleffner syndrome (epileptic aphasia), the progressive myoclonic epilepsies, & the syndrome of continuous spikes during slow-wave sleep (CSWS). Of these, the two most common are infantile spasms & Lennox-Gastaut. (1) West syndrome (infantile spasms): Spasms, arrest of psychomotor development. EEG: Hypsarrhythmia: Chaotic, high-voltage irregular slow activity w/ multifocal spikes & sharp waves, & periods of generalized attenuation, w/ an absence of virtually all nl activity. (2) Lennox-Gastaut: Epilepsy syndrome w/ mental retardation & multiple difficult-to-control sz types (tonic, atonic, & atypical absence most common). EEG: Generalized slow-spike-&-wave pattern occur in 1.5-2.5 Hz bilaterally

synchronous bursts. More irregular than 3 Hz spike-&-wave of absence szs. Another defining EEG feature is presence of paroxysmal fast activity (diffuse bilaterally synchronous bursts of 15-20 Hz activity lasting several seconds) during NREM sleep.

USES OF EEG

Diagnosis & management of status epilepticus (NCSE & GCSE)

NCSE: Nonconvulsive szs & NCSE p/w AMS (including coma) but absent/minor motor manifestations (e.g., intermittent myoclonic jerks, facial twitching, or nystagmus); definition of subtle & nonconvulsive status may overlap. NCSE can be primary or evolve from generalized convulsive SE (GCSE). Often difficult to dx; multiple etiologies. High prevalence in ICU pts w/ AMS/coma even w/o history of szs (8% in one study: Neurology 2000;54:340); higher rate (27%-34%) w/ h/o neurological dz, e.g., in neuro-ICU. (Clin Neurophysiol 2007; 118:1660). EEG in NCSE: Interictal patterns vary, w/ frequent abnl rhythms such as PLEDs & GPEDs on the continuum of cortical irritability (see Fig. 9.5 in] J Clin Neurophysiol 2005;22:79), but usually not considered frankly ictal. Time to detection: for pts ultimately found to have szs on EEG: (1) Overall: <24 h: 88%;<48 h: 93%; 7% required >48 h. (2) Comatose pts: <24 h: 80%; >24 h: 20% (vs. 5% for noncomatose);>48 h: 13 (Neurology 2004;62:1743).

GCSE: EEG classically evolves through five stages (Epilepsy Res 1990;5:49). Last four often w/o clinical convulsions (pt comatose). (1) Discrete clinical convulsive sz + typical generalized spike-wave discharges (d/c's); (2) Merging pattern w/ spike-waves & slow waves of waxing & waning amp. & freq; (3) Continuous spike-wave d/c's; (4) Epileptiform discharges punctuated by periods of ↓ activity; (5) GPEDs on flat background.

Diagnosis of epilepsy: often helped by finding IEDs (or less often, frank szs) on EEG.

Sensitivity of a routine EEG: In pts w/ dx of epilepsy: Single EEG: 29%-55%; 60%-80% w/ repeat recordings. Yield after fourth EEG is relatively limited. ˜20% of pts w/ szs will not have IEDs. Yield of repeat EEGs ↓ if initial EEG is entirely nl (Epilepsia 1987;28:331).

IEDs are recorded more often in: Children; TL epilepsy vs. other focal epilepsies; in sleep & after sleep deprivation; soon after a sz. Additional electrodes (foramen ovale, nasopharyngeal, anterior temporal, sphenoidal) can ↑ yield (Epilepsia 2006;47 Suppl 1:14).

Benzodiazepines & barbiturates: ↓ freq. of IEDs. Effects of other AEDs vary. IEDs are seen in ˜0.5% of nl individuals (Electroencephalogr Clin

Neurophysiol 1993;86:75). This number is higher in children & adults w/ neuropsychiatric disease.

Evaluation of first sz

Prediction of sz recurrence: Incidence of second sz in adults ˜40%-50% w/in 2 yr (Neurology 1991;41:965; Neurology 1993;43:478; Lancet 2005;365:2007). Average yield of abnl EEG after first sz ˜50%; epileptiform abnls in ˜30% (Neurology 2007;69:1996). Yield possibly ↑ in first 24 h (in 300 pts epileptiform abnlities noted in 51% of EEGs done<24h vs. 34% done later (Lancet 1998;352:1007). If first EEG is nl, sleepdeprived EEG done soon after further ↑'d likelihood of finding epileptiform abnlities.

Impact of EEG: Most studies find abnl EEG predicts a ↑ likelihood of sz recurrence; degree of ↑ risk varies b/n studies. Large meta-analysis found relative risk of epileptiform EEGs of 2.0 (Neurology 1991;41:965); more recent analysis of data from MESS (Multicenter Epilepsy & Single Sz) study found hazard ratio of 1.53 (Lancet Neurol 2006;5:317). The post-test probability of sz recurrence was 49.5% in

pts w/ epileptiform EEG abnlities, vs. only 27.4% w/ completely nl EEG (Neurology 2007;69:1996).

Localization of seizure onset: EEG critical in localization of focal epilepsies. IEDs typically (but not always) seen in epileptogenic zone. In TLE, clear lateralization (all IEDs from one side) strongly suggests unilateral focus, a/w good surgical outcome (Neurology 1990;40:413). EEG during sz usu reveals onset location & pathway of spread.

Diagnosis of psychogenic nonepileptic seizures (PNES): NL EEG during stereotyped event strongly suggests PNES. EEG helps distinguish epileptiform & non epileptiform events in pts w/ both. May need to capture multiple events before definitive dx of PNES. Can be falsely nl in pts w/ deep or midline frontal sz foc. Long-term video EEG monitoring (LTM, VEEG): Indications: (1) Characterization of paroxysmal neurological events; (2) PNES vs. szs; (3) nocturnal frontal szs vs. parasomnias; (4) Surgical planning —localization, characterization of sz types.

Delirium

GENERAL INFORMATION

Definition of acute confusional state, aka “delirium”: Altered mental state w/ impaired attention/speed/clarity/coherence of thought. Synonyms (roughly): Delirium, acute confusional state, toxic-metabolic encephalopathy. Delirium usu. considered an agitated acute confusional state (but not required in DSM IV).

DSM IV definition of delirium: Perceptual disturbance or change in cognition/level of consciousness characterized by (1) ↓ ability to focus/sustain/shift attn, (2) not better accounted for by pre-existing dementia, (3) develops over hours to days, (4) fluctuates over course of the day.

Presentation: Typical: ↑ vigilance, psychomotor & autonomic overactivity; agitation, excitement, tremulousness, hallucinations, delusions. Variations: Hypoactivity, hyperactivity w/ ↑ sympathetic activity, sleep Δs, emotional Δs (e.g., fear, depression, euphoria, perplexity). ↓ LOC can range from drowsiness to coma. Hypervigilance: Esp in EtOH or sedative w/d; less common in older pts. Other: Memory loss, disorientation, difficulty w/ language & speech. Elderly: Most common presentation: Quiet, withdrawn (often mistaken for depression).

Epid: 30% elderly medical pts 10%-50% elderly surgical pts.

Outcomes/prognosis (Nat Rev Neurol 2009;5:210): Short term: Long hospitalization, injury, institutionalization. Long term: Full recovery; long-term cognitive/fxnl disability, death. Not always transient & reversible (may last > 12 mo, esp w/ underlying dementia; up to 2/3 still dependent after 2 yr). High mortality: 1 mo: 14%, 6 mo 22% (2× higher than w/o).

WORKUP

HPI: Difference from baseline functioning, prior episodes, risk factors, predisposing conditions or medications, recent febrile illness, history EtOH/drug abuse, recent depression.

General examination: Vital signs, state of hydration, skin condition, potential infectious foci, dusky appearance, COPD, jaundice, hepatic failure, stigmata of renal failure, needle tracks, h/o drug abuse, cherry-red lips (e/o CO poisoning); Breath: Alcohol, fetor hepaticus, uremic fetor or ketones; Bitten tongue, fx/dislocation of the shoulder (e/o sz); Autonomic activation (tachycardia, sweating, flushing, dilated pupils; these responses blunted in

elderly pts).

Neurologic examination: Level of consciousness, inattention, focal signs, multifocal myoclonus, asterixis, postural action tremor; loss of VOR or nystagmus w/ unexplained ocular palsies sparing pupillary reactivity raise possibility of Wernicke encephalopathy.

Bedside tests of attention: Digit span: Repeat series of random numbers. Abnl: Inability to repeat >5. Vigilance "A" test: Read 60 random letters, pt taps on "A"; Abnl: miss > 2.

Diagnostic testing

- Finger stick gluc, Chem 10 (incl. Na, K, BUN, Cr, CO_2, gluc, Ca, Mg), CBC, UA, LFT, NH3, ESR, CRP, TSH/fT4, UA, RPR, TSH, CXR, Tox screen (blood & urine), drug levels if appropriate (e.g., digoxin, lithium, quinidine).

- B_{12}, methylmalonic acid, homocysteine, folate, thiamine.
- ABG (resp. alkalosis in early sepsis, hepatic failure, early salicylate intox, cardiopulm dz; met. acidosis (uremia, DKA, lactic acidosis, late phases of sepsis); poisoning w/ salicylates, methanol, & ethylene glycol).
- LP: In any febrile confused patient; also if delirium not well explained by prior w/u. Older pts w/ bacterial meningitis can p/w delirium rather than fever, HA, meningismus.
- Neuroimaging before LP if: obtunded, focal si/sx, papilledema, suspect ï ICP
- Imaging: Unnecessary if: clear treatable cause, no trauma, nonfocal exam, following cmds.
- EEG: (1) Exclude seizures, esp NCSE/subclinical szs. (2) Help w/ dx (diffuse b/l background slowing in metabolic encephalopathies, viral encephalitis; triphasic waves w/ hepatic encephalopathy, uremia, sepsis; PLEDs in temporal leads in HSV encephalitis; NCSE common in ICU w/ unexplained AMS; detection may require >24 h monitoring).

DIAGNOSIS OF DELIRIUM

Short Ddx (Mnemonic): "I WATCH DEATH"

Etiologies	Examples
Infection	HIV, sepsis, UTI, pneumonia
Withdrawal	EtOH, barbiturates, benzos
Acute metabolic	Acidosis, alkalosis, electrolyte Δs, liver failure, renal failure
Trauma	Postoperative, head injury, heat stroke, severe burns
CNS pathology	Hemorrhage, hydrocephalus, encephalitis, meningitis, abscess, seizure, stroke, tumor, vasculitis
Hypoxia	Anemia, CO poisoning, hypotension, pulmonary or cardiac failure
Deficiencies	B_{12}, folate, niacin, thiamine
Endocrinopathies	Hyper/hypoadrenocorticism, hyper/hypoglycemia, myxedema, hyperparathyroidism
Acute vascular	Hypertensive encephalopathy, stroke, arrhythmia, shock
Toxins or drugs	Drugs (prescription or illicit), pesticides, solvents
Heavy metals	Lead, manganese, mercury, arsenic, beryllium, thallium

- Etiology is frequently multifactorial. Two types of factors: (1) Precipitating factors: Virtually any medical condition in susceptible pt (see table below). (2) Factors that increase baseline susceptibility: Brain dz (dementia, stroke, Parkinson dz (˜50% pts w/ delirium)), advanced age, sensory impairment, psychiatric illness, sensory impairment (e.g.,

hearing & vision loss; loss of glasses or hearing aids), absence of a clock or watch, advanced cancer, postoperative state, anemia, severe pain.

Causes/Precipitants of Acute Confusional States (Not Exhaustive)

Toxins

- Prescription meds, polypharmacy
- Drugs of abuse: E.g., EtOH
- Intox/w/d (narcotics, cocaine, LSD, PCP)
- Poisons: E.g., ethylene glycol, methanol, insecticides, carbon monoxide
- Heavy metals

Infection: Sepsis, UTI, respiratory tract, skin, soft tissue, etc.

Metabolic derangements

- Electrolytes (↑ or ↓): Na, Ca, Mg, Phos
- Uremia, hyperammonemia
- Endocrine (↑

Brain disorders

- CNS infxn: Encephalitis, meningitis, brain or epidural abscess
- Seizures, esp. nonconvulsive status
- Head injury
- Hypertensive encephalopathy
- Psychiatric disorders

Systemic organ failure

- Cardiac failure
- Hematologic: Thrombocytosis, hypereosinophilia, leukemic blast cell crisis, polycythemia
- Liver failure: Acute, chronic
- Pulm dz, incl hypercarbia & hypoxemia
- Renal failure: acute, chronic

Physical disorders: Burns, electrocution, hyper-/hypothermia

Other: Dehydration, catheters, postop state (esp elderly pts), immobility (e.g., restraints), sensory deprivation, stay in ICU/long-term care unit, room changes for hospitalized pts, sleep deprivation

or ↓): Thyroid, parathyroid, pancreas, pituitary, adrenal

- Hypercarbia, hypoxemia
- Hyperglycemia, hypoglycemia
- Hyperosmolar, hypoosmolar states
- Metabolic errors: porphyria, Wilson's, etc.

Nutritional deficiencies

- B_{12}, thiamine, folate, niacin
- Wernicke encephalopathy

Trauma: SIRS, head injury, fat embolism

P.88

Drugs that Commonly Cause Confusional States (Not Exhaustive)

Analgesics	Anticonvulsants	GI drugs
NSAIDs, Opioids (esp meperidine)	Carbamazepine, Phenytoin, Valproate, Vigabatrin	Antiemetics, Antispasmodics, H2 blockers,

		Loperamide
Antibiotics, antivirals Acyclovir, Aminoglycosides, Amphotericin B, Antimalarials, Cephalosporins, Cycloserine, Fluoroquinolones, Isoniazid, Interferon, Linezolid, Macrolides, Nalidixic acid, Penicillins, Rifampin, Sulfonamides	**Antidepressants** Mirtazapine, SSRIs, TCAs **Cardiovascular meds** Antiarrhythmics, β-blockers, Clonidine, Digoxin **Corticosteroids**	**Herbal drugs** Atropa belladonna extract, Henbane, Mandrake, Jimson weed, St. John's Wort, Valerian
Anticholinergics Atropine, Benztropine, Diphenhydramine, Scopolamine, Trihexyphenidyl	**Dopamine agonists** Methyldopa, Amantadine, Bromocriptine, Levodopa, Pergolide, Pramipexole, Ropinirole **Hypoglycemic agents** **Diuretics**	**Hypnotics, sedatives** Barbiturates, Benzos, Muscle relaxants, Baclofen, Cyclobenzaprine **Other** Disulfiram, Donepezil, Interleukin-2, Lithium, Phenothiazines

DIFFERENTIAL DIAGNOSIS OF DELIRIUM

"Sundowning"—Evening behavioral deterioration; typically in demented pts. Focal syndromes (not exhaustive): Temporal-parietal: E.g., Wernicke aphasia (mimics confusion, but restricted to language). Bitemporal: transient global amnesia (TGA), visual agnosia, cortical deafness (either bitemporal or left temporal), Kluver-Bucy syndrome (apathy, visual agnosia, increased sexual activity, & increased oral behavior); due to bilateral amygdala damage. Occipital: Anton syndrome (cortical blindness & confabulation), 2/2 b/l occipital damage. Frontal: Akinetic mutism, incontinence; ↓ spontaneity, judgment, memory, emotion. Nonconvulsive status—Esp older pts; requires EEG for dx; suggestive features: b/l facial twitching, unexplained nystagmus, spontaneous hippus (spasmodic, rhythmic (<0.04 Hz), but irregular dilating &

contracting pupillary movements between the sphincter & dilator muscles), prolonged “post-ictal state,” automatisms (lip smacking, chewing, or swallowing movements), acute aphasia or neglect w/o a structural lesion. Dementia: Alzheimer’s dz: Usually insidious, progressive, w/o significant fluctuation, occurs over months-years; attention relatively intact; DLB: Sometimes confused w/ delirium 2/2 fluctuations & visual hallucinations. Primary psychiatric illnesses: (1) Depression: Like delirium a/w poor sleep, ↓ attention/concentration; (2) Mania: Can be confused w/ hyperactive delirium w/ agitation, delusions, & psychotic behavior; usually a/w prior mania or depression; (3) Schizophrenia: Delusions usually systematized, longer history, sensorium o/w clear.

MANAGEMENT OF DELIRIUM

General prevention & Rx of delirium: Four main strategies: (1) Avoid/remove aggravating factors. (2) Identify & treat causes. (3) Supportive/restorative care to prevent further physical & cognitive decline. (4) Control dangerous/disruptive behaviors.

Prevention/interventions: ↓ freq & duration, no proven effect on severity:(1) Orientation protocols, cognitive stimulation activities (structured activities), frequent reassurance, touch, verbal orientation from familiar persons. (2) Environmental modification & nonpharmacologic sleep aids for insomnia. (3) Minimize ambient noise, provide good lighting (e.g., windows). (4) Early mobilization, minimizing use of restraints. Prevent skin breakdown. (5) Visual aids (e.g., glasses) & hearing aids PRN. (6) Early volume repletion for pts w/ dehydration. (7) Pain mgt protocols (reduce severity/duration but not incidence of delirium). (8) Treat incontinence (present in >50% delirious pts). (9) Min risk of asp pneumonitis.

Avoid/prevent, if possible: Changes of environment (e.g., room changes), physical restraints, constipation, anticholinergic drugs, urinary & fecal catheters.

Delirium & pain: Complex reln b/n pain & delirium: Under-treated pain → agitation & confusion, but opioid use → delirium. “Crescendo pain” may represent a form of delirium. Meperidine in older pts often exacerbates delirium.

Supportive care: Prevent complications including immobility, aspiration, skin breakdown.

Managing behaviors: Hyperactive delirium (agitation, combative behavior): risk for falls, wandering off, removing tubes & lines: may need physical or

chemical restraints.

- Physical restraints: Last resort b/c: ↑ agitation, ↓ mobility, cause pressure ulcers, ↑ aspiration risk, prolong delirium. Alternatives: Sitter (preferably familiar person).
- Chemical restraints (psychotropic medications): Low-dose haloperidol can reduce severity & duration of episodes. Newer atypical antipsychotic w/ fewer extrapyramidal side effects, similar efficacy (quetiapine, risperidone, olanzapine).
- Benzos (e.g., lorazepam 0.5-1.0 mg): Onset rapid (˜ 5 min if given IV), BUT: Can ↑ confusion, sedation ("paradoxical reaction"); lorazepam an independent risk factor for delirium.

Pharmacologic Management of Delirium (Nat Rev Neurol 2009;5:210)

	Dose	Adverse Effects	Comments
Prophylactic Therapies			
Antipsychotics			
Haloperidol (Haldol)	0.5-1.0 mg PO bid	EPS, ↑ QTc	RCTs show ↓ sx severity, duration
Atypical Antipsychotics			
Risperidone (Risperdal)	0.5 mg bid	EPS, ↑ QTc	Similar efficacy to haldol. May ↑ mortality in demented pts—avoid long-term use
Olanzapine (Zyprexa)	2.5-5 mg qd		
Quetiapine (Seroquel)	12.5-25 mg bid		

Benzodiazepines: *Drugs of choice in delirium only for EtOH & opiate withdrawal*

Lorazepam (Ativan)	0.5-1 mg PO q4h prn	Paradoxical excitation, resp. depression, sedation, confusion	Not shown to improve delirium; use limited by adverse effects

Cholinesterase Inhibitors

Donepezil (Aricept)	5 mg qd	n/v, diarrhea	Case reports; no RCTs

PRN Therapy

Antipsychotics

Haloperidol	0.5 mg q4h prn (PO) or q60min (IM) prn	EPS, ↑ QTc	May ↓ delirium incidence Avoid IV route (short acting)

Cholinesterase Inhibitors

Donepezil	5 mg qd	n/v, diarrhea	No studies have shown efficacy

Rapidly Progressive Dementia

Definition: Deterioration of intellectual/behavioral/cognitive fxn (dementia) over weeks-months.

Epidemiology (from UCSF data: 825 RPD referrals, most “r/o CJD,” Neurol Clin 2007;25:783): 54% Prion dz (37% sporadic, 15% genetic, 2% acquired), 26%, neurodegenerative (i.e., classically “chronic” degenerative dzs), 25% autoimmune. 11% infectious, 11% psychiatric, 9% misc other; 28% undetermined (often leukoencephalopathy/encephalopathy of unknown origin).

DIFFERENTIAL DIAGNOSIS & WORKUP FOR RPD

DDx of RPD (Neurol Clin 2007;25:783): “VITAMINS”: Vascular, Infectious, Toxicmetabolic, Autoimmune, Metastases/neoplasm, Iatrogenic, Neurodegenerative, Systemic.

P.90

- Vascular: Infarcts (large vessel, thalamic, multifocal); TTP (2/2 microangiopathic thromboses), hyperviscosity (e.g., polycythemia vera, monoclonal gammopathy), cerebral venous thrombosis, dural arteriovenous fistulas, inflammatory cerebral amyloid angiopathy (I-CAA).
- Infectious: Viral encephalitis, HIV dementia, PML, subacute sclerosing panencephalitis (SSPE), fungal infxns, syphilis, parasites, Lyme dz, Balamuthia, Whipple dz.
- Toxic/metabolic: Deficiencies: B_{12} (cyanocobalamin), B_1 (thiamine), Vitamin E, niacin, folate; toxicities: bismuth, lithium, mercury, arsenic; electrolyte abnls; uremia, Wilson’s dz, portosystemic encephalopathy, acquired hepatocerebral degeneration, porphyria.
- Autoimmune: Lupus cerebritis, 1° or 2° CNS vasculitis, sarcoidosis, Hashimoto encephalopathy, paraneoplastic limbic encephalopathy, nonparaneoplastic autoimmune [e.g., anti-voltage-gated potassium channel (VGKC) antibody mediated].
- Metastases/neoplasm: Nonautoimmune paraneoplastic, CNS mets, primary CNS lymphoma, intravascular lymphoma (IVL), lymphomatoid granulomatosis (LYG), gliomatosis cerebri.

- Iatrogenic: Neurosurgery, XRT, medication side effects.
- Neurodegenerative: Creutzfeldt Jacob dz (CJD; sporadic, iatrogenic, familial), AD, DLB, FTD, CBD, PSP.
- Systemic/endocrine: Thyroid, parathyroid, & adrenal abnormalities.

Diagnostic workup: Generic & "as Indicated" Tests

Essential (all pts presenting w/ RPD)

- Blood: CBC, PT, PTT, chem7, Ca, Mg, Phos, LFTs, LDH, Vitamin B_{12}, homocysteine, MMA, TSH, free-T4, "Rheum screen" (ESR, CRP, ANA), RPR, HIV Ab, Lyme Ab, Anti-TG Abs, anti-TPO Abs, paraneoplastic/autoimmune Abs [minimum: anti: Hu (ANNA-1), Ma2 (Ta), CV2 (CRMP-5), amphiphysin, VGKC; consider also: Anti: Yo, nCMAG, Ma1, Ri (ANNA-2)].
- CSF: Cell count + differential, protein, glucose, IgG index, oligoclonal bands, VDRL.
- Urine: UA. Others: MRI brain (w/ FLAIR, DWI, ± gadolinium), CXR, EEG.

As indicated (directed toward specifically suspected dxs)

- Blood: Tumor markers (CEA, Ca-125, PSA), Vitamin E, copper, ceruloplasmin, anti-ds DNA, anti-smith, anti-Ro/SSA, anti-La/SSB, p-ANCA, c-ANCA, C3, C4, CH50, RF, anti- endomysial Abs, anti-gliadin IgA & IgG, ACE, anti-GAD Ab, other paraneoplastic Abs, HIV viral load, T-cell subsets, smear, viscosity, lactate & pyruvate, hypercoagulability testing.
- CSF: Cryptococcal Ag, viral PCRs & cultures, cultures: bacterial, fungal, AFB, AFB stain, cytology & flow cytometry, PCR for IgH gene rearrangement, Whipple PCR, 14-3-3 protein, NSE (neuron-specific enolase), tau (total & phosphorylated).
- Urine: Urine culture, copper (24 h collection, if ? Wilson dz), heavy metal screen (24 h collection, for lead, arsenic, mercury, bismuth, aluminum, lithium).
- Others: Full body PET + CT (cancer screening), mammogram, conventional angio, EMG/NCS, MR spectroscopy; Bx: brain/meninges, jejunum (for Whipple dz), skin (for IVL); Carotid U/S, TTE.

VASCULAR CAUSES OF RPD

Inflammatory cerebral amyloid angiopathy (Ann Neurol 2004;55:250)

Def: CAA a/w perivascular inflammation (?response to deposits of β-amyloid).

Epid: Small % of CAA; probably more common w/ APOE ε4 (esp. homozygous).

P/w: RPD (cognitive↓ over 1—4 mo), szs, leukoencephalopathy.

Dx: Clinical history + MRI findings, ± biopsy:MRI: multiple microhemorrhages on GRE; patchy or confluent WM ↑ T2/FLAIR lesions. CSF: mild-moderate ↑ protein (nonspecific). Brain bx: CAA + perivascular inflammatory response (w/o granuloma formation).

Rx: ?Benefit of steroids & cytoxan; avoid antiplatelet & anticoagulant meds.

INFECTIOUS CAUSES OF RPD

Most infectious RPD cases are atypical (i.e., uncharacteristically slow) presentations of common CNS infxns. Most common causes: HSV1, 2; CMV; EBV; enteroviruses; WNV

Rabies: p/w behavioral & neuropsychiatric Δs (e.g., agitation, bizarre behavior, hallucinations, extreme excitability); usu rapidly progresses to coma.

Polyomaviruses (JVC, BKV): Usu p/w multifocal neurodeficits or meningoencephalitis.

HIV: Four causes a/w RPD: (1) AIDS-dementia complex (usu in advanced AIDS); (2) during seroconversion; (3) neuro-IRIS (neuroimmune reconstitution inflammatory

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syndrome) when starting HAART; (4) opportunistic infxs. Amphetamine + HIV → accelerated HIV dementia.

SSPE (2/2 CNS infection w/ measles virus): In pts from countries where measles is common; children >> adults. P/w: dementia (chronic progressive or RPD), szs, myoclonus, ataxia, rigidity, visual Δs. Late in dz: spastic tetraparesis, diffuse hyperreflexia & upgoing toes, coma. Dx: (1) ↑ measles Abs (serum & CSF) in approp clinical setting; (2) EEG: periodic slow wave complexes + 3-10 Hz sharp waves a/w myoclonic jerks.

CNS Whipple dz: Rare but treatable bacterial infection due to Tropheryma whippelii. Epid: Onset: any age, typically 40-70s (median 50). P/w: Typically diarrhea, abdominal pain, ↓ weight, arthralgias, wasting, fever, lymphadenopathy; 15% present w/o GI S/Sx. CNS involvement: ˜5% p/w

neuro S/Sx; subclinical dz in up to 45% cases. 70% cognitive impairment, 40% psychiatric S/Sx. Other common S/Sx: eye mvmt palsies, myoclonus, sz, aseptic meningitis, hypothalamic involvement, ataxia, focal signs. “Classic triad”: Dementia, ophthalmoplegia, myoclonus (in <10% cases, but very specific). Oculomasticatory myorrhythmia: Pathognomonic (but uncommon). Dx: CSF: ↑ protein, ↑ lymphocytes 50% cases; others wnl. MRI: Nonspecific. PAS+ inclusions or T. whippelii in foamy macrophages on jejunal bx; PCR on jejunal bx specimen or CSF. Rx: usu w/ TMP/SMX 160/800 mg PO bid for 1-2 yr, w/ folate. Second line to TMP/SMX: penicillin G, penicillin VK, amoxicillin.

TOXIC-METABOLIC CAUSES OF RPD

Niacin deficiency: Pellagra (=“rough skin”): see chapter “Poisons & Vitamin Deficiencies”.

Heavy metals (arsenic, mercury, aluminum, lithium, lead): usu p/w florid acute encephalopathy [hours-days-faster than RPD (weeks-months)]; can present at RPD.

Manganese toxicity: Mostly in miners; Parkinsonism is a dominant feature; can p/w RPD.

Bismuth toxicity: w/ overuse of bismuth containing meds, e.g. Pepto-Bismol® (for PUD, diarrhea). Typically p/w: apathy, mild ataxia, HA; can progress to: myoclonus, dysarthria, severe confusion, hallucinations, sz, death. Toxic range: >50 µg/L.

Adult onset or presentation of pediatric metabolic disorders

Common features: Weakness, spasticity, ataxia; progression usu slow, but rarely rapid.

Porphyria: GI S/Sx, unexplained pain, worse S/Sx w/ new meds; fluctuating course.

Adult onset metachromatic leukodystrophy (AoMLD): Rarely p/w RPD; other leukodystrophies also rarely present as adult onset RPD.

Kufs dz: Rare; adult form of neuronal ceroid lipofuscinosis. Presentation: early adulthood onset; progressive myoclonic epilepsy, ± psychiatric S/Sx, ± catatonia.

AUTOIMMUNE CAUSES OF RPD

HASHIMOTO’S ENCEPHALOPATHY (STEROID RESPONSIVE ENCEPHALOPATHY)

Epid: (CNS Drugs 2007;21:799): Prev:˜ 2/100,000. Age of onset: 45-55 yr. F

> M (5:1). Associated autoimmune d/os: Autoimmune thyroid dz, SLE, DM 1, Sjögren's.

P/w: Nonspec course. Rapid improvement w/ steroids a required feature. Prodrome (not always present): depression, personality Δs, psychosis. Course: progressive or fluctuating encephalopathy w/ inattention, agitation or lethargy, psychosis, mood Δs, myoclonus, tremor, stroke-like episodes, szs, hallucinations.

Dx: ↑ anti-thyroid peroxidase (anti-TPO) Abs &/or ↑ anti-thyroglobulin (anti-TG) Abs. Most cases are euthyroid or subclinically hypothyroid. Levels of anti-TPO Abs don't correlate w/severity. Rare cases of anti-TPO neg dz. Anti-TPO Abs ↑'d in 10% gen population; % ↑'s w/ age, F gender. Imaging, EEG, CSF (TP may be ↑'d, ↑ lymphocytes), & brain bx findings nonspecific.

Rx: Corticosteroid responsiveness is a defining feature. Start Rx w/ high-dose IV methylpred (solumedrol), 1 g/day × 3-5 days. Short course may → relapse. Follow w/ maintenance PO prednisone 1-2 mg/kg/day, slow taper. Repeat methylpred pulses for relapses. Duration of Rx needed varies (4-6 mo-10 yr). Sometimes req steroid-sparing agents; e.g., IVIg, plasma exchange, azathioprine, cyclophosphamide, plaquenil, methotrexate, cyclophosphamide.

CELIAC DZ

Def: Sensitivity to gluten → inflammation & atrophy of small intestine mucosa. P/w: S/Sx of malabsorption: diarrhea, steatorrhea, nutritional & vitamin def. Secondary immune dz: atopic dermatitis, dermatitis herpetiformis, alopecia, aphthous ulcers. May be a/w

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other AI dz (e.g., DM, RA, Sjögren's, thyroid dz, collagen vascular dz, liver dz). Neurologic manifestations: Ataxia, neuropsychiatric S/Sx, sz, HA, neuropathy, dementia. Dx: ↑ serum anti-endomysial or anti-gliadin IgA or IgG; intestinal bx; MRI: Nonspecific. Rx: gluten-free diet.

NEURO-SARCOIDOSIS

Epid: 5% of sarcoid pts; some p/w RPD, ±multiple cranial neuropathies. Dx [Note: Must r/o other granulomatous dz (e.g., TB)]. MRI: Variable; common patterns: (1) enhancing granulomas at base of brain, particularly in the hypothalamic region, (2) nonenhancing T2 WM lesions, (3) thickening of basilar leptomeninges (resembles chronic meningitis), (4) DWI pattern can mimic CJD. CT chest: May show hilar lymphadenopathy. CSF: Normal or w/ mildly ↑ protein & lymphocytosis. Serum or CSF ACE ↑ in ˜50% cases; nonspecific. Bx req'd for definitive dx (usu of lung lesion). Rx: Steroids, IVIg, plasma exchange.

NEOPLASTIC CAUSES OF RPD

- Primary & secondary malignancies can p/w RPD; most are easily identified w/ imaging.
- Five more difficult diagnoses may p/w RPD: (1) primary CNS lymphoma, (2) IVL, (3) LYG, (4) lymphoplasmacytic lymphoma (Waldenström macroglobulinemia, WM), (5) gliomatosis cerebri.

INTRAVASCULAR LYMPHOMA (AKA ANGIOTROPIC LYMPHOMA)

Def: Rare subtype of diffuse large B-cell lymphoma (DLBCL); clonal proliferation of lymphocytes in small vessels w/ little or no involvement of surrounding parenchymal tissue.

- Usu no cells circulate in peripheral blood & no cells in CSF.
- F = M; ˜ I case/million pts; no known risk factors; rarely arises in setting of DLBCL.
- Four most common presentations: (1) CNS; (2) skin; (3) FUO; (4) hemophagocytic syndrome.

CNS IVL: Protean S/Sx: focal motor/sensory signs; generalized weakness, AMS, RPD, sz, dysarthria, ataxia, vertigo, amaurosis fugax. Ddx: Stroke, ADEM, GBS, CNS vasculitis, MS.

Dx: MRI: Multifocal ↑ T2, patchy enhancement on T1, ±edema, lesions usu of different ages; pattern suggestive of small vessel ischemia & demyelination. MRI may be normal. Serum: Nonspecific; ↑ serum ESR, LDH. CSF: ↑ TP, lymphs [but most w/ (−) cytology]; ±IgH gene rearrangement (by PCR). Brain bx: usu needed to make dx.

Skin IVL: ˜1/2 have skin involvement (—1/4 w/ skin involvement as sole presenting S/Sx). Highly variable findings: maculopapular rash, nodules, plaques, tumors, hyperpigmented patches, palpable purpura, ulcers, “peau d’orange.” ?preference for proximal extremities, lower abdomen, immediately under breasts.

- Reported initial misdxs: cellulitis, gangrene, vasculitis, Kaposi sarcoma, squamous cell CA.
- Bx usu diagnostic. Sometimes random skin bx (in absence of lesions) is diagnostic.

Fever of unknown origin (FUO) as presentation of IVL: ˜50% cases of IVL have fever. Random skin biopsy (if no visible lesions) in FUO sometimes → dx of IVL.

Hemophagocytic syndrome (Mostly in Asian pts [reasons unclear])

- +parenchymal involvement of reticuloendothelial system (unlike most IVL)
- p/w: fever, anemia, ↓ platelets, hepatosplenomegaly, marrow involvement

Prognosis/Rx for IVL

- Poor survival, worse w/o Rx; Rx = aggressive chemoRx ± XRT
- No RCTs; typically: (1) No CNS involvement: R-CHOP. (2) +CNS involved: R-CHOP + intrathecal or systemic MTX. (3) ?Autologous stem cell transplant.

LYMPHOMATOID GRANULOMATOSIS

Reference: “Lymphomatoid Granulomatosis,” eMedicine, Nader Kamangar, Anthony W O’Regan, Apr 16, 2009, http://emedicine.medscape.com/artic\le/299751)

Def: EBV associated systemic angiodestructive lymphoproliferative dz. Typically w/ prominent pulmonary involvement; may involve multiple extrapulmonary sites.

Epid: Rare; M > F (2:1); age usu >60. Frequently a/w immune dysfxn. A/w: Sjögren syndrome, chronic viral hepatitis, rheumatoid arthritis, renal transplantation, HIV.

Path: “T-cell-rich, B-cell lymphoma”: B-cell lymphoma (malignant, monoclonal B-cells, infected w/ EBV) a/w an exuberant, benign (polyclonal) T-cell reaction. Dx requires triad: (1) Polymorphic lymphocytic infiltrate; (2) Angiitis: 2/2 transmural infiltration of arteries & veins by lymphs; (3) Granulomatosis (central necrosis in lymphoid nodules; NOT granulomas).

P/w: Pulmonary involvement (>95%); skin (50%), CNS/PNS (25%); kidneys, liver less commonly; lymph nodes, spleen, bone marrow spared until advanced stages. Organ system-specific si/sx: Pulmonary: cough, dyspnea, ±PNA; hemoptysis (reflect cavitary lesions); Systemic: (“B-symptoms”): Fever, wt loss, malaise; Skin: Patchy red macules, papules & plaques, often in

gluteal regions extremities; often painful. CNS/PNS: Lymphocytes infiltrate meninges, cerebral vessels, peripheral nerves (˜25%); may have mass lesions; can present as RPD. Renal: Clinically sig dz uncommon (unlike Wegener's). Liver: Hepatomegaly in ˜10%.

Ddx: Other pulmonary granulomatoses: Bronchocentric granulomatosis & Churg-Strauss (allergic angiitis & granulomatosis; Necrotizing sarcoid granulomatosis; Wegener granulomatosis. Other types of malignant lymphoma: Hodgkin dz, nasal angiocentric lymphoma, non-Hodgkin lymphoma.

Workup: Laboratory abnormalities all nonspecific. Labs: CBC: Leukopenia (20%), lymphopenia (33%); T-cell subsets: May find low CD4 count; Hct wnl or slightly high; ESR: WNL to moderately elevated; Cr, LFT usu wnl. Imaging: CXR, chest CT: usu nonspecific; Bilateral nodules or masses in the lower & peripheral lung fields (80%-100%); Pleural effusions (33%); Pneumonitis or large masslike lesion (30%); Cavitation of nodules (30%); Pneumothorax (5%). Hilar & mediastinal lymphadeno pathy rare → consider alternative dx or transformation into aggressive lymphoma. Brain MRI: Lesions isointense or hyperintense on T1, hyperintense on T2-weighted images; enhancement may be punctate & linear (relatively specific for inflammation of deep cerebral vessels). Biopsy: Required for dx. Analysis for: cell phenotype, clonality, EBV infection.

Rx: Not well defined; ?role for: steroids, IFN-α 2b, focal XRT, ganciclovir, rituximab.

Complications: (1) Transformation into high-grade lymphoma can occur (13%-47%). (2) Progressive pulm dz w/ ↑ resp failure → PTX, infxn, hemorrhage. Hemoptysis, pneumothorax, opportunistic infxns may develop. Szs, confusion, mononeuropathy, diabetes insipidus.

Prognosis: Median survival ˜14 mo; >60% die <5 yr. Death usu 2/2 resp fail, sepsis, or hemoptysis. Poor prog: age < 30, neuro or hepatic dz, leukopenia, pancytopenia, anergy.

LYMPHOPLASMACYTIC LYMPHOMA (WALDENSTRÖM MACROGLOBULINEMIA)

Def: Malignant clonal prolif of B-lymphocytes → ↑↑ IgM levels. Si/Sx 2/2 ↑↑ IgM paraprotein & malignant cell infiltration of bone marrow & other tissues; like multiple myeloma (MM) except (1) organomegaly common in WM (uncommon in MM), (2) lytic bone lesions & renal dz uncommon in WM (common in MM). Rarely presents as RPD in setting of blood hyperviscosity (see "Bing-Neel syndrome"). In family of related d/os: myeloma (multiple or plasmacytoma), plasma cell leukemia, amyloidosis, smoldering myeloma,

MGUS, WM.

Epid: 1,500 cases dx'd/yr in US; accounts for ˜2% hematologic malignancies. Higher incidence in whites; mostly elderly; median age 65; M > F (slightly).

Path: (1) Monoclonal IgM (kappa or lambda) paraprotein → hyperviscosity & vascular complications 2/2 physical & immunological properties, e.g., hyperviscosity syndrome, cryoglobulinemia types 1 & 2, coagulopathies, sensorimotor peripheral neuropathy, cold agglutinin dz, anemia, primary amyloidosis; IgM deposition in skin, GI tract, kidneys, CNS. (2) Neoplastic cells infiltrate various organs, most commonly: bone marrow, spleen & lymph nodes; less commonly: liver, lungs, GI tract, kidneys, skin, eyes, CNS. (3) IgM sometimes has: rheumatoid factor activity, antimyelin activity (may → peripheral neuropathy), immunologically related lupus anticoagulant activity. Causes of WM: Multiple proposed, none proven: Kaposi sarcoma-associated herpes virus: HHV-8; Hep. C, Hep. G; genetic predisposition (occ. family clustering); Toxins: leather, rubber dyes, paints; T. cruzi.

Manifestations (Semin Oncol 2003;30:211): Insidious, nonspec onset; many dx'd incidentally. Common sx: gen weakness (66%), anorexia (25%), peripheral neuropathy (24%), ↓ wt (17%), fever (15%), Raynaud's (11%; 2/2 cryoglobulinemia). Si/Sx 2/2: (1) infiltration by malig cells (bone marrow in ˜100%; organomegaly ˜30%); (2) Amt & properties of IgM: hyperviscosity, cryoglobulinemia, cold agglutinins; (3) Deposition of IgM: Polyneuropathy, renal precipitation of IgM, immune complexes or amyloid, skin deposits: urticarial (Schnitzler syndrome) or diffuse; gut deposits of monoclonal IgM → diarrhea/malabs; (4) coagulopathy: bleeding (spont/minor trauma); easy bruising. Hyperviscosity S/Sx: spont/easy bleeding, dizziness, HA, blurry/double vision, ↓ hearing.

Organ system-specific features: GI: Malabsorption, GI bleeding, diarrhea; Pulmonary dz rare (3%-5%): nodules, masses, parenchymal infiltrates, pleural effusion. ID: Frequent

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infxns (2/2 B-cell dysfunction); Renal: Renal dz (but uncommon); Heme: Bleeding d/os: platelet, coagulation factor & fibrinogen dysfxn (2/2 intxn w/ plasma IgM); Skin: Purpura, bullae, papules, plaques & nodules, chronic urticaria (Schnitzler syndrome), Raynaud phenomenon, livedo reticularis, acrocyanosis; CV: CHF (but uncommon); Ophtho: Periorbital masses (retro-orbital & lacrimal gland infiltration → proptosis, oculomotor palsies;Organomegaly: liver (20%), spleen (19%), lymph nodes (15%); Amyloidosis: Heart, kidney, liver, lungs, joints.

CNS manifestations: (1) Mental status Δs (lethargy, somnolence, coma). (2)

Hyperviscosity syndrome: HA, vertigo, ataxia, hearing loss, confusion, strokes. (3) Bing-Neel syndrome (confusion, memory loss, disorientation, seizures, leukoencephalopathy, paralysis; can present as RPD). (4) Optho: Papilledema; sausage-shaped (distended, tortuous) retinal veins; hemorrhages. (5) Epidural spinal cord compression: Bowel-bladder dysfxn, sensory loss, back pain, paralysis. (6) Leptomeningeal infiltration: HA, hydrocephalus, multiple cranial neuropathies. (7) Paraneoplastic syndromes: cerebellar degeneration, motor neuron dz. (8) Hypercalcemia: HA, seizures, weakness, confusion, lethargy, coma.

PNS manifestations: Neuropathies due to WM: Neuropathy: Usu slowly progressive distal symmetric sensorimotor; variants: chronic ataxic neuropathy (Miller-Fisher syndrome), demyelinating w/ IgM anti-MAG Abs, demyelinating w/ monoclonal IgM non-anti-MAG antiganglioside Abs, axonal w/ IgM anti-peripheral nerve antigens; Cryoglobulinemic axonal neuropathy (ischemia); Amyloid polyneuropathy; Neurolymphomatosis; POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin Δs).

Other PNS complications of plasma cell disorders (including WM): (1) MGUS neuropathy (IgM = 60%; IgG = 30%; IgA = 10%). (2) Polyradiculopathy caused by epidural dz (neurolymphomatosis). (3) Sensory motor demyelinating neuropathy: (1) Anti-MAG present; often IgM MGUS related; (2) Anti-MAG absent (often MGUS related); (3) Waldenstrom macroglobulinemia. (4) Sensory motor axonal neuropathy: (1) Cryoglobulinemia w/ demyelinating & axonal features; (2) Related to chemotherapeutic agents. (5) Motor sensory demyelinating neuropathy: (1) Osteosclerotic myeloma & Castleman dz; (2) POEMS. (6) Sensory motor neuropathy w/ dysautonomia: Amyloidosis.

Workup: Dx requires: (1) monoclonal IgM spike, (2) malignant cells (usu by marrow bx).

Lab findings: CBC, smear: ↓ Hct (normocytic normochromic; in 80% cases); ↓ WBC, ↓ plts.

- Peripheral blood smear: May show plasmacytoid lymphocytes, rouleaux formation.
- LDH, uric acid level, ESR, LFTs, total protein levels, albumin-to-globulin ratio [findings: ESR, CRP & uric acid often elevated, Cr sometimes increased, hypercalcemia in ˜4% pts, Ï LDH (signifies extent of WM-tissue involvement)].
- RF, cryoglobulins, direct antiglobulin test, cold agglutinin titer: may be

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- β-2 microglobulin (nonspecific; level increases w/ dz burden).
- Coagulation tests: PT, PTT, fibrinogen can be abnl.
- ↑ plasma viscosity.
- UPEP: Light chains (Bence Jones protein + in ˜40% cases; > 1 g/day ˜3% cases).
- SPEP: May show monoclonal spike, but cannot demonstrate that spike is IgM.
- Immunoelectrophoresis & immunofixation: identify type of immunoglobulin, clonality of light chain, & monoclonality & quantification of the paraprotein.
- EMG/NCS: If exam shows peripheral neuropathy.

Imaging: CXR: ±infiltrates, nodules, effusion, e/o CHF. CT abdomen/pelvis: May show lymphadenopathy, hepatosplenomegaly. MRI spine: May show bone marrow involvement (˜90% cases). CSF (in pts w/ AMS): May show ↑ protein, IgM paraprotein.

Procedures: (1) Bone marrow aspiration & biopsy w/ flow cytometry usu required for dx. (2) If suspect primary amyloidosos (i.e., due to neuropathy, nephrotic syndrome, CHF): abdominal fat-pad needle aspiration w/ BM bx (look for amyloid deposits w/ Congo red stain).

Rx: (1) Indolent/smoldering/asymptomatic WM (serum IgM monoclonal protein &/or bone marrow lymphoplasmacytic infiltration) w/o end-organ damage): usu followed clinically; monitor w/ periodic labs: M component, immunoglobulin, serum viscosity. (2) Symptomatic WM: (1) Rx of IgM paraprotein complications; (2) dz modifying Rx. Rx include: IVIg, plasmapheresis, alkylating agents, IFN-α, purine nucleoside analogues, high-dose chemotherapy, splenectomy, rituximab, thalidomide, bone marrow transplantation, experimental agents. (3) Hyperviscosity syndrome: Urgent plasmapheresis (80% IgM is in the intravascular space; should remove >1/2 of intravascular volume to sufficiently lower viscosity). Measure viscosity before & after pheresis; remove 2-4

U plasma q1-2wk (to avoid recurrent emergency hyperviscosity syndrome); replace plasma w/ albumin or saline.

Prognosis: Usu indolent; survival ˜7.5 yr if macroglobulin level ↓ 75%. Most common causes of death: infxn, CHF, renal failure, stroke, GIB.

Transformation → aggressive immunoblastic variant uncommon (˜5%). A/w ↑ risk lymphoma, myelodysplasia, leukemias. Poor prognosis: (1) age > 65, (2) Hb < 10 g/dL, (3) Alb< 4.0 g/dL, (4) ↑ β-2 microglobulin.

GLIOMATOSIS CEREBRI (AKA INFILTRATIVE DIFFUSE ASTROCYTOSIS)

Rare; diffuse glial overgrowth w/ infiltration ≥2 lobes. Any age; typically 40-50s. Usu p/w minor deficits; may p/w RPD. MRI: diffusely infiltrative, min mass effect, no necrosis; most don't enhance. Prognosis poor. Survival ˜50% at 1 yr,˜25% at 3 yr,˜ 5% at 5 yr. Rx: no surgical options; no demonstrated ↑ survival w/ chemoRx so far; trials ongoing.

NEURODEGENERATIVE CAUSES OF RPD

CREUTZFELDT JACOB DZ

Epid: ˜1/million/yr. ˜85% sporadic (sCJD); ˜15% inherited (aut. dom.): Gerstmann-Straussler-Schenker dz or fatal familial insomnia;< <2% iatrogenic.

sCJD (sporadic CJD)

Epid: Usu insidious; age 50-70; F = M; Median survival 5 mo; 85% die w/in 1 yr.

WHO clinical criteria sCJD (limited sensitivity): Probable CJD PSWC or 14-3-3 CSF protein in pt w/ dz duration <2 yr, satisfying: Progressive dementia & at least 2 of: Myoclonus, Visual or cerebellar signs or symptoms, pyramidal or extrapyramidal signs or symptoms, akinetic mutism. Possible CJD same as "Probable CJD" but w/o satisfying EEG or CSF criteria.

P/w: Nonspecific prodrome: (in ˜1/3 pts): Fatigue, HA, depression, mood Δs, behavior Δs, sleep pattern Δs, vertigo/dizziness, wt ↓, pain, anxiety, anorexia. Typical presentation: Mix of cognitive, cerebellar, extrapyramidal, behavioral, psych si/sx. Especially: Dementia, progressive aphasia, apraxia, pyramidal signs, myoclonus, & choreiform-athetoid movements.

Dx: Exclude treatable causes simultaneously. (1) Brain bx: Gold standard for dx (at autopsy; problematic during life 2/2 risk to surgeons & cost: surgical equipment usu must be discarded). (2) MRI: FLAIR & DWI Se 92%, Sp 94% (Neurology 2004;163:443): Typical MRI: Cortical hyperintensity ("cortical ribbon sign") &/or striatal hyperintensity. NO WM lesions/ enhancement. Possible mimics (usu easy to distinguish): Striatal hyperintensity: neurofilament inclusion body dz, Wilson dz, Wernicke enceph., vasculitis, anti-CV2 paraneoplastic dz. Cortical ribboning: sz, vasculitis, autoimmune/paraneoplastic dz. (3) EEG (Neurol Clin 2007;25:783): Early on:

Nonspecific diffuse or focal slowing. Advanced dz: ±1-2 Hz triphasic sharp waves (“Periodic sharp wave complexes”). Periodic Sharp Wave Complexes (PSWC): Se ˜50%-65% w/ repetitive testing over dz course; Sp ˜90%; ˜10% false positives (e.g., rarely in: AD, DLB, vascular dementia, Hashimoto encephalopathy, toxic metabolic encephalopathies). (4) CSF: Routine studies typically normal; may have mild protein elevation,+OCBs. 14-3-3 protein: controversial utility; Se 48%, Sp 65% (Neurol Clin 2007;25:783). Total-tau protein & NSE may have slightly ↑ Se, Sp.

vCJD (variant CJD) (Ann Neurol 2008;64:97)

Occurs younger than “traditional” sCJD; ages 12-74, median 29. Begins w/ psych illness >6 mo; neuro si/sx later: Dementia, ataxia, dysesthesia, mvmt d/o (chorea, myoclonus, dystonia). EEG rarely shows PSWCs (unlike sCJD). MRI: like sCJD; distinguished by “pulvinar sign” (bright pulvinar c/w putamen). Tonsillar bx (brain bx not always nec). Linked to bovine spongiform encephalopathy.

Gerstmann-Straussler-Schenker dz: Rare (˜1 per 100 million cases). Autosomal dominant, onset ˜40s. Features: Cerebellar degeneration (ataxia, incoordination), dementia (no myoclonus). Time to death 2-10 yr. Dx: FHx, prion protein (PrP) gene mutations.

Fatal familial insomnia: First seen in Italian families, usu death in 13 mo. Usu autosomal inheritance, can be sporadic. Features: Progressive insomnia, dream-like confusional state, ↓ memory, dysautonomia (HTN, ↑ HR, hyperhydrosis, hyperthermia). MRI/EEG/14-3-3 usu nl.

CJD VS. ATYPICAL PRESENTATIONS OF COMMON NEURODEGENERATIVE DZS

Rarely present as RPD: AD, DLB, CBD, FTD, PSP, but lack MRI signature of CJD

- CBD, DLB, late AD si/sx shared w/ CJD: Myoclonus, extrapyramidal signs.

P.96

- DLB: Typically p/w rapid cognitive fluctuations, Parkinsonism, vivid recurrent wellformed visual hallucinations; can rarely show PSWs on EEG (overlap w/ CJD).
- FTD: Typically p/w “frontal syndrome” (behavioral, cognitive, personality Δs → dementia).
- CBD: Typically p/w “cortical-basal” syndrome: dementia, Parkinsonism,

alien limb syndrome, myoclonus; visual sensory & motor deficits. These all can occur in CJD.

- Typical PSP: Early falls; dementia, symm. bradykinesia; axial & postural instab., aphasia
- NIBD (Neurofilament Inclusion Body Dz): Few cases described; duration 2-4 yr (onset to death). Clinically resembles FTD or CBD.
- Fahr dz: Basal ganglia calcification is hallmark; p/w mvmt & neuropsych d/o. Usu very slowly progressive, but RPD presentation has been reported.
- ?Fragile-X: One reported case p/w RPD.

Dementia

GENERAL INFORMATION

Definition: (1) Acquired loss of cognitive abilities or comportment w/ impairment of ≥2 of: (a) Memory (ability to learn new information, or recall previously learned information), (b) Language, (c) Executive function (planning, organizing, sequencing, or related abilities), (d) Visuospatial abilities, (e) Gnosis (recognition/identification of objects or people, w/ intact elementary sensation), (f) Praxis (ability to do skilled motor tasks, w/ intact elementary sensorimotor function), (g) Other intellectual abilities (e.g., calculation), (h) Social/emotional abilities (e.g., regulating drives; interacting appropriately); (2) Preserved elements of basic attention (i.e., absence of encephalopathy). (3) Compromises complex activities of daily living (ADLs), social or occupational function.

May be subdivided based on time course: Chronic dementia: Progresses over months to years. Rapidly progressive dementia: Subacute time course of weeks to months.

Delirium distinguished from dementia based on: Impaired attention, rapid onset (hours to days), fluctuating course. However, some dementias can have prominent fluctuations in attention, such as dementia w/ Lewy bodies (see below). Mild cognitive impairment (MCI) & normal aging distinguished from dementia based on impact on ADLs (see below).

Epidemiology: Aging: Most significant known risk factor (i.e., age mainly >65), relatively rare hereditary & aquired forms. Affects >4 million Americans (˜1 in 20 above 65, 1 in 5 above 85); Cost >$ 100 billion annually.

Etiology: Most common causes: (1) Sporadic Alzheimer dz (AD) (>50% of demented pts in the United States). (2) Cerebrovascular dementia (10%-20%). Multiple etiologies in same pt common (i.e., mixed Alzheimer’s/cerebrovascular dz). Other causes (Table 12.1): Prion dzs, Hashimoto encephalopathy → see rapidly progressive dementia. Dementias w/ movement d/o as salient clinical feature → see chapter “Movement Disorders”. Pediatric dementias: most common = neuronal ceroid lipofuscinoses. See Pediatrics chapter.

Table 12.1 Causes of Dementia

Primary/Degenerative

Sporadic

AD, dementia a/w parkinsonism (dementia w/ Lewy bodies [DLB], Parkinson disease [PD], progressive supranuclear palsy [PSP], multiple system atrophy, other [e.g., Fahr dz, Hallervorden-Spatz, neuroacanthocytosis]), frontotemporal dementias (FTD), motor neuron disease-associated, ALSparkinsonism-dementia complex of Guam, prion diseases

Hereditary/genetic

Adult onset: Familial forms of AD, FTD, PD, prion dzs, Down syndrome, Huntington disease, Wilson disease, Kufs disease

Pediatric: Neuronal ceroid lipofuscinoses, storage diseases, adrenoleukodystrophies

Secondary/Acquired

Toxic

Alcohol, metals (e.g., heavy metals, aluminum/dialysis dementia), carbon monoxide, radiation-induced

Metabolic

Vitamin deficiencies (e.g., B_1, B_{12}, nicotinic acid), chronic endocrinopathies (hypothyroidism, adrenal insufficiency, parathyroid disease). Chronic metabolic disturbance (chronic renal disease, chronic liver disease, chronic anoxic states, mitochondrial disorders)

Infectious

Prion diseases, AIDS dementia complex, syphilis, progressive multifocal leukoencephalopathy (PML, due to JCV)

Psychiatric

Depression (pseudodementia), conversion disorder

Inflammatory

Vasculitis, multiple sclerosis, Hashimoto encephalopathy

Neoplastic

Primary CNS tumor, gliomatosis cerebri, metastatic CNS tumor, primary CNS or systemic non-Hodgkin lymphoma

Vascular

Diffuse (Binswanger disease), multi-infarct dementia

Traumatic

Chronic subdural hematoma, post-traumatic dementia (dementia pugilistica)

Epileptiform

Recurrent

P.97

APPROACH TO DIAGNOSIS OF DEMENTIA

HISTORY

Careful history from pt and family members. Determine symptoms, w/ special care; Initial symptom especially important. Consider the following domains: (1) Cognitive (such as memory, language, praxis). (2) Neurobehavioral (motivation, sleep, appetite). (3) Neuropsychiatric (mood, hallucinations, delusions). (4) Functional consequences (ADLs). (5) Other neurologic (abnl movements, falls, imbalances). (6) Temporal course: Rapidity of onset, course —progressive? fluctuating? stepwise? (7) Non-neurologic sxs: e.g., fever, wt loss, cardiorespiratory, rash. (8) PMH may suggest potential acquired etiologies (Fig. 12.1). (9) Medications. (10) Family history may give clue to hereditary dementias. (11) Social history may reveal causes of acquired dementia (e.g., smoking for vascular dementia/chronic pulmonary dz, alcohol abuse for alcohol- & nutritional deficiency-related dementias, multiple sexual partners or sexual orientation → HIV or syphilis).

EXAMINATION

Divided into mental status, neurologic & general medical examination.

General medical: Critical to identifying neuromedical causes of dementia.

Mental status: Including orientation; attention; memory; language; executive function; praxis. Visuospatial and intellectual function.

Standardized tests can be useful, including the mini-mental state examination (sensitivity for dementia ˜70%; specificity ˜90%) & Montreal cognitive assessment (MoCA) tools (the latter w/ normative data available online at www.mocatest.org). Queen Square Screening Test for Cognitive Deficits is a useful pocket-sized companion (Warrington, 1989).

General neurologic: CN, motor, sensory, reflexes, cerebellar, gait.

Neuropsychological assessment: Standardized testing by neuropsychologist: determine pattern & degree of deficits in different cognitive domains; helps in evaluation to assess mood, psychosis.

DIAGNOSTIC STUDIES

Laboratory tests: Consider the following lab tests but tailor to individual patients. Basic (chem10, urea/creatinine, LFTs, Ca/PO_4, CBC, PT/INR, PTT, ESR/CRP). Endocrine studies (hemoglobin A1c, TSH). Metabolic (fasting

lipid panel, vitamin B_{12}). Infectious (syphilis serology, HIV). Lumbar puncture. Other laboratory studies dictated by history & examination (e.g., rheumatologic, vasculitic labs; tox screens; paraneoplastic). Nonlaboratory tests to r/o medical illness as indicated (e.g., EKG, CXR, echocardiogram).

Neuroimaging: Structural imaging: Brain MRI preferable to head CT with contrast. Vascular imaging (in cases of suspected multi-infarct dementia). Functional imaging: SPECT (single photon emission computed tomography) & PET measure resting

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P.98

cerebral blood flow & metabolism. Chemical imaging: MR spectroscopy; amyloid imaging [e.g., PET imaging w/ Pittsburgh compound B (PIB), promising biomarker for AD not yet in widespread use].

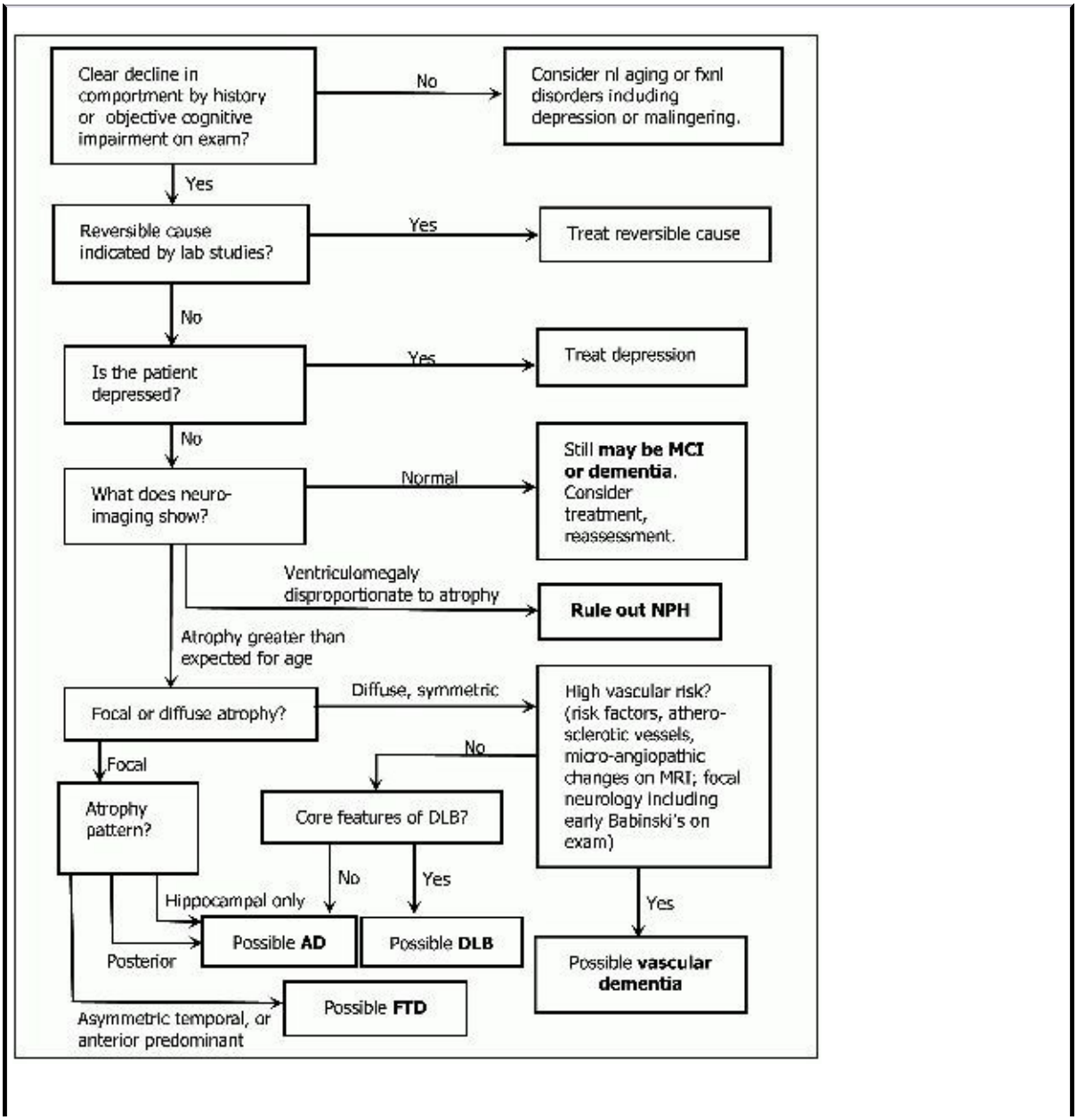

Figure 12-1 Clinical pointers in diagnosing the more common primary degenerative dementias. AD = Alzheimer disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, NPH = normal pressure hydrocephalus. Adapted from Dementia Handbook. ed. RJ Harvey, NC Fox, and MN Rossor. London: Martin Dunitz (1999).

Other testing: EEG (e.g., suspected CJD, nonconvulsive seizure disorder), EMG/NCS (suspected motor neuron dz), cerebral angiography (suspected CNS vasculitis), brain bx (uncertain dx). Genetic testing: e.g., tests for Huntington dz, familial Parkinson dz, spinocerebellar ataxia (Table 12.2).

Table 12.2 Clinical Differentiation of the Ma

Dz	First Sx	Mental Status	Neuro Ψ	
AD	Memory loss	Episodic memory loss	Initially nl	
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive, language; spares drawing	Apathy, disinhibited hyperorality, euphoria, depression	P o g ri a
DLB	Visual hall., REM sleep d/o, delirium, Capgras' syndrome, parkinsonism	Drawing & frontal/executive; spares memory early; delirium prone	Visual hall. depression sleep d/o delusions	
CJD	Dementia, mood, anxiety, mvmt d/o, visual symptoms	Variable	Depression, anxiety	ri p c

Vascular	Variable: apathy, judgment/problem solving difficulty; falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, depression	n s n

(Adapted from Bird TD, Miller BL. Dementia, Harrison's Online, Acces

P.99

TREATMENT OF DEMENTIA

Disease modifying pharmacotherapy: None available; some promising agents in trial.

Symptomatic pharmacotherapy: Cholinesterase inhibitors for AD. NMDA receptor antagonists for AD. Antidepressants for depression, anxiety. Benzodiazepines for anxiety. Neuroleptics for agitation, psychosis (typically use atypical neuroleptics (e.g., olanzapine [Zyprexa, Zydis], quetiapine [Seroquel]); for acute severe agitation requiring parenteral medication consider IV or IM haldol or lorazepam); can cause significant adverse reaction in DLB. Stimulants, catecholamine enhancers, dopaminergic agonists for inattention, ↓ arousal, apathy. Antiseizure medications for mood stabilization.

Treat comorbid medical disorders: May be potentiating cognitive decline. Control of vascular risk factors (smoking cessation, lipids, diabetes); Treat liver & renal dz; Correct vision & hearing (glasses, hearing aids).

Remove medications: That may be worsening cognition (e.g., unnecessary antiseizure medications, sedative-hypnotics, narcotics, medications w/ anticholinergic side effects).

Behavioral/environmental: Organizational/time management strategies. Increased structure & order (including cleaning living area). Set routine; sleep hygiene; memory strategies (mnemonics, rehearsal, cue cards).

Cognitive training: Psychosocial support: Support groups; social worker referral.

NORMAL AGING

Normal brain aging = nl brain Δs & clinical S/Sx over time in the absence of any dz. Normal & pathologic brain aging distinguishable molecularly, neuropathologically, clinically. Typical clinical manifestations: decrement in one or more of visual & verbal memory, visuospatial abilities, immediate/working memory, & naming. By definition, must not →

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compromise of ADLs, occupational, or social function. May be difficult to differentiate from earliest S/Sx of progressive dementia; referral to neuropsychologist can be helpful in establishing pt's own current "baseline." Current preventative strategies: Reducing vascular risk (e.g., smoking cessation, DM control, optimizing lipid profile); reducing alcohol consumption; regular exercise to optimize cardiovascular fitness.

MILD COGNITIVE IMPAIRMENT

Definition

Transitional dx b/n normal cognitive function & dementia (most commonly AD). Dx'd when there is a cognitive complaint, & objective e/o cognitive dysfxn on neuropsychological assessment but: (1) relative preservation of basic ADLs; (2) minimal impairment (at most) of instrumental ADLs. MCI is amnestic if only memory is impaired: can also affect multiple domains or a single nonmemory domain.

Etiology, pathogenesis: As for dementia.

Clinical features: Cognitive deficits w/ limited severity; MoCA test (Se & Sp ˜90%) considerably more sensitive but less specific than MMSE for MCI detection (Se 18%; Sp 100%).

Diagnosis/workup: Dx is currently clinical, w/ neuropsychological assessment. W/u outlined above. Consider comorbid ¥ d/os, including anxiety & depression, medication effects, substance abuse, chronic pain as potential etiologies or exacerbating factors. Always assess vascular risk (e.g., smoking history, & fasting lipid profile, hemoglobin A1c).

Prognosis/prognostic workup: MCI → dementia (annual conversion rate ˜5%-10% per year). Increased risk of conversion to dementia a/w smoking history, hyperlipidemia, ApoE4 genotype, medial temporal lobe volume loss on MRI, temporo-parietal hypometabolism on FDG-PET, or CSF β-amyloid levels indicating cerebral amyloid burden.

Treatment: No pharmacotherapy proven to lower long-term risk of conversion to dementia. Reduce vascular risk (e.g., smoking cessation, diabetes control, optimizing lipid profile); reduce alcohol consumption; regular exercise to

optimize cardiovascular fitness. Treat comorbid depression w/ nonanticholinergic drug (e.g., SSRIs like sertraline or citalopram). Cognitive training & psychosocial support.

ALZHEIMER DISEASE

Definition: Defined histopathologically by extracellular neuritic plaques & intraneuronal neurofibrillary tangles (NFTs) in cerebral cortex, out of proportion to any other concomitant pathology.

Epidemiology: Most common dementia in Western countries, affects >5% of people age >70. The annual indirect & direct costs total more than $100 billion. Old age & positive FHx are the most important risk factors.

Etiology: 95% sporadic; genetic + environmental factors (reflected by significant discordance of onset age, presentation & duration in monozygotic twins w/AD, including familial forms). Low levels of education, head trauma, vascular dz, diabetes may increase risk. NSAIDs may decrease risk. APOE (encoding apolipoprotein E) genotype → most significant known genetic risk modifier for sporadic AD; E4 allele confers dose-dependent increased risk & earlier age of onset & E2 allele is protective. Relative risk w/ E4/E4 is 14.9; E3/E4, 3.2; E2/E4, 2.6; & for E2/2, 0.6. Approx. ˜5% of cases early onset familial, w/ autosomal dominant pattern. Identified causative genes: APP (chromosome 21, encoding amyloid precursor protein). PS-1 (chromosome 14, encoding presenilin-1 protein). PS-2 (chromosome 1, encoding presenilin-1 protein). Down syndrome pts (trisomy of chromosome 21) who live beyond 40 develop a dementing illness w/typical AD neuropathology.

Pathology: Extracellular amyloid plaques (diffuse or dense core) & intraneuronal NFTs. Nucleus basalis of Meynert (a cholinergic nucleus) prominently affected, as is norepinephrine-secreting locus coeruleus. Gross pathology: atrophy of hippocampus & medial TL & other areas of cortex, occasionally w/ parieto-occipital preponderance; enlarged ventricles (hydrocephalus ex vacuo). Amyloid plaques: Aggregated β-pleated sheets of β-amyloid protein. NFTs: Hyperphosphorylated forms of microtubule binding protein tau & appear ultrastructurally as paired helical filaments; NFTs more closely follow neuronal loss & clinical phenotype.

Pathogenesis: Amyloid hypothesis: Current leading hypothesis: soluble Aβ oligomers (not large insoluble aggregates) are toxic → tau hyperphosphorylation, neuronal dysfxn & degeneration.

Consensus guidelines (DSM-IV; American Psychiatric Association, 1994): Defects in multiple cognitive domains, including memory & one or more of:

aphasia, apraxia, agnosia, executive dysfxn. Impaired social and/or occupational function. Gradual, progressive course. Symptoms are NOT associated w/ other CNS dz, occurring exclusively in the context of a delirium, better accounted for by psychiatric illnesses such as depression.

Clinical features: Prominent impairment of short-term memory followed by visuospatial & language deficits. Typically chronic, progressive (sometimes w/ plateaus). Difficulties w/ADL's accompany dz progression. Disrupted sleep-wake cycle, agitation & confusion at night ("sundowning") in later stages, & psychiatric sx including depression & delusions (paranoid are most common; 10% have Capgras syndrome). End-stage AD: akinetic, mute, rigid & confined to bed; sz & myoclonus common. Duration to death (typically from medical causes including infection, pulmonary embolism, cardiac arrest, malnutrition) typically 8-10 years. Exam: Cognitive dysfxn, unmasking of primitive reflexes (e.g., grasp, palmomental, pout), Babinski sign a late feature (if present early may suggest vascular component). Nonmemory initial complaints in ˜20% cases (e.g., language or navigational difficulty). Rarely, presents w/ visuospatial complaints (so-called "posterior cortical atrophy"). Can have Balint syndrome (simultagnosia, optic ataxia, oculomotor apraxia). Disturbed olfaction often a very early but nonspecific feature of AD.

Diagnosis/workup: Dx currently clinical, w/ neuropsychological assessment. Consider comorbid \|/ d/os. Assess vascular risk (smoking history, measuring fasting lipid profile, hemoglobin A1c). MRI: Often demonstrates hippocampal & medial TL volume loss (often involving PLs also). Atrophy confined to FL, TL more suggestive of FTD. Prominent microangiopathic change &/or multiple cortical/subcortical infarcts is suggestive of vascular dementia). SPECT/PET: ↓'d metabolic activity/blood flow in posterior TL/PL; PIB imaging for amyloid deposition & ↓ Aβ/tau ratio in CSF may become standard dx procedure in near future. ApoE4 genotype not specific enough to be used in clinical practice.

Treatment: Currently no dz-modifying therapies available. Rivastigmine, Donepezil, Tacrine, Galantamine (acetylcholinesterase inhibition); Memantine (NMDA-receptor antagonist) (Table 12.3). Cholinesterase inhibitors can cause GI upset (nausea, diarrhea), altered sleep, nightmares, bradycardia (usually benign), bronchospasm & muscle cramps. Vitamin E may slow dz but controversial b/c possible cardiac side effects at high doses. Nonpharmacologic multidisciplinary mgt is cornerstone of Rx, including cognitive training, Y support for pt & family & eventually, institutionalization w/in dementia care facility. SSRIs (e.g., citalopram, sertraline) & neuroleptics (haldol, quetiapine, risperidone, or olanzapine) generally useful in Rx of comorbid mood d/o & agitation (see Table 12.2). Beware parkinsonism

complicating neuroleptic use.

Table 12.3 FDA-approved Pharmacotherapy for AD

Drug	Tx Regimen (Doses in mg)
Rivastigmine	Initial: 1.5 bid; may ↑ by 3 mg/day (1.5/dose) q 2 wk based on tolerability (max dose: 6 bid)
Donepezil	Initial: 5 mg/d at bedtime; may ↑ to 10/day at bedtime after 4-6 weeks
Tacrine	Initial: 10 mg qid; may ↑ by 40/day q6wk; max: 160/day; best given separate from meals. Monitor ALT: ALT >3 to ≤5 × ULN: ↓ dose by 40/day, resume when ALT wnl. ALT >5 × ULN: Stop Rx, may rechallenge when ALT wnl.
Galantamine	Initial: 4 mg bid for 4 wk; if tolerated, ↑ to 8 bid for ≥4 wk; if tolerated, ↑ 12 bid. For moderate renal or liver impairment, max dose is 16 total/day. Contraindicated w/ severe renal or liver impairment.
Memantine	Initial: 5 mg qd; ↑ 5 to target of 20 mg/day; wait at least 1 wk b/n dose changes. Doses >5 mg/day should be given in two divided doses. For severe renal impairment, max: 5 mg bid.

(ULN = upper limit of normal.)

FRONTOTEMPORAL DEMENTIA

Definition: Dementia defined by marked selective cerebral atrophy of frontal and/or temporal lobes. Synonymous w/ frontotemporal lobar dementia. Clinically, two types of FTD are defined: (1) behavioral variant FTD (bvFTD), (2) Primary progressive aphasia (PPA) [further subdivided into semantic dementia & progressive nonfluent aphasia].

Epidemiology: Earlier onset than AD, peak: 40-60s (mean ˜60 yo), where it is

almost as common as AD. May account for up to 10% of dementia cases. Old age & +FHx are most important risk factors.

P.102

Table 12.4 Current Understanding of AD & FTD S Vulnerability & Molecular-Genetic Features

Dz	Early Deficit	Early Network/Region	Early Vulnerable Neurons	Protein	
AD	Episodic memory	MTL-posterior cingulate-lateral TP	ERC layer II pyramidal neurons	Aβ 42, Tau	P
BvFTD	Social-emotional fxn	R > L ACC-frontal insula, frontal pole, amygdala, striatum	VENs?	Tau = TDP-43	P
SD	Semantic knowledge or emotional meaning	L or R temporal pole, amygdala, aACC, frontal insula	Unknown	TDP-43 > Tau	P
PNFA	Motor speech & language fluency	L inferior frontal cortex, precentral insula, striatum	Unknown	Tau > TDP-43	P
FTD-ALS	Social-emotional fxn or motor power	ACC-frontal insula network or bulbar > spinal motor nuclei	VENs? Or lower > upper motor neurons	TDP-43	

(ACC = anterior cingulate cortex; APP = amyloid precursor protein; ER
entorhinal cortex; MTL = medial temporal lobe; PGRN = progranulin; PNFA
progressive nonfluent aphasia; VENs = Von Economo neurons. Reproduced v
permission from Seeley WW. *Curr Opin Neurol* 2008;21(6):701-707.)

Etiology: Most cases sporadic; but as many as 50% of pts may have a +FHx (in one recent series: 73% not clearly inherited; 27% autosomal dom) [mutations: 11% tau, 6% progranulin, 10% other (Table 12.4)]. Multiple other genes implicated in rarer familial forms of FTD. Two loci on cs have linked to FTD p/w amyotrophic lateral sclerosis (FTD-ALS). Unlike AD, APOE genotype does not modify FTD risk.

Pathology: Gross: Marked cortical atrophy affecting FLs &/or TLs. May have pallor of substantia nigra. Histopathology: neuronal loss, microvacuolation of neuropil w/in superficial cortical layers, subcortical gliosis, & sometimes prominent neuronal loss of subcortical structures (e.g., striatum, substantia nigra pars compacta).

Broadly, FTD is defined by neuronal intracytoplasmic inclusions that: (1) Stain + for tau (FTD-tau): e.g., Pick dz, corticobasal degeneration (CBD), PSP. (2) Stain + for ubiquitin & TDP-43 but not for tau (FTD-U) e.g., subset of sporadic FTD & also hereditary FTD caused by progranulin mutations. (3) Stain for neither tau nor TDP-43 (a very small proportion).

Pick dz: Specific sporadic tauopathy w/ severe circumscribed atrophy of frontal & anterior temporal lobe; histopathology = ballooned neurons, intraneuronal tau-positive Pick bodies (but no NFTs) & argyrophilic grains, glial tau-positive inclusions.

Pathogenesis: FTD-tau & FTD-U presumably represent different dzs w/ similar patterns of differential neuronal vulnerability (see Table 12.4), & hence similar clinical phenotype.

Tauopathies: Include several distinct dzs—including AD, FTD-tau, CBD, PSP. Tau hyperphosphorylation likely confers toxicity, by gain of toxic function (e.g., by aggregation itself, aberrant signal transduction, actin stabilization) &/or loss of fxn (e.g., microtubule destabilization) mechanisms.

FTD-U: Recently TDP-43, an RNA-binding protein, has been shown to aggregate in these dzs. TDP-43 aggregation also occurs in ALS (mutations in TARDP, the encoding gene, cause some familial forms of ALS) & w/in muscle in inclusion body myositis.

Clinical features: Three clinical patterns of progression are defined, which have a loose correlation w/ pattern of cortical atrophy & histopathology (see

Table 12.2): (1) bvFTD—correlated w/ atrophy of R frontal lobe w/ tau = TDP-43 pathology; p/w prominent behavioral abnormality & executive dysfxn (including disinhibition, impulsivity, rigid thinking, impaired planning & judgment, loss of social graces, apathy, perseveration, stereotyped behavior, utilization behavior); primitive reflexes may become unmasked (e.g., grasp, palmomental, snout). (2) Semantic dementia (a subset of PPA)—correlated w/ L-sided anterior temporal atrophy w/ TDP-43 > tau pathology—

p/w fluent aphasia associated w/ impaired naming & impaired knowledge of word meaning. (3) Primary nonfluent aphasia (a subset of PPA)—correlated w/ atrophy of L frontal lobe & tau > TDP-43 pathology, including significant overlap w/ PSP & CBD—p/w apraxia of speech & a nonfluent aphasia. Other features: In contrast to AD, memory & visuospatial functions are relatively spared, although that may be difficult to demonstrate on formal testing. Parkinsonism (bradykinesia, rigidity, tremor) commonly associated some forms of FTD → falls, axial rigidity, impaired vertical gaze suggestive of PSP (initially down, then up; can be overcome by vertical oculocephalic maneuver). Asymmetric presentation w/ limb apraxia, dystonia & tremor—so-called “alien limb”—is a classic presentation of CBD (PSP & CBD discussed in more detail in the chapter “Movement Disorders”). FTD-ALS: May p/w weakness, & UMN + LMN signs; this spectrum presumably represents a spectrum of neuron vulnerability to TDP-43 pathology. Rarely, pts w/ FTD present w/ muscle pain & found to have inclusion body myositis.

Diagnosis/workup: Dx: Clinical grounds, w/ neuropsychological assessment. W/u includes judicious subset of dementia workup outlined above. MRI: Often demonstrates asymmetric frontal and/or anterior temporal lobe volume loss. SPECT/PET may show decreased blood flow/metabolic activity in these areas.

Treatment: Currently no dz-modifying therapies available. SSRIs, neuroleptics, stimulant medications (see Table 12.2) may help w/ behavioral dysfxn, but neuroleptics may ↑ parkinsonism; mood stabilizers (e.g., depakote) may be helpful. Cognitive training & psychosocial support are important aspects; family education is critical. Tau kinase inhibitors are in Phase 1 clinical trials.

DEMENTIA WITH LEWY BODIES

Definition: Dementia w/ vis halluc, parkinsonism & fluctuating course with Lewy bodies on pathology. If parkinsonism present >12 months before cognitive impairment is detected, dx is Parkinson dz w/ dementia.

Epidemiology: Second most common late-onset degenerative dementia in

elderly (20% of dementia). Mean age of onset 75 yr (age range 50-83 yr). Duration of illness: mean 3.5 yr (range 1-20 yr).

Etiology: Mostly sporadic and thought to have complex genetic/environmental etiology, although mutations in the alpha-synuclein-encoding SNCA gene can cause a DLB phenotype.

Pathology: Lewy bodies: Intracytoplasmic eosinophilic inclusions w/in cortical neurons composed of alpha-synuclein, ubiquitin, & neurofilament proteins. Decrease in acetylcholine & other neurotransmitters. Minimal cortical atrophy.

Pathogenesis: Presumed to involve a gain of toxic function associated w/ alpha-synuclein post-translational modification, oligomerization, and/or aggregation.

Consensus diagnostic criteria (Neurology 1996; 47:1113): Core features (must have 2 for probable DLB, 1 for possible DLB): (1) Fluctuation in cognition w/ pronounced variation in level of alertness/attention. (2) Recurrent visual hallucinations. (3) Motor parkinsonism (+ in 50% cases at presentation, 25% never show motor signs). Features supportive of DLB diagnosis: Repeated falls; Syncope; Transient loss of consciousness; Neuroleptic sensitivity; Systematized delusions (Capgras syndrome usually an earlier feature than in AD); Nonvisual hallucinations; REM sleep behavioral disorder; Dysphagia & impaired swallowing.

Clinical features/diagnosis: Typical features: Progressive dementia in elderly pt w/ late onset of parkinsonism, episodic confusion w/ hallucinations or paranoid delusions common. Variable presentation: Parkinsonism (limb & axial rigidity, ˜50% tremor) can be early or late in onset, mild or prominent. Late in illness: Amnesia, dyscalculia, visuospatial disorientation, aphasia, apraxia (similar to AD), & impaired swallowing. Sensitivity to neuroleptics resulting in worsening of parkinsonism or confusion. General exam → orthostasis from autonomic involvement. Neurologic examination → inability to do clock-drawing (tests executive & visuospatial function); Rigidity; Resting tremor (less common); Gait impairment.

Diagnostic workup: Dx on clinical grounds, w/ neuropsychological assessment. MRI: r/o other pathology (esp. vascular dementia); will often demonstrate diffuse atrophy; hippocampal atrophy may be present. PET/SPECT may show (activity in posterior parietal/occipital lobes.

Treatment: Parkinsonism: L-dopa/C-dopa. Start 100/25 1/2 tab daily & increase by 1/2 tab to 1 tab tid. May be effective for motor features early in illness, although not all respond. Side effects of nausea, hypotension, delirium, & hallucinations occur early in treatment course & limit use.

Cognitive decline: Anticholinesterase inhibitors (see Table 12.3). Depression: SSRIs are the drug of choice. Hallucinations/behavior disturbances:

Atypical neuroleptics. Avoid antipsychotics: Risk irreversible parkinsonism, NMS. First withdrawal L-dopa/C-dopa medications to see if behavior improves; If not, use atypical antipsychotic w/ caution (see section on AD for doses); Clozapine may be particularly useful in avoiding extrapyramidal effects; monitor CBC.

VASCULAR DEMENTIA

Definition: Decline in cognitive fxn due to accumulation of deficits from multiple strokes. Can be concurrent w/ AD ("mixed dementia") w/ a spectrum of dementia syndromes from pure vascular dementia to pure Alzheimer's. Synonyms: Vascular dementia, post-stroke vascular dementia, subcortical ischemic vascular dz & dementia, small-vessel dementia, strategic-infarct dementia.

Epidemiology: 15%-20% of dementia. Prevalence increases by age: 1.5%-5% of people 70-80 years, >40% for >80 years.

Etiology: Risk factors: Age, HTN, hyperlipidemia, DM, CAD/CHF, recurrent stroke, smoking, sleep apnea, hyperhomocysteinemia.

Pathogenesis: Large artery strokes, small vessel dz, cardioembolic events, intracranial stenosis combined w/ hypoperfusion. Genetic forms of vascular dementia (e.g., CADASIL).

NINDS-AIREN criteria for probable vascular dementia (Neurology 1993;43(2): 250): Acute onset of dementia demonstrated by impairment of memory & two other cognitive domains, such as orientation, praxis or executive dysfxn. Relevant cerebrovascular lesions are demonstrated by neuroimaging. Temporal relation between stroke & cognitive loss is evident. Preexisting mental impairment excluded including delirium, altered mental status.

Clinical features/diagnosis: Typical features: Abrupt onset of cognitive impairment— especially involving executive functioning—followed by stepwise decline; often w/ unilateral sensorimotor changes & aphasia; changes in mood or personality or depression may also occur. Variable presentation: Subcortical vascular dementia may present as cognitive slowing, executive dysfxn, & impairment of gait & bladder control. Distinguishing from pure AD: Gait disturbance less common in AD, early memory loss, & impairment of language more common in AD. Neuro exam: Impaired MMSE; Asymmetric weakness or sensation; Gait disturbance.

Diagnostic workup: Imaging: MRI shows multiple infarcts, ± white matter changes. Neuropsych testing: Executive dysfxn & impaired learning/retrieval but relatively spared recognition memory (in contrast to AD: recognition memory usually impaired as well).

Treatment: Acetylcholinesterase inhibitors (AchEIs: donepezil, galantamine, & rivastigmine) may have some benefit.

NORMAL PRESSURE HYDROCEPHALUS (NPH)

Introduction: Hydrocephalus w/o sustained ↑ ICP. Peaks in sixth or seventh decades. Typical features are: progressive hydrocephalus on imaging & triad of: (1) Dementia (FL dysfxn w/ ↓ attention, concentration, & executive fxn; ± apathy). (2) Impaired gait (ataxic or apraxic gait, classically described as a "magnetic gait"). (3) Incontinence (typically later in the course).

Pathogenesis: Multiple theories. Classical theory: CSF production > absorption, potentially 2/2 insufficient absorption through arachnoid villi granulations; processes affecting subarachnoid space (e.g., subarachnoid hemorrhage, meningitis, trauma) may thus predispose to NPH. Another theory: Initial pressures in NPH are high, but normal pressures eventually result from ↑ ventricle size, while forces on white matter ↑ ventricles expand. Another theory: Critical intermittent spikes in intraventricular pressure. Another theory: Transmantle gradient (pressure difference between ventricles & subarachnoid space) is driving force in expanding ventricles (not absolute intraventricular pressures, w/ ventricular expansion possible even w/ very small transmantle gradient. Ventricular expansion, through whatever mechanism, thought to damage periventricular WM & corona radiata, including sacral motor projections (explaining the clinical triad).

Diagnostic workup: Important to recognize b/c potentially reversible; however, just as important not to overdiagnose to prevent futile, risky (death or disability 7% in one series) surgery. MRI: Hydrocephalus out of proportion to cortical atrophy; periventricular/periaqueductal T2 FLAIR hyperintensity (2/2 ↑ transependymal flow) LP: High volume (30-50 mL) → showing transient improvement in cognition & gait (temporary lumbar drain may be useful).

Treatment: Ventriculoperitoneal shunt: Long duration & extensive cortical atrophy or WM sz dz on MRI ↓ prospects of success). Adjunctive pharmacotherapy (stimulants, dopaminergics) if impaired attention, apathy.

Movement Disorders

HYPOKINETIC MOVEMENT DISORDERS

PARKINSON DISEASE (PD)

Introduction: Most common neurodegenerative movement disorder. Men:women 3:2 predominance (unclear why), mean onset 60 yo (range: 40-70). Course variable. Primarily sporadic disease, but several familial forms identified (13 PARK genes to date associated with parkinsonism) → genetic forms associated with earlier onset PD (<50 yo).

Pathophysiology: Pathologic hallmark: Degeneration of dopaminergic nigrostriatal projection neurons. Loss of pigmented neurons in substantia nigra & other pigment nuclei (more widespread pathology identified). Lewy bodies (eosinophilic cytoplasmic inclusions) → composed of alpha-synuclein (normally found in unfolded form, but in Lewy bodies high concentrations aggregate as filaments) and ubiquitin.

Clinical features/diagnosis

Diagnostic criteria: Cardinal features are bradykinesia, rest tremor, rigidity, asymmetric onset. Features pointing to an alternate diagnosis are early (<3yrs) prominent instability/falls, early (<3yrs) freezing, early (<3yrs) hallucinations, dementia preceding motor symptoms or in 1st yr; supranuclear gaze palsy; severe, symptomatic dysautonomia; documented condition known to cause parkinsonism, e.g., drugs. Definite diagnosis only with autopsy.

Other features: 40% develop dementia → see chapter Dementia for dementia with Lewy bodies. ANS → bowel/bladder dysfxn, orthostatic hypotension.

Features

Early signs

↓ blinking (nl blink rate 15-20/min, PD → 5-10). ↓ facial expression (hypomimia). ↓ smell sensitivity.

Bradykinesia

Most characteristic feature of PD and most disabling. Slow mvmts,

Tremor

Resting 3-5 Hz “pill rolling.” Can involve lips, chin, but head/neck unusual. First sx in 70% pts. Usually asymmetric at dz onset. ↑ w/ anxiety, contralateral mvmt, ambulation. Can also have action tremor (8 Hz). Postural tremor most disabling; need to differentiate from ET. Not always

first noted w/ fine motor tasks; micrographia (small handwriting). Difficulty turning in bed → late finding. Gait → slow, reduced arm swing, shuffling, freezing, turning en bloc. Monotone, hypophonic dysarthria. Sialorrhea (failure to swallow).

Postural instability

Worsening balance → falls; tested via pull test. Festination—chasing center of gravity. Retropulsion/propulsion.

alleviated with L-dopa or dopamine agonists.

Rigidity

Increased muscle tone, cogwheeling. ↑ w/ contralateral motor mvt/mental activity (Froment sign). Significant cause of disability, pain. Postural deformities ("striatal hands"), camptocormia (flexed posture), head drop.

Differential diagnosis: (1) Parkinson-plus syndromes: eventually diagnosed in about 25% of pts w/ original dx of PD; poor response to dopaminergic therapy; worse prognosis; more rapid progression. Other notable features are: rapid onset, early dementia, prominent autonomic symptoms, early frequent falls. (2) Structural (tumor, hydrocephalus, hematoma, trauma), vascular (stroke, vasculitis), infectious, (postencephalitic, prion disease, AIDS, SSPE), toxic (carbon monoxide, manganese, MPTP, rotenone, paraquat), metabolic [hepatocerebral degeneration, hypoxia, hypocalcemia (Fahr's)]. (3) Drug-induced or tardive Parkinsonism: reversible (may take months), found to cause 20% of PD in one study; consider this if rapid onset of PD sx occurs; drugs that cause it → antipsychotics, antiemetics, amiodarone, valproate, lithium, Ca^{+} channel blockers.

Treatment

L-dopacarbidopa: Most effective med, active within 30 min of med ingestion, doesn't help all sxs. Starting med early in dz doesn't ↓ long-term efficacy. Start 25/100 mg tid. Med trial for 3 mo titrate to at least 1 g/day → if no improvement, consider atypical PD or other d/o (only 10% of path proven PD have no response to med). If d/c, taper slowly as abrupt cessation can cause hyperpyrexia/rigidity or neuroleptic malignant syndrome (NMS).

L-dopa side-effects: Dyskinesias, vivid dreams, sleep disturbance, visual hallucinations, hypotension, constipation, compulsive behavior (e.g., gambling). Nausea → give med w/ meal or crackers (but high protein meal decreases med absorption).

Carbidopa: ↓ peripheral side effects of L-dopa (nausea/hypotension). Daily

dose of 75 mg needed; can increase as needed.

Dopamine agonists: Slightly less efficacious than L-dopa but still first-line alternative. Thought to ↓ risk (by 3—4×) of dyskinesias/motor fluctuations in first 5 yr of tx vs. L-dopa. In elderly can cause confusion, delirium, hallucinations. Ergot derivatives (pergolide) associated with valvular disease, nonergots preferred (e.g., pramipexole & ropinirole). Side effects → decreased impulse control (less common w/ L-dopa) → gambling, hypersexuality, hypomanic states.

Other meds: (1) Rest tremor → consider amantadine, anticholinergic (limited by side effects), beta blocker, or primidone. (2) Psychosis → quetiapine or clozapine (atypicals less chance of worsening PD)

Dopamine agonist vs. L-dopa: (Which to start?) (1) Head to head comparisons → ↓ motor complications (i.e., dyskinesia, mtr fluctuations) but worse motor fxn in agonist group at 5 yr f/u (NEJM 2000;342:1484; J Neurol Neurosurg Psych 1994;57:1034). (2) Large 14 yr f/u UK trial agonist vs. L-dopa → outcome/motor complication similar, but still L-dopa group shows better motor fxn (Neurology 2008;71:474). (3) Agonist → ↓ motor complications (at expense of worse motor fxn) at 5 yr; eventually this adv is lost. (4) Either considered first line, even in younger pts. (5) Eventually those treated with agonist will require adjunctive L-dopa.

Neuroprotection: Coenzyme Q10 may be protective (currently in trial). Controversional evidence for disease modification exists for rasagiline (TEMPO study), but much less clear evidence for L-dopa (DATATOP study), and no evidence for riluzole and agonists.

Surgery: Indicated in pts who are L-dopa-responsive but developed motor fluctuations/dyskinesias (increases“on” time), intractable tremor, dystonia. Benefits of surgery rarely exceed original drug effect. Ablation (such as pallidotomy or thalamotomy) used in 50s, currently less preferred than DBS (unless DBS contraindicated). Two major targets for DBS: globus pallidus interna (GPi) and subthalamic nucleus (STN).

Long-term complications

Motor fluctuations: Delayed onset of L-dopa or wearing off between doses, often predictable. Linked to low plasma levels of meds. Tx: (1) Advise pt to avoid taking L-dopa with highprotein meals; tighten dose interval (more frequent doses of L-dopa at same dose); consider controlled-release levodopa/carbidopa (not effective in later stages). (2) Add COMT inhibitors: → half-life of L-dopa, e.g., entacapone (give w/ each dose of L-dopa). Avoid use of tolcapone given liver toxicity, needs LFT monitoring. (3) MAO-B inhibitors: ↓ dopamine breakdown in CNS (selegiline, rasagiline); avoid w/

SSRI or TCA; avoid tyramine-rich foods (sausage, aged cheese, salami) that can cause HTN crisis. (4) DBS if above fails.

Dyskinesia: Involuntary choreiform mvmts, often linked to high plasma dopamine levels. As PD progresses, dyskinesia occurs at lower & lower L-dopa/agonist doses. Cause unclear, but exogenous dopaminergic stimulation in denervated striatum contributes. At 5 yr, ∽ 11% risk of dyskinesia, ∽ 10 yr 33%, >10 yr ∽90%. Tx: Reduce L-dopa dose, switch from controlled-release to immediate-release if dyskinesias in late afternoon or evening, switch to Dopa agonist monotherapy, or add amantadine (NMDA receptor antagonist) or clozapine (Neurology 2004;62:381).

MULTIPLE SYSTEMS ATROPHY (MSA)

Introduction

Alpha-synucleinopathy → parkinsonism, cerebellar, autonomic, & pyramidal sx's. Sporadic dz, ∽3/100 K, onset 60 yo, mean survival 6 yr, M > F. 33% pts w/ late onset cerebellar ataxia & 8% w/ parkinsonism → develop MSA. Rapid sx progression. Early functional disability. Dementia uncommon.

Pathology: Glial cytoplasmic inclusions (alpha-synuclein-rich). MSA-P → striatonigral system atrophy. MSA-C → olivopontocerebellar atrophy. ANS sx → cell loss in brainstem (PRF, dorsal motor vagus nucleus) + spinal cord (parasympathetic preganglionic for bladder/sexual, intermediolateral column for hypotension).

Clinical manifestations

MSA-P (Parkinsonism, prev. known as striatonigral degeneration, or SND): Parkinsonism main feature, in 80% of pts. Progressive akinesia/rigidity. Irregular, myoclonic (jerky) tremor > rest tremor. Orofacial or craniocervical dystonia anterocollis and laryngeal stridor common, w/ quivering high pitched dysarthria.

MSA-C (Cerebellar, prev. known as olivopontocerebellar atrophy, or OPCA): Gait/limb ataxia, scanning dysarthria, in 20%. Cerebellar oculomotor problems. If +FH consider SCA & not MSA

Autonomic: Urogenital sxs: Urinary retention or incontinence; early erectile dysfxn in approx. all pts. Orthostatic hypotension: symptomatic in 68%; recurrent syncope in 15%; L-dopa may worsen it.

Imaging: (MRI) putaminal, olivopontocerebellar atrophy. T2 hyperintensities in pons, mid-cerebellar peduncles."Hot cross bun" signal → due to cruciform degeneration of pontocerebellar fibers. GRE (gradient echo) → hypointensity

in putamen ± slit-like hyperintense rim around putamen (latter related to gliosis). ADC → ↑ signal in putamen (due to degeneration), not seen in PD, but seen w/ PSP.

Treatment

Parkinsonism: 30% initially responsive to L-dopa, but declines over years; dopamineinduced confusion can ensue.

Orthostatic hypotension: Avoid large meals, increase salt intake, avoid straining during urination/defecation, no EtOH/drugs, elastic stockings, head up tilted bed. Fludrocortisone or midodrine first-line. Supine HTN (sometimes associated w/ severe orthostatic hypotension) → treat only if SBP > 200, start nighttime short-acting Ca^{2+} antagonist. Impotence → penile injections (prostaglandin), sildanefil (but can worsen hypotension).

Speech/bulbar dysfxn: Inspiratory stridor can develop; monitor sleep apnea.

PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

Introduction: Progressive dz w/ vertical gaze difficulties & falls/gait instability within first year of onset. 5% of pts in mvmt d/o clinic have PSP; no gender difference; onset 60s (age < 40 yo unlike PSP). Cause unknown; pathology: neurofibrillary tangles in brainstem & basal ganglia, tau deposition, sparing of cerebral cortex. Definitive dx via autopsy. MRI: Atrophy of midbrain may be seen; “Mickey Mouse sign” demonstrates atrophy on axial midbrain cuts; beaked “hummingbird” appearance of midbrain on midsagittal view.

Clinical features

Parkinsonism (symmetric unlike PD): Bradykinesia, rigidity (axial > appendicular, unlike PD), rarely pill rolling rest tremor. Frequent falls & gait difficulty (common presenting complaints).

Visual: Slowing of vertical saccades → initially downgaze limitation, convergence, slowing horizontal/vertical saccades (overcome by VOR). Bell phenomena (closing eyelids causes eyes to roll up) & convergence eventually lost. Nontargeted saccades (“look left/right”) affected first over targeted (“look at my finger, then my nose”). Optokinetic nystagmus; square-wave jerks; eyelid apraxia.

Bulbar sxs: Dysarthria (“growling” speech). Pseudobulbar sx: emotional incontinence— apathy > disinhibition > dysphoria, anxiety > irritability.

Other features: Open, unblinking eyes (surprised look), masked facies, or blepharospasm & involuntary eye closure. Neck extension (in PD usually flexed); Dystonia of extremities.“Applause sign” — preservation of automatic

behavior (perseverative clapping).

Treatment: L-dopa: Up to half of PSP pts have short-lived moderate benefit. Amantadine: 100 mg bid; about 15% have modest benefit. Multidisciplinary approach: PT/OT/social services.

CORTICOBASAL DEGENERATION (CBD)

Introduction: Progressive asymmetric parkinsonism w/ cortical dysfxn. Onset > 60 yo (possible female predominance). Rare but possibly accounts for up to 6% of parkinsonism.

Clinical features

Motor: Parkinsonism/dystonia. Unilateral, asymmetric → usually affects arm. Fast tremor, unlike PD tremor. Stimulus sensitive myoclonus (in some pts). Gait disorder + postural instability. Dystonia → present in most pts, asymmetric, painful; progresses to “dystonic clenched fist” (dystonic flexed hand, held in a fist, fingers clenched around adducted thumb).

Cortical dysfxn: Asymmetric ideomotor apraxia (i.e., cannot imitate symbolic gestures such as tool use). Alien limb phenomenon → limb moves on its own accord, pt unaware of it, can grasp objects, & not release them; can interfere w/ voluntary mvmt. Cortical sensory loss (e.g., agraphesthesia; not primary sensory).

Cognition: Dementia may be presenting (or only) sign (some CBD do not develop movement sxs). Fronto-striatal-parietal predominance. Nonfluent aphasia common (overlap w/ FTLD).

Eye movements: Difficulty + delay initiating saccades (usually horizontal, unlike PSP); once initiated saccades are nl.

Diagnosis: Clinical, though can be difficult. Insidious, progressive dz, w/ both: (1) Cortical dysfxn (one of following); apraxia, alien-limb, neglect, cortical sensory loss, aphasia (formal neuropsychiatric testing useful). (2) Extrapyramidal dysfxn (one of following): rigidity, dystonia.

Brain imaging → nl early in dz, then asymmetric posterior frontal & parietal cortical atrophy.

Dopamine transporter SPECT: Abnl unlike other dementias (AD), but this is abnl in other Parkinson-plus syndromes as well. Path: Focal cortical/substantia nigra atrophy, w/ tau inclusions (like in PSP); PSP & CBD possibly spectrum of same dz.

Treatment: L-dopa: May help, though most pts resistant. Dementia:

Cholinesterase inhibitors unhelpful (probably because basal forebrain cholinergic neurons not involved in dz). Dysphagia: Important late sx, PEG may be needed.

OTHER HYPOKINETIC MOVEMENT DISORDERS

Stiff person syndrome Continuous isometric contraction of axial & proximal muscles, assoc w/ pain, opisthotonus (hyperextension of back muscles); associated w/ glycine receptor gene mutations; autoimmune association (elevated anti-GAD or amphiphysin antibodies).

Myotonia/paramyotonia *Myotonia*: episodic sustained muscle contractions causing impaired relaxation & inability to move, elicited by tactile stimuli, causing mild or severe temporary weakness, improves w/exercise. Associated w/ *CLCN1* gene mutations. *Paramyotonia congenita* (*Eulenburg's disease*): as above, but worsens w/ exercise & cold weather. Also associated w/ hyperkalemic periodic paralysis. Face & arms affected more than legs. Associated w/ *SCN4A* gene mutations.

HYPERKINETIC MOVEMENT DISORDERS

TREMORS

Introduction: Involuntary rhythmic oscillations of a body part.

Approach: Aggravating/relieving factors? Stress, anxiety, lack of sleep, caffeine intake, alcohol. Document frequency of tremor (i.e., high 12 Hz or low 3 Hz). Labs to consider: TSH, glucose, screening for heavy metals (if suspect exposure), Wilson dz (LFTs, ceruloplasmin, 24 h urine copper excretion, slit lamp exam for KF rings), pheochromocytoma (urine catecholamines/metanephrines or serum-free metanephrines). Physiologic testing (EMG-tremor study): Can be helpful; EMG recorded at rest, w/ posture, w/ movement, w/ weighting, & w/ tapping a specific frequency to check entrainment (tap least affected hand to metronome and see if other hand tremor begins matching tap frequency = entrain).

Rest Tremors

PD	Second most common tremor in adults (after essential tremor). Starts unilateral in one hand, low frequency (4-6 Hz), often "pill-rolling," assoc w/ other sxs of PD.
Rubral tremor	Due to midbrain injury (possibly due to lesion of superior cerebellar peduncle, substantia nigra, & red nucleus). Always associated w/ signs of midbrain/cerebellar lesions. Slower frequency than PD (3-5 Hz); large amplitude. May cause combined rest, postural, action, & intention tremor.

Postural & Action Tremor

Essential tremor	See below.
Enhanced physiologic tremor	Most commonly confused w/ essential tremor. N1 → low amplitude, high frequency tremor (8-12 Hz), usually not visible. *Causes*: Emotions (anxiety, fear, excitement, fatigue). Medical illness (hypoglycemia, fever, thyrotoxicosis, EtOH/opiate withdrawal, pheochromocytoma). Toxins (mercury, lead, arsenic). Long list of medications, see box below. *Tx*: Reduce/remove offending agent.

Postural Tremor

Dystonic tremor	Focal tremor in area affected by dystonia. <7 Hz, irregular amplitude. Cervical dystonia → isolated head tremor, look for subtle unusual positioning of head, shoulder elevation, or active dystonic muscles (from dystonia). Sensory trick: Pt touches his limb in a certain way to decrease tremor (unlike essential). Tx: consider botulinum toxin injection, esp. for cervical dystonic tremor.
Orthostatic tremor	High frequency, 13-18 Hz. Bilateral LE (pt c/o unsteadiness w/ standing, improves w/ walking). Auscultate gastroc or quad → thumping sound (due to rippling of m.). Tremor same throughout body (if it affects trunk & hands).

Responds to clonazepam, gabapentin.

Intention Tremors

Cerebellar tremor	Low frequency <5 Hz. Lesion affecting dentate nucleus or superior peduncle. Usually only intention tremor, but can occur w/ posture. Tremor ↑ as hand moves closer to target, usually large amplitude. Other signs: Dysmetria, dysrhythmia (rapid alternating mvmts). Occasional titubation of the head or trunk.
Other causes	Due to lesion along cerebellar path from dentate nucleus to thalamus. Most common causes: Stroke, multiple sclerosis, midbrain lesion (trauma or stroke). Other less common causes: Degenerative dz of cerebellum, severe essential tremor, Wilson dz, mercury poisoning.

Other Tremors

Task-specific tremor	Occurs *only* during specific tasks (and at no other time), most commonly writing. Can be associated w/ task-specific dystonia.
Neuropathic tremor	Postural, intention tremor, bilateral. Occurs w/ large fiber neuropathies (hereditary neuropathy, in recovery phase of GBS, or CIDP). Due to muscle weakness/loss of proprioceptive input. Occurs in limbs affected by neuropathy.
Psychogenic tremor	Sudden onset, occurs at rest, postural, or intention. Tremor may disappear w/ distraction. May appear bizarre/large amplitude. Pt reports being fatigued from tremor (essential tremor usually doesn't cause fatigue).

ESSENTIAL TREMOR

Introduction: Rhythmic shaking of arms (95% cases; wrist flex/extension); also involves: head ("no-no" head tremor) (34%), tongue/LE (30%), voice (12%), face (5%) (Pract Neurol 2007;7:222). ∽75% of pts → disability & decreased quality of life. Incidence increased w/ age, dx at mid-to late-adulthood, no gender difference. +FH in up to 70% cases (felt to be heritable disorder, autosomal dominant, but some pts w/o FH). Pt w/ 1° relative → 4.7×

risk of getting essential tremor. Pathophys → dysfxn of network including thalamic, inferior olivary nuclei, cerebellum, & sensorimotor cortex.

Diagnosis: Must consider secondary causes of tremor: Medications; Metabolic disorders: hyperthyroid, hyperparathyroidism, hypoglycemia; Electrolyte abnl: Mg, Ca, or Na; Drug withdrawal: E.g., EtOH, cocaine. Exam → nl except for tremor (advanced cases may have difficulty with tandem gait, impaired smooth pursuit). Broad ddx: See above.

Red flags: Unilateral tremor, leg tremor, rigidity, bradykinesia, rest tremor. Gait disturbance; Focal tremor; Sudden or rapid onset on meds that worsen tremor. Isolated head tremor w/ abnormal posture (head tilt or turning).

Medications Commonly Causing Tremors

Neuroleptics, reserpine, tetrabenazine, metclopramide, antidepressants (especially TCA); lithium; cocaine; alcohol; bronchodilators; theophylline; caffeine; dopamine; steroids; cyclosporine; valproate; perhexiline; amiodarone; procainamide; calcitonin; thyroid hormones; chemotherapy (vincristine, adriablastine)

Differential Dx & Main Features of Tremors

Dx	Tremor Description
Essential tremor	Hand tremor, postural/intention, 4—12 Hz
Enhanced physiologic	Usually hands, postural/intention, 8-12 Hz
Orthostatic tremor	Legs, postural
Parkinson	Rest, unilateral, hand, rest, 3-6 Hz, other PD signs
Wilson dz	Upper/lower extremities, postural/intention, 4—6 Hz, pts < 40 yo, liver dz, dystonia, etc.

Treatment

Nondisabling mild symptoms → lifestyle modifications (no caffeine, no nicotine, avoid meds that cause tremors).

Moderate to severe tremors → about 25%—55% of pts do not benefit from meds. First line: Propranolol or primidone. Second line: Other β-blockers, gabapentin, topiramate, BZD, botulinum toxin (focal/segmental dystonic tremor; inject to cause subclinical weakness, not very effective).

Disabling medication resistant tremors → surgery: DBS of thalamic VIM nucleus. Bilateral: Better but w/ more side effects than unilateral. Bilateral: 78% improvement in tremor scores; side effects—dysarthria, balance difficulties. Unilateral: 46% improvement; side effects—paresthesias, disequilibrium, cognitive problems.

Meds	Dose	Adverse Effects
Propranolol	40 mg bid → max dose 320 mg/day	Bronchospasm, fatigue, hypotension
Primidone	12.5-25 mg QHS → max 750 mg/day (divided bid ortid)	Sedation, confusion
Gabapentin	300 mg daily → max 3,600 mg/day	Somnolence
Topiramate	25 mg QHS → max 200 mg bid	Anorexia, concentration difficulties, nephrolithiasis

DYSTONIA

Introduction: Involuntary, repetitive twisting mvmts or abnl posturing caused by sustained muscle contractions. Movements → slow or rapid, due to contraction of both agonist & antagonist muscles (which also affects adjacent muscles, compensatory activity). Predictable, patterned, directional movement involving the same muscle groups (unlike chorea). No urge to perform movements & no relief from movements (unlike tics). Can be decreased via sensory trick (geste antagoniste). Tonic sz can also cause twisting movements & should be considered.

Classification

Types of Classifications

Anatomical distribution	Helps w/ prognosis: Cervical dystonia can show complete remission, which is less likely w/ generalized dystonia. **(1)** Focal → single region/body part, e.g., cervical dystonia, blepharospasm, writer's cramp. **(2)** Segmental → ≥2 adjacent regions, e.g., Meige syndrome (blepharospasm + oromandibular dystonia), writer's cramp (task-specific; e.g., musician's dystonias). **(3)** Multifocal → ≥2 nonadjacent regions. **(4)** Hemidystonia → ipsilateral arm/leg; implies secondary causes (stroke, trauma). **(5)** Generalized dystonia → leg(s), trunk, & one other region.
Age of onset	*Early onset* (*<26 yo*): Affects/begins in extremities. Usually start focal → progress to generalized. *Late onset* (*>26 yo*): Usually affects/begins in neck or cranial muscles (rarely limbs).

Primary dystonia: No other neurologic abnormalities (except myoclonus/tremor). No underlying secondary cause (no structural brain abnl, no inborn errors of metabolism) except some genetic mutations.

Primary Dystonia

Primary focal dystonia	10× more common than primary generalized torsion dystonia. More common in adults, begins mid-life, more common in women (except writer's dystonia), occurs in neck, face, arm. Can progress over 1-2 yr, but then becomes static. **Cervical dystonia:** Most common focal & primary dystonia. 30-50 yo, begins w/ neck stiffness & ↓ head mobility → abnl head posture + neck/shoulder pain, + sensory trick (touch face) to reduce sxs. Ddx: cervical disc dz. **Cranial dystonia (usually > 40 yo):** Blepharospasm, oromandibular dystonia, spasmodic dysphonia. **Blepharospasm:** Most common cranial dystonia. Causes ↑ blink rate, forced eye closure, difficulty w/ eye opening. Sxs increase w/ bright light, reading, driving. **Oromandibular dystonia:** Involuntary clenching (bruxism), opening, deviation of jaw.

Primary generalized torsion dystonia	Progressive, disabling, begins in kids (not always), genetic. Many cases autosomal dominant trait (DYT1 locus) → CAG deletion in torsion A gene. Torsion A: Unknown fxn in brain. Prevalent in Ashkenazi Jews. Starts as focal dystonia → progresses to: 65% generalized or multifocal, 10% segmental, 25% remain focal.

Secondary dystonia: Large number of diverse causes. Due to an underlying pathology, usually additional neurologic signs/symptoms are present, abnormal brain imaging/labs.

Secondary Dystonia

Degenerative disorders	Other neuro si/sx present, usually d/o affects basal ganglia *Many causes*: Wilson dz, PD/Parkinson plus, Huntington's, DRPLA, spinocerebellar degeneration, PANK2, familial basal ganglia calcification (Fahr's). Lysosomal storage d/o (Krabbe's, Neimann-Pick); Ceroid lipofuscinoses; Mitochondrial (Leigh's, Leber's); Neuroacanthocytosis, Lesch-Nyhan syndrome; Ataxia telangiectasia; Gangliosidoses; MLD; Homocystinuria; Hartnup disease; Glutaric aciduria; Methylmalonic aciduria.
Drug-induced dystonia	L-dopa, antiepileptics, dopamine agonists, calcium channel blockers, antipsychotics, SSRIs. Can be due to toxins: CO, manganese toxicity, carbon disulfide.
Acquired structural lesions	Produce hemidystonia or focal limb dystonia. Brain imaging → lesions in BG (putamen & thalamus). Due to perinatal injury, kernicterus, stroke, hemorrhage, MS, trauma, infxn, tumor.
Dystonia-plus syndromes	Not associated w/ neuropath findings (unlike degenerative d/o). Other neuro signs present (e.g., parkinsonism, myoclonus). **Dopa-responsive dystonia (DYT5, Segawa**

	syndrome): Rare, presents in early childhood. Autosomal dominant and recessive, due to point mutation in enzyme important in the synthesis of tetrahydrobiopterin (cofactor for dopamine synthesis). Begins as foot dystonia, leading to gait problems → progressive generalized dystonia ± parkinsonism. Marked diurnal variation, worse at end of day. Early development nl, sometimes mistaken for cerebral palsy. Tx: Dramatic response to L-dopa. **Myoclonus-dystonia (DYT11):** Rare, children, dystonia of arms, trunk, bulbar w/ brief myoclonic jerks. Autosomal dominant, mutation in gene encoding sarcoglycan.
Other causes	Paraneoplastic, encephalitis, psychogenic, cervical cord or peripheral injury.

Diagnosis: (1) Hx, exam. (2) Send DYT1 gene if: Generalized or focal dystonia, pt < 26 yo at onset; or limb dystonia, typically pt > 26 yo; if +FH of dystonia <26 yo. (3) Brain MRI to rule out underlying pathology. (4) Consider: CBC, CMP, Mg, Ca, coags, LFTs, TFTs, ESR, ANA, RPR. L-dopa trial to r/o dopa-responsive dystonia. CSF, bld smear, serum AA, urine OA, sulfates, lysosomal enzymes. Wilson dz: slit lamp exam for Kayser-Fleischer ring ∽ 100% sensitive, serum ceruloplasmin ∽85% sensitivity, 24 h urine copper, genetic testing. EEG, VER, PET can be useful.

Treatment: Symptomatic treatment (rarely symptoms can be life-threatening as in dystonic storm: hyperthermia, rhabdomyolysis, myoglobinuria). Physical therapy + braces + splints: help improve posture & prevent contractures. Immobilization of a limb can exacerbate dystonia in certain pts.

L-dopa: Small subset respond to it, consider it in all pts w/ childhood/young onset w/ generalized/segmental dystonia, usually no L-dopa-induced fluctuations/dyskinesias occurs, if no improvement in 1 mo L-dopa-responsive dystonia unlikely.

Antidopaminergic meds: Mixed efficacy, usually not used due to side effects.

Anticholinergic meds: Trihexyphenidyl (starting at 1 mg daily up to 12 mg daily) can be tried for generalized/segmental dystonia if 1 mo trial of L-dopa fails.

Other meds: Most pts need combination of meds; other meds include muscle relaxants.

Botulinum toxin: Helpful w/ focal dystonia or to control severe aspect of generalized/segmental dystonia (e.g., cervical dystonia). Blocks acetylcholine release at neuromuscular junction.

Surgery: DBS of internal globus pallidus preferred over surgical ablation (pallidotomy); both stop abnormal discharge from globus pallidus; max benefit may not appear until 3-6 mo.

CHOREA

Introduction: Abrupt, rapid, or continuous movements that flow randomly from one body part to another, can be dance-like, often incorporated into normal movement/behavior. Manifestations range between mild restlessness to severely disabling movements interfering w/ speech, feeding, & gait (ballism most severe form). Motor impersistence noted on tongue protrusion (aka "jack-in-the-box tongue") or handgrip (aka "milkmaid grip"). Pendular or "hung-up" reflexes. Temporarily suppressible.

Causes: Huntington dz (see below). Storage diseases; genetic metabolic conditions: Wilson's, Niemann-Pick, Lesch-Nyhan, pantothenate-kinase-associated neurodegeneration (Hallervorden-Spatz), ataxia telangiectasia. Leukodystrophies: Pelizaeus-Merzbacher. Autoimmune: Sydenham chorea (rheumatic fever, RF; also known as St. Vitus' dance), SLE, polyarteritis nodosa, Behcet's, chorea gravidarum (50% idiopathic; in other cases associated w/ RF, SLE, APLS; usu first preg; 50% first trimester, ∽ 30% second trimester, can be treated if severe & disabling w/ haloperidol, VPA, CBZ). Acquired metabolic conditions: Hypo-/hyper-Na, hypo-/hyper-Gly, hypo-Ca/Mg, RF, hyperthyroidism, hyperparathyroidism; Beri-beri, pellegra, B_{12} def. Toxins: Mercury, manganese, thallium, CO poisoning, alcohol, toluene. Medications: Dopamine antagonists, L-dopa, TCAs, AEDs, steroids, OCPs. Other: Physiologic chorea of infancy, anoxic injury (CP), encephalitis, kernicterus, AIDS, migraine, infarcts in rare cases, aging (senile chorea).

HUNTINGTON DISEASE (HD)

Introduction/pathology: Progressive, fatal, autosomal dominant. Onset 25—45 yo. Triad of mvmt, behavioral, & cognitive dysfxn. Gene on chromosome 4 w/ expanded trinucleotide repeat (CAG). Repeat (usually) expands w/ subsequent generation, leading to anticipation (i.e., earlier onset of dz, particularly paternal inheritance). Huntingtin protein found in all human cells. In HD, mutant gene → toxic gain of fxn. Striatal degeneration, marked cortical atrophy/thinning.

Clinical features: Chorea, later parkinsonism, dystonia, spasticity in severe disease. Motor impersistence. Unable to maintain constant voluntary contraction. Milkmaid's grip → fluctuating pressure on handshake. Cognition: Executive fxn affected, memory usually spared, deterioration of speech faster than comprehension, dementia late. Neuropsych: Personality change, agitation/irritability, anxiety, depression (suicide potential high), social withdrawal, apathy, psychosis, sexual dysfxn, substance abuse.

Diagnosis: Perform genetic counseling prior to genetic testing in all pts. Predictive genetic testing in asx pts: Usually not offered for suicidal pts or children (genetic counseling request). Diagnosis confirmed w/ genetic testing (help exclude other diagnoses), done even if +FH. MRI: May show atrophy of caudate/putamen, cortex.

Treatment: Supportive only, weight maintenance, family counseling. Chorea → dopamine antagonists (but usually not used due to parkinsonian side effects), tetrabenazine. Psychosis → newer neuroleptics. Anx/dep → mood stabilizers, SSRI.

MYOCLONUS

Introduction: Sudden, brief, shock- or jerk-like involuntary movement. Symptomatic (i.e., secondary) myoclonus most common (72%), epileptic myoclonus (17%), essential myoclonus (11%). Myoclonus can be classified per location: (1) Cortical: e.g., encephalopathy, posthypoxia. (2) Cortical/subcortical: e.g., seizures. (3) Subcortical-supraspinal: Essential myoclonus. (4) Spinal: Propriospinal & segmental spinal myoclonus. (5) Peripheral: Rare, hemifacial spasm.

Physiologic myoclonus: Occurs in healthy individuals, little to no disability, nl exam. Examples: Sleep jerks (hypnic jerks), hiccups, anxiety-induced, exercise-induced, benign infantile myoclonus with feeding.

Essential myoclonus: Idiopathic or genetic, progresses slowly, subcortical, nl exam. Some associated disability (usually mild), usually the most prominent or only clinical finding. Hereditary form: Onset < 20 yo, dominant inheritance (variable severity), benign course, myoclonus throughout upper body.

Epileptic myoclonus: Occurs as a component/part of epilepsy or as only manifestation of epilepsy (myoclonic sz), or as one of multiple sz types. EEG → ictal epileptiform discharges.

Secondary (symptomatic) myoclonus: Due to a wide range of underlying dz (storage d/o, neurodegenerative, metabolic, paraneoplastic, encephalopathy, infectious, CNS injury/inflammation). Usually chronic or subacute

progression. Often associated w/ AMS, sz, ataxia, & other mvmt disorders. Drug-induced myoclonus: Important consideration, reverses w/ d/c of offending med.

Drugs that Cause Myoclonus

Psych meds (TCA, SSRI, MAOI, lithium, antipsychotics); Drug withdrawal; Antibiotics (quinolones); Narcotics; Anesthetics; Contrast; Cardiac meds (Ca channel blockers, antiarrhythmics); Antiepileptics (gabapentin, pregabalin).

Psychogenic jerks: Inconsistent, decrease w/ distraction/suggestion, spontaneous periods of remission, acute onset w/ sudden resolution, underlying psych pathology.

Treatment of Myoclonus

First line → *valproate, clonazepam* (levetiracetam useful). Valproate: Titrate slowly, daily dose of 1,200-2,000 mg. BZD → clonazepam (may need 15 mg/day). Levetiracetam: Increased evidence for efficacy. Barbiturate: Phenobarbital. Phenytoin/carbamazepine: Helpful only in small %. Zonisamide: Usually effective daily dose of 200-600 mg; side effects of somnolence, anorexia, dizziness; rare side effects of SJS, renal stones; better for cortical. Sodium oxybate, tetrabenazine, anticholinergics.

TICS

Definition: Intermittent, repetitive stereotyped movements and/or sounds; rhythmic or nonrhythmic; discrete onset & ending. Voluntary movement made in response to an involuntary & irresistible urge to move; suppression usually associated w/ uncomfortable feelings of urges to move or vocalize. Differentiating between tics & myoclonus: (1) Myoclonus interferes w/ voluntary action & aggravated by action; tics do not interfere w/ action. (2) Tics are suppressible; myoclonus is not. (3) Often preceded by subjective sensation of urge to move. (4) Myoclonus usually abates during sleep; tics not completely suppressed. Differentiating between tics & dystonia: (1) In dystonia, the body moves of its own accord; tics are under semi-voluntary control of the pt. (2) In tics, body position & movements return to normal between tics. Precipitating factors: Stress, anxiety, boredom.

Simple vs. complex: Based on observation of behavior.

Simple: Involves a single movement or sound. (1) Clonic: Brief rapid

movement, e.g., blinking, sniffing, throat clearing. (2) Tonic: Holding a posture for a brief period, e.g., closing eyes for a few seconds. (3) Dystonic: Pulling or twisting movement w/ abnormal posture for brief period; can appear painful but is usually not; e.g., facial distortion, neck extension.

Complex: Sequence of movements: e.g., clapping a certain number of times, touching the

chin after coughing; may be difficult to distinguish from a compulsion.

Sensory: Repeated stereotyped sensation w/o movement, e.g., a scratching in the throat; can progress to become the symptom preceding a motor tic.

Vocal tics: e.g., coughing, throat clearing, barking, grunting, coprolalia in rare cases.

Diagnostic considerations: Evaluate for comorbid conditions such as ADHD, OCD, & anxiety disorders. Evaluate for precipitating factors such as stress, medications, drug abuse, streptococcal infection (questionable association of tic disorders w/ strep infections). In patients w/ a normal neurologic examination, often no further workup is indicated. Tourette syndrome: Multiple motor tics &>1 vocal tics, onset before 18 yo; ADHD & OCD may be associated; Dx is clinical but should rule out other causes of tics.

Treatment: Warranted when tics are interfering w/ schoolwork, social functioning. Txof associated ADHD, OCD, anxiety disorders often more important than Tx of tics. Education (pt, family, school), reassurance, manipulation of environment, identifying & treating triggers. Clonidine, guanfacine, clonazepam are first-line treatments. Neuroleptic medications are second-line (risperidone). Botulinum toxin can be considered if dystonic tic. DBS in severe intractable tic disorders; further studies needed.

Other Hyperkinetic Movement Disorders

Hyperekplexia Startle disorder often considered a subtype of essential myoclonus. Exaggerated startle response to sudden unexpected stimuli; resistant to habituation. Attacks of generalized hypertonicity resulting in falls; considered reticular reflex myoclonus. Familial hyperekplexia: Autosomal dominant w/ variable penetration; onset of rigidity in neonatal period; assoc w/ alpha-1 subunit of glycine receptor gene point mutations; treated w/ clonazepam.

Hemiballismus Violent type of chorea → wild flinging, large amplitude mvmt on one side of body (usually proximal m.). Most commonly caused by lesion (stroke, ICH) of STN or putamen. Self-limited, resolves in weeks to months. *Tx (difficult)*: haloperidol, propranolol, phenytoin, clonazepam, baclofen; pallidotomy for extreme cases.

Stereotypy Repetitive, stereotyped, involuntary movements appearing purposeful to a certain degree but serving no obvious purpose; e.g., wringing hands, head nodding, body rocking. Occurs in autistic spectrum disorders such as Rett syndrome. Can be suppressed. Also seen in ∽10% of nonautistic kids as well as FTD & psychosis.

Differentiating between tics & stereotypy: **(1)** Can be difficult, as both can involve complex motor or vocal acts. **(2)** Tics tend to begin in school age; stereotypy start earlier. **(3)** Stereotypy more often rhythmic/symmetric v. tics. **(4)** Tics can wax & wane; stereotypy tends to be more persistent. **(5)** Tics can be of short duration; stereotypy last longer.

GAIT DISORDERS

Gait	Description
Cerebellar	• Leaning forward, wide-based, lurching irregularly • Unable to tandem; associated w/ other cerebellar signs such as dysarthria, dysmetria, dysdiadochokinesia • Causes are many & include cerebellar degeneration from EtOH & phenytoin, strokes, tumor, MS, the spinocerebellar ataxias, ataxia telangiectasia, DRPLA, episodic ataxias
Frontal	• Upright posture; impaired postural reflexes • Slow, magnetic gait, can have impaired initiation

	• Can be related to bifrontal lesions, subcortical disease (e.g., microvascular angiopathy), normal pressure hydrocephalus
Proprioceptive, or sensory ataxia	• Romberg sign present, wide-based, high stepping gait • Associated w/ loss of sensation (e.g., proprioception & vibratory) • Causes: Vitamin B_{12}/E deficiency, Friedrich ataxia, peripheral neuropathy
Spastic (scissoring)	• Increased tone in hip & knee extension resulting in one foot stepping across the path of the other w/circumduction b/l • Causes include MS, spinal cord lesions, spastic paraparesis
Hemiparetic	• Usually involves circumduction of the affected leg due to increased tone in hip & knee extension & relative weakness of hip & knee flexion, w/ the ipsilateral arm held flexed • Often due to CNS lesion causing unilateral weakness & spasticity
Parkinsonian	• Slow, shuffling steps, sometimes festinating, asymmetric arm swing, stooped posture, turning en bloc, difficulty w/ initiation
Steppage	• Related to foot drop or severe sensory ataxia, slapping foot down to feel floor • Affected leg: Flexed at the hip in exaggerated way to elevate the foot & prevent tripping from weakened dorsiflexion & toe drag

Cautious	• Increased time in double stance (aka double support—when both feet are on the ground); normal gait spends ∽20% of time in double stance; slow speed; can have wider base
Antalgic	• Shorter swing phase on contralateral side (limp due to pain)
Myopathic	• Waddling (“duck-like”) w/ exaggerated lordosis
Astasia-abasia	• Nonphysiologic gait w/ exaggerated lurching but normal base

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P.115

DRUG-INDUCED MOVEMENT DISORDERS

Introduction: Caused by dopamine receptor antagonists → neuroleptics, anti-nausea meds (compazine), or meds for gastroesophageal d/o (e.g., metoclopramide)

Acute

Dystonia (most common Rxn): Occurs within minutes. Tx: anticholinergic (benztropine or diphenhydramine) or BZD (lorazepam).

Other disorders: Tics, chorea.

Subacute: Akathisia → motor restlessness, Tx d/c offending agent or BZD, anticholinergic, β-blocker, dopamine agonist.

Tardive syndromes (chronic): Develops months to years after neuroleptic Tx.

Tardive dyskinesia: Most common form, choreiform mvmts of mouth, lips, tongue. In 1/3 of pts, d/c offending med → sx resolution (but not always). Differentiation from HD: in HD, voluntary tongue protrusion impaired (“jack-in-the-box tongue”), forehead & eyebrows and gait affected in HD, but relatively spared in tardive dyskinesia. Atypical antipsychotics decrease risk of getting this d/o. Tx: Stop antipsychotic (slowly titrate off, abrupt d/c worsens sxs); Valproate, anticholinergics, botox; Refractory cases → reserpine (often not used as causes depression) or tetrabenazine.

Tardive dystonia: Mvmt of axial muscles → rocking of trunk/pelvis. Tx: Valproate, anticholinergics, botox.

Behavioral Neurology

APHASIA

Aphasia: Abnormalities of symbolic communication (language). Inability to translate nonverbal images (thought) into language and/or inability to translate language into nonverbal thoughts (lexical-semantic) and/or inability to sequence words & word endings to convey relationships among words (syntactic). Affects written code in auditorily based languages (e.g., English) or written code in ideogram-based languages (e.g., Chinese).

Fluency: Free-flowing quality & rate of speech, from spontaneous speech, phrases >4 words.

Prosody: Cadence & intonation of speech, typically a nondominant hemisphere finding.

Circumlocution: Use of unnecessarily many words to express an idea, example: a tool used for cutting things such as paper & hair.

Paraphasia: Word substitution. Phonemic paraphasia: Substituted word w/ similar sound (e.g., ben for pen). Semantic paraphasia: Substituted word w/ similar meaning (e.g., pencil for pen).

Neologism: New word only understood by speaker.

Jargon: Strings of neologisms or improperly combined real words.

Phonemes: Smallest meaning-carrying sounds.

Morphology: Grammatical construction of word endings & connector words for tenses, possessives, & singular vs. pleural.

Lexicon/semantic: Word availability (i.e., the internal dictionary).

Syntax: Grammatical construction of phrases & sentences.

Discourse: Organized & logical expression of thoughts.

Epidemiology: US prevalence: 1 million. 1 yr incidence in US: secondary to head trauma: 200,000; secondary to stroke: 100,000. About 20% of strokes produce aphasia.

DIFFERENTIAL DIAGNOSIS OF APHASIA

Motor speech d/os (i.e., abnlities of articulation): Examples: Dysarthria, speech apraxia & stuttering. Intact comprehension of spoken & written language.

Psych thought d/os (i.e., abnlities of thought content): Usually seen in psychosis, mania. Bizarre, illogical lang that is fluent & syntactically/grammatically intact.

Muteness: Absence of speech output in an alert pt. Common etiologies: Frontal lobe synd (e.g., abulia), basal ganglia synd (e.g., Parkinson), psych synd (e.g., catatonia), severe

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dysarthria (e.g., mech d/o of the larynx). May be present in aphasia. Mute aphasics (“global aphasia”) usually have severe comprehension, reading, & writing deficits also. Exception is patients w/ severe motor speech d/o (as can be seen in primary progressive aphasia), in which pt may be mute 2/2 motor speech d/o but w/ much lesser abnlities in other aspects of language.

Aphemia: Nonfluent syndrome initially presenting w/ muteness & progressing to speaking w/ phoneme substitutions & pauses. Not a true aphasia as all other language functions, including writing, are intact. Rare & usually transitory. Due to small lesions in Broca’s area or inferior precentral gyrus. May be considered a speech apraxia.

Pure word deafness: Inability to understand or repeat spoken language, in the absence of deafness for nonverbal sounds. Not a true aphasia as the deficit can be bypassed w/ reading. Speaking, naming, reading, & writing are intact. Classic localization: b/l temporal lesions that disconnect Wernicke’s area from both aud cortical areas (also reported in lesions of left temporal white matter tracts). Better defined as verbal auditory agnosia.

APHASIA EXAMINATION

Spontaneous speech: Listen for fluency, paraphasias, neologisms, circumlocution, & jargon (see definitions above).

Constrained speech: Have pt describe picture such as “Cookie Theft Picture,” listen for word-finding (lexical retrieval difficulties, paraphasias, word/sound substitutions, syntactic constructions.

Repetition: Test small grammatical words (“no ifs, ands or buts”) initially as they are most diff for Broca aphasics. Keep sentence length short to avoid simultaneously testing for attentional deficits. Multisllabic words (hippopotamus) can be helpful to diagnose apraxia of speech, dysarthria or other motor speech d/os.

Naming: Test low frequency words (“lapel, lens, band”) first as they are most diff. Listen for circumlocutions, paraphasias, neologisms, perceptual misidentifications. Use cue for perceptual misidentifications (e.g., if

“mushroom” called “umbrella,” cue w/ “something you eat”). When visual identification is intact, use phonemic cue for name retrieval errors (e.g., for “mushroom,” cue w/“mu” or “mush”). Test for one-way errors (pt cannot name, but recog name from choices) & two-way errors (pt cannot name or recognize name from choices) e.g.,“point to the picture of the penguin.”

Comprehension: Test both oral & written comprehension (e.g., state “stick out your tongue,” then write “close your eyes”). Test for semantic errors (e.g., “Does a cork float?”). Test for syntactic errors: (e.g., “If the lion were eaten by the tiger, which animal is still alive?”)

Reading aloud: Have pt read entire paragraph. Listen for subtle grammatical mistakes. Have pt read nonsense words. Have patient read irregular words (dough, height, pint).

Writing: Have pt write spontaneously. Write to dictation; copy; write nonsense words; write a description of cookie theft pictures or other complex pictures.

CLASSICAL APHASIA TYPES

Categorization of the Classic Aphasia Types

Aphasia type	N	Fl	C	Rep	Re
Anomic		[check mark]	[check mark]	[check mark]	[check mark]
Broca’s			[check mark][a]		[check mark][a]
Wernicke’s		[check mark]			
Conduction		[check mark]	[check mark]		[check mark]
Transcortical motor			[check mark][a]	[check mark]	[check mark][a]
Transcortical mixed				[check mark]	

Transcortical sens	**[check mark]**	**[check mark]**
Global		

[a] While comp & reading are listed as intact, pts usually do have deficits i domains spec related to agrammatism. Deficits are not as wide-ranging as in tl receptive aphasias. Deficits are blacked-out. [check mark] indicates intact abil naming; Fl, fluency; C, comprehension; Rep, repetition; Re, reading; Wr, writi

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Localization for Classic Aphasia Types

Type	Localization
Broca's	Lesion of Broca area plus surr frontal areas (Note: Lesion to Broca area alone usu. presents as incomplete Broca aphasia or aphemia.)
Transcortical motor	Lesion to regions anterior or superior to Broca area
Wernicke's	Wide range of lesions (Note: While lesions of Wernicke area disrupts aud comprehension, Wernicke area is not the anatomic center for aud comprehension. Comprehension involves parietal, temporal, & frontal regions, of which Wernicke area is a part.)
Transcortical sens	Lesion to regions posterior or inferior to Wernicke area
Global	Lesion(s) to frontal & temporoparietal regions
Transcortical mixed	Lesion to regions adjacent to both Broca & Wernicke areas
Anomic	Lesion to left temporal cortices: Temporal pole: Proper nouns; Inferior temporal lobe: Animals; Posterior temporal lobe: Tools

Conduction Lesion to supramarginal gyrus or 1° aud cortex. [Note: Conduction aphasia is NOT caused by a pure white matter lesion (arcuate fasciculus) though white matter below angular & supramarg gyri might be involved.]

Note that there is a Broca area (inferior frontal gyrus including operculum) & Wernicke area (posterior third of superior temporal gyrus) & there is a Broca aphasia & Wernicke aphasia. Lesions to the area do not always produce corresponding aphasia, & conversely the aphasia can be produced by lesions outside of the corresponding area.

Additonal findings in Broca Aphasia: Lack of prepositions, conjunctions, & word order (e.g., “Go I home tomorrow”), difficulty w/ comprehension & reading aloud related to agrammatism. Test: “The girl kisses the boy, who was kissed?”, phonemic paraphasias are common, preponderance of nouns & selective difficulty naming verbs, tip of the tongue phenomenon (i.e., hesitation in getting words out) pt is typically aware of language deficit, often leading to frustration, assn w/ right hemiparesis (proximity to motor strip).

Additional findings in Wernicke Aphasia: Unintelligible speech content due paraphasias (both phonemic & semantic), circumlocutions, neologisms & generic words (e.g. “thing” or “stuff”), pt often relatively unaware of language deficit, sometimes leading to anger & hostility, but not frustration, assn w/ right heminanopsia (close proximity to temporal optic radiation).

Caveats to classical aphasia types: Language processing is not dependent on Wernicke & Broca areas alone-depends on many neural sites linked as systems & working in concert. Classical aphasia types based on stroke/vascular territories. Tumors, degenerative diseases, etc often don’t follow classic categorization. Automatic speech (e.g., expletives or counting or singing) usually localize to non-dominant hemisphere & are preserved in most aphasias including global.

Handedness, cerebral dominance & aphasia: 99% of right-handers have left hemisphere language dominance & 2/3s of left-handers have left hemisphere language dominance. Anatomic asymmetry: dominant hemisphere is usually larger (esp temporal lobe). Right sided lesions typically cause deficits in prosody (see prosody section). Crossed aphasia in right-handers (rare): aphasia from right hemisphere lesion in righthander that cannot be explained (e.g., by forced right-handedness, known childhood central nervous system impairment, etc), presumably 2/2 crossed or mixed dominance. Atypical syndromes in left-handers (rare): left-handers without left cerebral dominance may develop aphasia from lesion in either hemisphere; may be left

hemisphere dominant for comprehension & right hemisphere dominant for speech production (or vice versa); recovery may be more complete 2/2 shared dominance.

Subcortical aphasias: Exaggeratedly fluent aphasia (w/ mild deficits in comprehension & repetition). Localization: Anterior lateral nuclei left thalamus. Assoc w/ attentional & memory defects. Defective comprehension w/ or w/o repetition deficits. Localization: Head of left caudate, anterior limb of left internal capsule. Association w/ dysarthria & right hemiparesis.

APROSODIA

Prosody: Emotional aspects of language that convey info beyond that transmitted by word choice & word order. Acoustic features: Pitch, intonation, melody, cadence, loudness, timber, tempo, stress, accent, timing of pauses.

P.118

Kinesics: Limb, body, & facial mvmts that accompany discourse & modulate verbal message. Pantomime: mvmts to express mutually agreed upon symbols: (e.g., peace sign). Gestures: mvmts that color, emphasize, & embellish speech. Spontaneous kinesic mvmts during discourse are usually a mixture of pantomime & gesture.

Testing production of spontaneous prosody & gesturing: Observe spontaneous speech for prosody & gestures. Ask emotionally loaded questions.

Testing repetition of prosody: With a happy tone, make a declarative sentence that lacks emotional words, ask pt to repeat w/ the same affective intonation. Repeat process for sad, tearful, disinterested, angry, & surprised tones.

Testing comprehension of prosody: Stand behind pt to avoid giving clues from gestures. Again make a declarative sentence that lacks emotional words, in a happy tone. Either ask pt to name underlying emotion or, if unable, choose from a list of emotions. Repeat process for sad, disinterested, angry, & surprised tones.

Testing comprehension of gestures: Stand in front of pt & gesture conveying a particular mood w/o speaking. Again ask pt to name underlying emotion or, if unable, have him choose from a list of emotions. Consider using photographs of actors depicting different emotions.

AMNESIA

Memory formation: Registration: Info perceived via sens channels. Encoding: Info further processed for identification & assoc. Storage: Info amassed in mult brain locations as “engrams.” Consolidation: Info further stabilized over

mins to yrs, controversial if truly separate from encoding.

Memory subtypes based on temporal factors: Ultra-short—term (sens, iconic, echoic) memory: Memory lasting millisecs based on input along sens channels. Short-term (working) memory: Active holding & manip of info while "online;" incl preparation of stored material for retrieval, lasts millisecs to mins; max capacity is usually 7 ± 2 items. Long-term memory: Info stored "off-line" lasting mins to decades.

Memory subtypes based on content: Explicit memory (declarative): Long term memory revealed through intentional retrieval/awareness, two types: episodic & semantic. Episodic memory: Memory of autobiographical events (e.g., graduation). Semantic memory: Memory of facts & concepts, independ of spec experiences (e.g., Boston is capital of MA). Implicit memory: Long term memory revealed w/o conscious awareness, two types: procedural memory & priming. Procedural memory: Memory of skills, both motor & cog (e.g., driving, playing a musical instrument). Priming: Influence that a previously perceived stimulus has on one's response to a future stimulus. Perceptual priming: Priming w/ stimulus that has ident sens structure to response (e.g., after being given word list including "boot," subject will more likely say boot when asked to produce words beginning w/ "bo"). Conceptual priming: Priming w/ a stimulus that belongs to same category or concept as response (e.g., after being given word list including "apple," subject will more likely say "orange" when asked to produce food list.

Amnesia: Memory impairment. Anterograde amnesia: Inability to form new memories after onset of amnesia. Retrograde amnesia: Inability to retrieve memories stored prior to onset of amnesia: either due to permanently lost memories or inability to explicitly retrieve memories.

Localization of memory: Memory is not controlled by a single center, but by a distributed network. Short-term memory: fronto-parietal network (largely 2/2 attentional dysfn). Long-term memory: Implicit memory: non-limbic areas likely including cerebellum, basal ganglia, & heteromodal assn areas of temporal & parietal lobes. Explicit memory: limbic areas especially Papez circuit (centered around hippocampus, hippocampus > fornix > mammillary body > mammillothalamic tract > anterior thalamic nuclei > cingulate gyrus > presubiculum > entorhinal cortex) has critical function in facilitating storage & retrieval of memories. Actual storage is not well understood, but postulated to occur throughout association cortex. Prefrontal & parietal cortex function in encoding & retrieval of episodic memory; temporopolar cortex functions in retrieval of semantic memories.

TRANSIENT GLOBAL AMNESIA (TGA)

Amnesia (for present & recent past, i.e., anterograde w/ recent retrograde) & "bewilderment" lasting ∽4-6 h (range 15 min-24 h). N1 behav except for repetitive questioning (e.g., "Why am I here?"). Usually oriented to self only, no impairment of consciousness. May have mild HA, nausea. Nl neuro exam except for memory. Intact language, intellectual activity, registration. Retrograde amnesia shrinks & resolves around time pt can again retain new info. After recovery, pt has no memory of event & will have patchy memory of recovery.

Hodgkin & Warlow criteria (1990): (Used for research purposes, meeting criteria predicts good outcome.) Event is witnessed. Clear-cut anterograde amnesia during the attack. No clouding of consciousness, loss of personal identity, cog impairment (other than amnesia), focal neuro deficit. Attack resolves in <24 h. Excluded: pts w/ recent head injury, drug use, sz d/o, major medproblems, or event triggered by procedure.

Epidemiology: Middle-aged & elderly (ages 50-80), 5.2/100,000. Recurrence rate ∽5% | in elderly. Possible precipitants: Physical activity, emotional stress, submersion in cold or hot water, sexual intercourse, minor diagnostic procedures involving sedation. Migraine ↑ pts are at slightly ↑ risk. No association w/ vascular risk factors compared to agematched controls, although can consider stroke work up in older patients or those with vascular risk factors.

Pathophysiology: Unknown. Not sz: EEGs negative. SPECT during attacks showed unilateral or b/l hypoperfusion of temporo-basal region series (J Nucl Med 1998 Jan;39(1):155). MRI DWI imaging: Hippocampal/medial temporal lobe lesions (2 of 31 in acute stage, 26 of 31-48 h later) (Neurology 2004;62(12):2165). May be related to migraine, venous congestion, or bitemporal hypoperfusion.

Differential diagnosis/workup: Temporal lobe szs (TLE): Amnestic episodes much shorter in TLE (< 1 h more predictive of sz). TLE usually not fully alert w/ limitation of higher cog fxn during episode. Post-ictal period, consider EEG. Vertebrobasilar insufficiency: Not TGA if exam demonstrates findings (ataxia, vertigo, diplopia, vis changes) other than amnesia. Head injury/cerebral contusion: Visible signs of injury, primarily retrograde amnesia. Encephalitis: Fever, leukocytosis,↑ ESR or CRP. Functional amnes/ia: Younger pts w/ 1° retrograde amnesia. Intoxication/drug use: Often somnolent, + tox screen. Management: Reassurance. Prognosis is benign if typical presentation.

FUNCTIONAL AMNESIA

Presentation: Often variable, transient, or longstanding. May be in setting of minor head trauma, PTSD, depression, anxiety, stress, or chronic fatigue synd. May be a/w fugue: sudden unexplained travel away from home (dissociative fugue by DSM IV criteria). May be a/w multiple personalities (dissociative identity d/o by DSM IV criteria).

Risk factors: Underlying underdeveloped personality, problematic childhood, sexual abuse.

Management: Similar to conversion d/o (see section below).

DISORDERS OF COMPLEXVISUAL PROCESSING & APRAXIA

Achromotopsia: Acquired color perception deficit involving all or part of vis field w/ relative preservation of form.

Agnosia: Acquired inability to recognize objects, people, sounds, or smells; i.e., inability to attach appropriate meaning to objective sense-data.

Agraphia: Acquired inability to write.

Alexia: Acquired inability to read despite preservation of adequate vision.

Apraxia: Acquired inability to execute skilled mvmts & gestures, despite having desire & physical ability to perform them. Vis acuity, ability to perceive several objects simultaneously (i.e., no simultagnosia), & motor ability all must be preserved to have apraxia.

Anatomical classification: Ventral vs. dorsal. Ventral (i.e., inf or temporo-occipital): The “what” system; functions in discrimination & identification; lesions result in vis agnosia, prosopagnosia, Anton synd, pure alexia, Gerstmann synd, achromatopsia. Dorsal (i.e., superior or parieto-occipital): The “where” system; functions in kinesthesia & spatial perception; lesions result in ideational apraxia, ideomotor apraxia, limb kinetic apraxia, constructional disturbance, dressing disturbance, & Balint synd.

Syndrome	Definition/Localization/Association
Vis object agnosia	**Def:** Inability to visly recognize a familiar object (despite nl vision) **Localization:** B/L lesions in inferior temporo-occipital assoc cortex, large left unilateral temporo-occipital lesion
Prosopagnosia	**Definition:** Inability to recognize familiar faces;

	still able to: ○ Recognize that an object is a face, nose, mouth, etc. ○ Recognize facial emotions ○ Perform complex perceptual tasks **Localization:** B/L inf temporo-occipital assoc cortex; R temporal lobe
Pure alexia (alexia w/o agraphia)	Pts able to see sentences, words, & letters; easily demonstrable by having pt copy; not a true aphasia (but rather agnosia) b/c spoken language & comprehension preserved **Localization:** Any lesion disconnecting both vis assoc cortices from language areas ○ Usually from two lesions: Callosal lesion (disconnecting hemispheres) & left occipital lesion (disconnecting left vis association cortex from left language cortex) ○ Occasionally from one lesion: Inferior & posterior to L occipital horn (causing both connections) Commonly a/w right hemianopia, semantic memory deficits
Achromotopsia	**Definition:** Acquired color perception deficit involving all or part of vis field w/ relative preservation of form **Localization:** ○ Ventral (inferior) vis association cortex (fusiform & lingual gyri) or subjacent white matter ○ Inferior lesion can cause achromatopsia in upper & lower quadrants, while superior lesions do not cause achromatopsia ○ No laterality (i.e., right, left, & b/l lesions have all been implicated)

Cortical blindness

Cortical blindness (**Anton synd**): Obliteration of vision + denial of blindness

○ Localization: b/l obliteration of vis cortices or optic radiations

○ Both blindness & denial are often transient

"Blindsight": Cortically blind pt not consciously aware of a vis stimulus, but able to perceive image at basic level (geometric forms, mvmt, bright light). Pt can still accurately point to a flash of light in inoperative field. Likely possible due to intact connections to vis parietal cortex

Gerstmann synd

Definition: Acalculia, left-right confusion, finger agnosia, agraphia

Acalculia:

○ Test oral & written addition, subtraction, multiplication, & division

○ Attentional deficits, aphasia, alexia, & neglect can cause a secondary acalculia & should be evaluated prior to diagnosing primary acalculia

Left-right confusion:

○ Test right & left on both pt's & examiner's body

○ Increase complexity w/ multi-step testing (e.g., "point to my left ear w/ your right hand")

○ Aphasia & neglect can cause secondary left-right confusion & should be evaluated prior to diagnosing primary left-right confusion

Finger identification deficit (i.e., finger agnosia):

○ Ask pt to match his own fingers to outline drawing of a hand

○ Aphasia can cause secondary finger agnosia & should be evaluated prior to diagnosing primary finger agnosia

Agraphia (see separate section for further discussion)

	Localization: Left angular gyrus
Balint synd	**Definition: Simultanagnosia, optic ataxia, ocular apraxia** **Simultagnosia** (or vis disorientation): Unpredictable perception & recognition of only part of the vis field (“seeing the trees but not the forest”) **Optic ataxia** (aka visuomotor ataxia): Impairment of target pointing under vis guidance. Usually no evidence of tremor **Ocular apraxia:** Inability to shift gaze at will toward new vis stimuli in periphery **Localization:** b/l damage of the occipitoparietal region. Most commonly due to b/l (occipitoparietal) watershed (MCA/PCA) infarcts from hypotensive episode
Ideomotor apraxia	**Definition:** Inability to pantomime mvmt on command, but able to perform it in natural setting **Localization:** Left parietal lobe or white matter projections
Ideational apraxia	**Definition:** Inability to carry out multi-step activity using a real object even though individual mvmts required for activity are intact (ex: fold letter, place in envelope & seal envelope). Usually occurs in confusional states & dementia. No true localization, but is likely due to attentional & executive function deficits
Limb kinetic apraxia	**Definition:** Apraxia of fine mvmts, leading to awkward & inaccurate mvmt. Present in pantomiming & spontaneous limb usage **Localization:** Probably left parietal lobe
Constructional apraxia	**Definition:** Inability to construct copy of visly presented model (not a true apraxia) **Localization:** Right parietal lesion, left parietal

	lesion (less common)
Dressing apraxia	**Definition:** Inability to dress self (not considered a true apraxia). Most freq occurs in pts w/ dementia. May be 2/2 neglect, Balint synd, etc. Doesn't occur in isolation, doesn't have particular localization

P.121

NEGLECT

Normally, probability of stimulus attracting attention is a fxn of its novelty & sig, regardless of location. In neglect synds, a stimulus' probability of attracting attention ↓s in proportion to its relative spatial location (usually leftness). Neglect occurs almost exclusively after right hemisphere lesions. Neglect from right sided lesions is more frequent, severe, & lasting. Most striking examples of right unilateral hemineglect have been described after b/l lesions. Pts w/ right unilateral hemineglect should raise susp for b/l lesions.

Presentation: Mult modalities (motor, sens, & motivation) may be reduced on affected side.

Common examples: Shaving, grooming, or dressing only on right, failure to eat food on left side of tray, failure to read words on left side of page (neglect dyslexia).

Localization: Neglect results from damage to a network involv the post-parietal cortex, frontal eye fields, & cingulate gyrus. Calling it a "parietal sign" is flawed because it can result from lesions outside of the parietal lobe. Frontal lesions can cause neglect in mult modalities just as severe as parietal lesions. Cingulate gyrus lesions causing neglect are unusual, but functional studies clearly indicate cingulate involvement. Right, & left-sided thalamic lesions causing neglect have also been reported.

Prognosis: Depends on underlying cause. In stroke, most pts recover over 9—43 wk (Neurology 1983;33:345). Persistent neglect may occur w/ large lesions w/ both cortical & subcortical involvement. Clinical recovery a/w resolution of cortical hypometabolism on PET (Neuropsychologia 1993;3:115).

Management: No consensus exists on ideal tx for pts w/ neglect. Most therapies tend to be task specific w/ogeneralizability. Cog & behavtx including vis training/exploration. Passive sens stimulations: Stimulates awareness of the left vis field. Sensorimotor adaptation (prism adaptation): Prism induces optical shift of vis field to right, likely causing subconscious learning. Produces sustainable improvement: 5-7 min exposure can lead to 24

h of improvement & 2 wk of twice daily tx can lead to 5 wk of improvement (Neuropsychology 2002;40:718; Brain 2002;125:608). Dopamine agonists (esp bromocriptine): Case reports have shown mixed results, no RCTs. Methylphenidate: Case reports have shown mixed results, no RCTs.

PSYCHIATRY FOR THE NEUROLOGIST

Psych mental status exam: Appearance & behav: Body type, posture, attire, grooming, alertness, comfort, unusual behav. Motor activity: Posture, gait, abnl mvmts, hyperactivity. Mood (pt's perception) & affect (i.e., examiners perception): Range, intensity, stability, appropriateness. Speech & language: Similar to neuro exam, also comment on volume, speed. Thought content: E.g., suicidality, violence, delusions, obsessions, phobia (discussion of these topics does not "plant" idea). Thought process: E.g., tangential, circumstantial. Perception: E.g., illusion, halluc, neglect; may occur in any of five senses. Insight (understanding of situation) & judgment (decision making regarding situation).

Attention & orientation: Similar to neuro exam. Memory & other cortical functions: Similar to neuro exam.

ANXIETY D/OS

Most common type of psych d/o in adults, lifetime incidence near 25%. Commonly comorbid w/ mood d/os, substance abuse, & other anxiety d/os.

Types: Panic d/o:≥2 unexpected panic attacks, with 1 mo of persistent apprehension. Agoraphobia: Fear of public/open places. Specific phobia: Most common anxiety d/o, anxiety toward feared stimuli. Social phobia: Fear of social or performance situations. Obsessive-Compulsive d/o: Recurrent intrusive thoughts that are relieved by specific behav. General anxiety d/o: 6 mo of anxiety, often over trivial matters. Posttraumatic stress d/o: Traumatic/serious life event, pt will relive trauma.

Treatment: Includes SSRIs, cog behav tx.

MOOD D/OS

Unipolar depressive disorders

Commonly occur 2/2 neurologic dz: (30%—50% of stroke, 10%-20% of Alzheimer, 27%-54% of MS, 40% of Parkinson's, 33% traumatic brain injury). SIGECAPS criteria: Sleep change (either more or less), Interest lower (anhedonia), Guilt, Energy reduction, Concentration reduction, Appetite change (either more or less), Psychomotor slowing/agitation, Suicidal thoughts. Major depressive episode: Lasts ≥2 wk, incl low mood or

anhedonia, & meeting four of eight SIGECAPS criteria. Dysthymic d/o: Only requires two of SIGECAPS criteria, but lasts ≥2 yr.

Treatment: Antidepressants. Maximum response to drugs takes about 6 wk, but begins to occur in 1-2 wk. Early intervention improves acute outcome. Treatment should be continued after recovery for at least 6-9 mo. If recurrence occurs, consider long term maintenance. Refer to psych if sxs severe, pt is refractory to, does not want or would not benefit from pharmacotx, is requesting psychotx, might benefit from multimodality tx [psychotx (often synergistic w/ meds)], ECT (for severe depression w/ catatonic features).

Prognosis: Major depressive episode usually will last ∽6 mo but can vary widely. Risk of recurrence after one episode: At least 50%, after two episodes: At least 70%.

Bipolar disorders

- Mania: Elevated, expansive, or irritable mood. Manic episode: Lasting ≥1 wk, including euphoria & ≥3 of DIGFAST criteria or irritability & ≥4 of DIGFAST criteria, w/ sig functional impairment. DIGFAST: Distractibility, injudicious behav, grandiosity, flight of ideas, activity ↑, sleep need ↓, talkativeness. In severe cases, psychotic features may be present.
- Hypomania: Criteria similar to mania except must only last >4 days & should not cause sig functional impairment.
- Bipolar I: At least one manic episode usually w/ recurrent major depressive episodes.
- Bipolar II: At least one hypomanic episode usually w/ recurrent major depressive episodes.
- Cyclothymic d/o: Mult episodes of subsyndromal depressive & hypomanic periods over two or more yrs. 2° causes of mania: Right hemispheric damage, dopamine agonists, stimulants.

Treatment: Mood stabilizers: Li, carbamazepine, valproate, lamotrigine. While most of mood stabilizers are freq used by neurologists, if only treating bipolar, should defer to psych. Antidepressants are contraindicated as they can worsen manic episodes.

PERSONALITY D/OS

Stable, lifelong constellation of personality traits suff maladaptive to → impairment (axis II).

Cluster A: Odd or eccentric. Paranoid: Distrusting & suspicious. Schizoid: Socially detached & emotionally restricted w/o concern. Schizotypal: Bizarre w/ magical thinking.

Management: Give written instructions as pts are uncomfortable speaking. Use atypical antipsychotics if overtly paranoid w/ stress.

Cluster B: Dramatic, emotional, or erratic, often diff in office. Antisocial: Disregard for others, ruthless. Borderline: Unstable relationships w/ marked impulsivity. Histrionic: Excessively emotional & attention seeking. Narcissistic: Grandiose, entitled.

Management: Discuss case directly w/ other care providers & family. Provide them w/ identical message as pt. Strictly enforce rules regarding prescriptions, phone calls, appointment length. Treat misbehav firmly w/o anger. Use atypical antipsychotics if overtly anxious or psychotic (common). Avoid benzos as they reduce inhibition.

Cluster C: Anxious & fearful. Avoidant: Soc inhib, inadequate, hypersensitive. Dependent: Submissive w/ need to be taken care of. Obsessive-compulsive: Preoccupied w/ order, perfectionism, control.

Management: Use SSRIs for depression (common). Assign a support person who can regularly give pt instructions. Have literature for obsessive-compulsive.

THOUGHT D/OS

Psychosis: Delusions: Fixed false beliefs (e.g., control, egomania, grandeur, infidelity, persecution, reference, somatic). Halluc: Most commonly aud, though vis & tactile may also be present. Disorganized speech, behav.

Schizophrenia

Occurs in 1% of population. 30% of all hospital beds are occupied by schizophrenics. At least 10% of homeless are schizophrenics. Onset usually late teens to mid-twenties. Positive sxs: Psychosis; Negative sxs: Avolition, flattened affect, paucity of speech; neurocog def in verbal memory, short-term memory, & executive function, cause more disability than positive or negative sxs.

Pathophys: Likely multifact w/ both envir (birth during winter, maternal infxn, socioeconomic class) & genetic (chrom loci on 6, 8, 10, 13, 22) factors. Psychotic (positive) sxs likely 2/2 dopamine hyperactivity in mesolimbic pathway. Structural imaging shows changes in frontal & temporal cortices, hippocampus & thalamus, disruptions in subcortical-cortical pathways. Felt to

be neurodev rather than neurodegen as imaging changes seen at sx onset & clinical sx's remain stable or even improve w/ aging.

DDx: Psych: Schizoaffective d/o, depression or mania w/ psychotic features, sev personality d/o, PTSD. Drug/med-induced: PCP, LSD, amphetamine, cocaine, ETOH, ecstasy, barbiturate/benzo w/d, anticholinergics, levodopa, dopaminergics, glucocorticoids. Neurodegen dz: Dementia w/ Lewy bodies (vis rather than aud halluc), AD, FTD, Huntington's, homocystinuria, metachromatic leukodystrophy, Lafora's, cerebral liposes, Fabry's, Fahr's, Hallervorden-Spatz, Wilson's. ID: Pneumonia, UTI, meningitis, encephalitis, bacteremia, AIDS, neurosyphilis, CJD. Toxic/metabolic/nutritional: Thyroid, adrenal, B_{12} def, Wernicke-Korsakoff's, heavy metals, carbon monoxide. Structural/functional: Trauma, neoplasm, NPH, CVA, temporal lobe epilepsy (olfactory, gustatory, or tactile halluc).

Workup: CBC, chem. 10, B_{12}, RPR, TSH, UA, blood cx, Utox, serum tox, chest x-ray. Consider HIV, neuroimaging, EEG, lumbar puncture, ESR, heavy metal screen, ceruloplasmin, adrenal studies, porphyria studies. Consider other dx strongly if older than 45.

Treatment: Antipsychotics (see chart below), mostly treat positive sxs w/far less effect on negative & neurocog sxs. Psychosoc tx: Psychotx, fam support, soc & vocational training.

Course/prognosis: Initial ↓ in fxn at sx onset followed by long-term stability of poorer functioning. Poorer prognosis w/ early onset, h/o head trauma, or comorbid substance abuse. Exac & relapses common 2/2 med nonadherence. High suicide rate: Nearly 10%.

Schizoaffective d/o

Persistent psychosis w/ intermittent depressive and/or manic episodes. W/U similar to schizophrenia & mood d/os. Prognosis generally better than schizophrenia, but worse than mood d/o. Tx is w/ antipsychotics, antidepressants, and/or mood stabilizers depending on presentation.

CATATONIA

Immobility, staring, mutism, rigidity, withdrawn (w/ refusal to eat), posturing, grimacing, waxy flexibility, echolalia, stereotypy, negativism (doing opposite of what asked), verbigeration (continuous & directionless repetition of words/phrases). Although pts appear to have altered level of consciousness, they'e typically hyper-alert & can recall details of episode after recovery.

DDx: Parkinsonism, akinetic mutism, locked-in synd, neuroleptic malignant synd, serotonin synd, persistent vegetative state, non-convulsive status, stiff-

person synd.

Workup: Close monitoring of vital signs 2/2 difficulty discriminating from NMS., chem. 10, LFTs, CPK, UA, EEG.

Complications: Volume depletion & acute renal failure; pneumonia; DVT/PE; skin breakdown; contractures; NMS as pts are often being treated w/ neuroleptics.

Associations: Usually occurs in context of another illness. Mood d/os, thought d/os, cocaine intox, benzo w/d, neurologic conditions (tumor, dementia, encephalitis).

Treatment: Benzos: Exquisitely responsive (nearly 80% of time), usually in 1-3 h. Schizophrenics are exception (success in 20%—30% of cases) w/ longer tx usually required. ECT: Consider if benzos fail for several days.

ADDICTION

Substance abuse

Loss of control while using & preoccupation w/ a substance, → continued use despite adverse consequences & physiological sxs (tolerance & w/d); unique from pharmacologic dependence that can occur w/ many meds & is a result of repeated use. To avoid above semantic confusion, addiction is often used for substance dependence.

At risk: Use that has resulted in or that substantially increases risk for adverse med, psych or social conseq. Falls short of substance dependence b/c no loss of control or preoccupation.

Pathophys: Neuropsych illness disrupting brain pleasure centers; reward pathways are same as those a/w food & sex; Neurotransmitters: Dopamine, serotonin, & opioids; brain changes likely 2/2 both genetic vulnerability & learned behav from repeated use & envir, cultural, soc, econ, & fam influences.

NIAAA guidelines for safe alcohol consumption: Adult women should drink ≤ 10 drinks/wk. Adult men should drink ≤14 drinks/wk. Adults >65 should drink ≤7 drinks/wk. No adults should binge drink (>5 drinks/day).

Epidemiology/associations: 4.6% of American population meet criteria for alcohol dependence. 3% of US population meet criteria for drug (non-alcoholic, non-tobacco) dependence. Alcohol dependence is a/w acute pancreatitis, cirrhosis, cardiomyopathy, hypertension, trauma, MVA, most psych d/os, cog impairment, Wernicke-Korsakoff synd, multiple sleep d/os

including sleep apnea. Cocaine & other stimulants ↑ risk for MI & stroke.

Screening: Ask about frequency & quantity of use. CAGE question naire: Two or more ?s answered yes is concerning for problem drinking: Cut back: Have you ever felt you should cut down on drinking? Annoyed: Have you ever been annoyed by others criticizing your drinking? Guilt: Have you ever felt guilty about your drinking? Eye opener: Have you ever had a drink first thing in the morning to steady nerves/get rid of hangover?

Management: W/d from opioids/cocaine is unpleasant, but not life-threatening; w/d from alcohol & benzos can be life threatening (status epilepticus, hemodynamic instability). Involve fam & friends for support & to provide pressure to obtain help. Pts w/ high-relapse or w/d potential or w/ serious med or psych comorbidities should be admitted.

- Outpt management includes psychotx, self-help groups (e.g., AA), soc services, supervised living (e.g., halfway house), & pharmacotx (methadone, suboxone, naltrexone).

SOMATOFORM D/OS

Conversion d/o

Sens or motor sx suggestive of but not explained by organic d/o. 9%-20% of referrals to neurology clinics. Sx initiation or exacerbation proceeded by conflict or other stressor. In reality, stressor is often hard to identify, at least initially. Paradox: b/c only a clinician comfortable recog neuro sxs as nonphysiologic can make dx, a neurologist usually must make a psych dx while the “inexperienced” psychiatrist must go along only reluctantly.

Risk factors: Painful med procedures, parental illness, or trauma in childhood, esp. sexual or physical abuse.

Presentation: La belle indifference: pt unconcerned with sxs. “G/ive-way” weakness: pt may exhibit discontinuous resistance during strength testing. Apply pressure in an irregular intermittent manner so that pt cannot coordinate relaxation. Hoover sign: w/ pt lying on back, hold heal of strong leg & ask pt to lift weak leg. In conversion d/o, pt will not push down into your hand w/ the strong leg. Numbness: Numbness may stop at hairline or directly at the midline, vibration on forehead may be felt more strongly on one side (despite a single frontal bone), or the pt may nlly manipulate an object w/ a numb hand. Vertigo: Vertigo may improve or be reproducible w/ hyperventilating. Gait (astasia-abasia): In conversion d/o, pt may be unable to stand despite nl mvmt/power in legs. Tremor: In conversion d/o, by tapping at a different frequency than tremor, physician may be able to alter tremor

frequency. Non-epileptic spells (pseudoszs): See epilepsy chapter.

Prognosis: Unfavorable w/ sxs often lasting greater than a decade.

Other somatoform d/os

Somatization d/o: Mult somatic complaints (four pain, one sexual, one neurologic, two GI) over several yrs, before age 30, resulting in medTx and impairment of fxn; med d/o have been r/o'd. Usually pts seek med help from mult docs. Chronic, usually appears during adolescence.

P.125

Hypochondriasis: Preoccupied w/ concerns of a serious condition, despite neg w/u, causing impairment in fxn. Misinterpret bodily signs and sxs.

Body dysmorphic d/o: Overly preoccupied with thoughts concerning imagined or slight defects in appearance → impairment in fxn. Thoughts dominate their lives.

Factitious d/o: Not actually somatoform d/o but should be considered in ddx. Driven to intentionally fake sxs to assume a sick role (without any external motivations, e.g., money); more common in women. Pts give dramatic hx, but vague and inconsistent. Factitious d/o by proxy: Person indirectly assumes sick role by intentionally producing sxs in someone under their care (usually mother to a child).

Malingering: Not considered a psych condition. Feigning illness 2/2 external motivation (avoid work, money, etc.).

Management of somataform/conversion d/o

r/o organic explanations: Should be adequate, but not nec exhaustive if susp high enough. If susp high from onset, involve psych immediately rather than after organic etiologies have been ruled out; expedites process & lets pt know from onset that psych eval is part of w/u rather than "they can't figure out what's wrong, so they think I'm crazy." If pt is unwilling to seek psych evaluation, do not immediately give up on pt: Schedule reg appts rather than urgent or as-needed visits to avoid incentive for somatization. Avoid ordering tests unless signs rather than sxs suggest it. This keeps down costs & avoids psychological suggestion. Try to identify pt's hopes & motivation & tailor tx accordingly. Avoid placebo for ethical & psych reasons (may just as likely cause deleterious effect as positive effect). Cog-behav tx, group tx, psychodynamic psychotx, hypnosis have all been shown effective. Treat assoc mood & anxiety d/os.

PHARMACOTHERAPY

Antidepressants

Rapid w/d (esp of SSRIs) can lead to depression & suicidality even in stable pt or pt on another antidepressant. Wean 50% per wk until at smallest poss dose, then QOD. Beware that most sxs occur at end of taper. Cons slower wean if sxs occur.

Serotonin synd: Occurs when mult meds alter serotonin metabolism (classically SSRI w/ an MAOI). Presents w/ altered mental status, tachycardia, hypertension, hyperthermia, hyperreflexia, autonomic instability, shivering, myoclonus, tremor, DIC, rhabdomyolysis, behav changes, agitation, delirium, coma, death. Purely clinical diagnosis, no labs are useful. Etiologies: usu drug induced (SSRI, MAO-A>>MAO-B), carcinoid tumor, tryptophan. Ddx: NMS, catatonia, malignant hyperthermia, anticholinergic excess, benzo w/d, heat stroke, panic attack. Serotonin synd shares mult features w/ NMS, but causes more hyperreflexia & does not cause muscle rigidity or dystonia. TX: Stop offending agent, largely supportive tx (may include cardiac monitoring, ICU admission, mechanical ventilation), consider benzos, cyproheptadine (4-8 mg PO tid, do not exceed 0.5 mg/kg/d).

Antipsychotics

All about equally effective (typical & atypical) w/ exception of clozapine (and perhaps risperidone) which is more effective for refractory dz. Clozapine is not used first line because it can cause agranulocytosis & szs. Mechanism: Blockade of dopamine (D_2 receptors in limbic system & basal ganglia). May also have affinity for D_1, D_3, D_4, $5HT_2$ receptors. Receptor affinity profile varies between drugs. Side effects: Neuroleptic malignant synd: Present w/ dysautonomia (tachycardia, hypertension, diaphoresis, hyperthermia), motor abnlities (lead-pipe rigidity, dystonia, akinesia), mutism, dysphagia, agitation, szs, coma, death. Clinical picture can wax & wane. Occurs over hours to days. More commonly occurs in first few weeks after antipsychotic initiation, can occur anytime. Mortality rate up to 20%. Commonly see elevation in CK, LFTs, WBC. Risk factors: High doses, rapid escalation of dose, IM administration, dehydration, prior history. Ddx: Serotonin synd, malignant hyperthermia, catatonia, anticholinergic excess, benzo w/d, heat stroke, panic attack. Shares mult features w/ serotonin synd, but may be distinguished by less hyperreflexia & more rigidity/dystonia. TX: Stop offending agent (may take a long time in pts receiving depot antipsychotics), largely supportive tx (cardiac monitoring, ICU admission, mech ventilation, electrolyte monitoring, IV fluids, cooling blanket, Tylenol), cons dantrolene (start 1 mg/kg IV, up to 10 mg/kg/day in divided doses, watch for hepatotoxicity & CHF), bromocriptine (2.5-10 mg IV or PO q4-6 h), amantadine (100-300 mg PO BID, Sinemet (25/250 PO TID/QID). Other side effects (see Mvmt D/o

chapter).

Anxiolytics [benzodiazepines (with the exception of BuSpar)]: Important side effects: Short acting benzos can lead to rebound anxiety, respiratory depress, hypotension, teratogenicity in first trimester. Mechanism: Stimulate GABA-A receptors. See toxin chapter for discussion of overdose & w/d.

Poisons and Vitamin Deficiencies

STIMULANTS

Cocaine

Oral, injected, snorted, smoked (“crack” or “freebase”). Blocks presynaptic reuptake of dopamine, NE, 5HT (esp in ventral tegmental area, nucleus accumbens, prefrontal cortex) → euphoria; blocks voltage gated Na-channels → local anesthesia, cardiac arrhyth; alpha- & beta-adrenergic: HTN, tachycard, vasoconstrict. Detect in blood, urine, hair, sweat, saliva; crosses placenta & into breast milk; elim mostly in urine. Neuro manifest of acute intox: Szs; stroke: Ischemic (vasospasm, intravascular thromb from ↑ platelet agg) & ICH (reperfusion or HTN). Mvmt d/os: dystonic reactions, buccolingual dyskinesia, choreoathetosis, akathisia.

Rx: Supp measures; avoid β-blockers (coronary vasoconstriction, end-organ ischemia); watch for hyperthermia; szs: BZs best; Valproate second line. If SE, CT abd, r/o ingestion of cocaine pack; meds: none FDA-approved; disulfiram, modafinil, topiramate, tiagabine, baclofen, citalopram, ondansetron, bupropion; buprenorphine for co-addiction to opiates.

Withdrawal: Depression (sometimes suicidal ideation, psychomotor retardation), craving, fatigue, anhedonia, ↑ sleep, increased REM sleep; ± musculoskel pain, tremor, invol mvmts, myocardial ischemia. Rx: Supp (sleep, food); β-blockers/BZs for severe sxs.

Methamphetamine

Sympathomimetic amine. Oral, pulmonary, nasal, IM, IV, rectal, vaginal; causes release & prevents reuptake of epinephrine, norepinephrine, dopamine, serotonin. Alpha- & beta-adrenergic receptor stim: Tachycardia, HTN, hypertherm, & eventual vasospasm; mydriasis, diaphoresis, agitation, paranoia, psychosis, chorea, coma.

Sympathomimetic crisis: Sev agitation, szs, hyperthermia, metabolic acidosis, hyper-K, HTNive crisis, cardiac arrhyth, cardiovascular collapse, stroke/ICH. Long duration of action (20 h). MDMA is amphetamine derivative w/ a similar presentation that may trigger severe hypo-Na due to SIADH & fatal szs.

Dx: Mainly clinical; urine testing equivocal.

Rx: Supportive. Correct electrolytes (special attention to Na in case of

MDMA). BZs may help by ↓ hyperadrenergic drive. Atypical antipsychotics. Severe HTN: BZ, nitroprusside or phentolamine. Severe hyperthermia: Cooling blankets, paralysis w/ nondepolarizing agent; szs: BZ. Avoid β-blockers (including labetolol).

Phencyclidine (PCP)

Dissociative anesthetic similar to ketamine. Snorted, smoked, ingested, or injected. Noncompetitive NMDA receptor antagonist. Sympathomimetic effects by blocking reuptake of dopamine, norepinephrine, serotonin. Opiate receptor: Analgesia, sedation, anticholinergic.

Presentation: Violent/bizarre behavior, incoordination, vertical & horizontal nystagmus. Dissociative sx. Distorted perception of visual & auditory stimuli, psychosis, tachycardia, hypertension, diaphoresis, hypersalivation, flushing, hyperthermia. High doses: Disorientation, agitation/violence, acidosis, szs, resp arrest, coma. Sympathomimetic (tachycardia, HTN, hyperthermia, vasospasm, mydriasis, diaphoresis).

Diagnosis: Clinical, immunoassay urine screening.

Rx: Supportive measures. If psychotic episodes: BZ; consider neuroleptics if ECG OK. HTN: BZ, nitroprusside, phentolamine, labetalol. Gastric lavage for early presentation, potentially lethal dose. Focal deficits, HTNive urgency → imaging to r/o stroke. Dystonia: Diphenhydramine 1 mg/kg. Szs: BZ.

OPIOIDS

Heroin: Pure opioid agonist; IV, IM, smoked, sniffed, ingested. Metabolized to active metabolites (including morphine). Prescription opioid abuse: Oxycodone, hydrocodone, morphine. Regular use induces tolerance, which predisposes to withdrawal. Three classes of receptors: Mu, analgesia, euphoria, respiratory depression, cough suppression, miosis, sweating, nausea, & vomiting. Kappa & Delta are analgesic.

Presentation: Trigger a “rush”: somnolence, calmed sensation, apathy, feeling of self-sufficiency. Anticholinergic effects (constip, ↓ bowel sounds, urinary retention, dry mouth). N/V, itching. Overdose → respiratory depression, coma, hypothermia, szs. Miotic pupils (but normal/large pupils do not exclude opioid intoxication; e.g., meperidine, propoxyphene, or concomitant use of anticholinergics or sympathomimetics).

Dx: Urine drug screen up to 3—4 days after last use.

Rx: Supportive measures. Hypercapnia needs to be excluded if GCS < 13. Naloxone IV: Goal = normal ventilation (not normal level of consciousness).

Breathing spontaneously: Start w/ 0.05 mg, titrate up every few minutes until RR > 12. Apnea: Start w/ 0.2 −1 mg. Cardiorespiratory arrest: Start w/ 2 mg. Once ventilation restored, 2/3 dose for ventilation reinstitution qh. If no resp after 5-10 mg, dx must be reconsidered. QRS prolongation: IV Na bicarb: bolus 1-2 mEq/kg. If complex narrows → bicarb infusion (mix 132 mEq of $NaHCO_3$ in 1 L D5W, & infuse at 250 mL/h). QTc prolongation (>500 ms) or torsades de pointes. If due to methadone therapy, d/c or switch to buprenorphine. Correct low Ca, K, Mg. Activated charcoal, gastric emptying only for potential coingestions.

Opioid W/D: Occurs after 3 wk of daily heroin, sooner w/ partial agonists (buprenorphine)/agonist-antagonists (pentazocine). After last dose: 3—4 h: Fear of w/d → craving, anxiety. 8-12 h : Anxiety, insomn, yawning, rhinorrhea, lacrimation, salivation, stomach cramps, mydriasis, arthralgia, & myalgias. 1-3 days: HTN, tachycardia, tremor, myoclonus, f/c/n/v/d, piloerection; sz.

Rx: Methadone: 10 mg IV or 20 mg PO; at prior or slightly higher dose if sx are 2/2 discontinuation. Buprenorphine (partial agonist): only for pts on it prev. Buprenorphine/naloxone: For induction & detoxification or maint Rx. Other adjunctive nonopioid agents (for refractory W/D sx, or detox): Clonidine (α-2 blocker): W/ methadone when dose tapered below 15 mg. Monitor for hypotension; taper gradually (to avoid HTN rebound. Dosing: 0.1-0.3 mg q2h first 24 h; then 3—4×/day, reducing by 0.1-0.2 mg daily for 10-14 days.

BARBITURATES

Physiology & metabolism: Potentiate effect of GABA at $GABA_A$ receptors by ↑ duration of chloride channel opening. Divided according to kinetics: Short-acting: Anesthetics. Intermediate action: Butalbital (Fiorcet/Fiornal), amobarbital (Amytal), pentobarbital (Nembutal), butabarbital (Butisol), mephobarbital (Mebaral), secobarbital (Seconal), Long-lasting: Phenobarb, primidone. Lethal doses: 6-10 g of Phenobarb, 2-3 g for other barbs.

Presentation: Sedation, lethargy, respiratory depression, slurred speech, depressed mood, mild cognitive impairment, anterograde amnesia/impaired short-term memory, impaired psychomotor function. Severe toxicity → ataxia, hypotonia, delirium; ultimately cerebral edema & pulmonary edema.

Dx: Mainly clinical. Confirmed by serum or urinary barbiturate levels.

Rx: Supportive measures. Gastric lavage if presenting w/in 2—4 h of ingestion. Activated charcoal protocol. HD may help w/ long-lasting barbs. Urine alk w/ long-lasting barb OD.

ALCOHOL INTOXICATION

General considerations

ABCs; routine supportive measures. Labs: glucose, chem 10, LFTs, serum Osm, serum & urine tox screens (including: EtOH, methanol, ethylene glycol, isopropyl alcohol, acetaminophen, salicylate). Osm gap: suspect alcohols other than EtOH for Osm gap > 10 after correcting for EtOH:

- Osm = 2 × Na + blood urea nitrogen (BUN)/2.8 + glucose/18 + ethanol/4.6
- Osm gap = Osmol measured - Osmol calc

Thiamine 100 mg + folate 1 mg + MVI 1 amp to 1 L of D5NS + 3 g $MgSO_4$. Narcan empirically if resp comp. Consider hypoglycemia, coingestants, head trauma (mimics alcohol intoxication). CT head if suspect trauma, SDH. Suspect DKA if: appears very ill, vom, or hyperventilating (check ABG, AG). Expect ↓ of blood alcohol level (BAL) of 20 mg/dL / h w/ EtOH. Charcoal does not bind alcohols. Coingestion of other toxins is common. Check pockets (beware of needles).

Ethanol

Most commonly abused drug. 0.5 lb EtOH = 12 oz beer, 5 oz wine, or 1.5 oz of 80-proof distilled spirit.

Physiology & metabolism: Stimulates GABA-A receptors, suppresses NMDA-type receptors. Peak serum levels: 30-90 min after ingestion w/ empty stomach. Chronic use → (1) downregulation of GABA receptors → tolerance; (2) upregulation of glutamate receptors (to maintain normal state of arousal). Abrupt discontinuation → imbalance (less GABA-ergic, more glutamatergic effects). Metabolism follows zero-order kinetics. Alcohol dehydrogenase.

Presentation/syndromes: Acute intoxication: Breath, somnolence, slurred speech, nystagmus, disinhibited behavior, ataxia. Severe intoxication → lethargy, coma. Hypoglycemia → focal deficits, szs, coma.

Wernicke encephalopathy: Encephalopathy, oculomotor dysfxn, nystagmus, ataxia.

Korsakoff syndrome: Wernicke’s + selective amnesia + confabulation.

Marchiafava-Bignami: Dementia, spasticity, dysarthria, gait instability. Onset: Acute, subacute, chronic. 2/2 demyelination/necrosis of corpus callosum,

WM.

Cerebellar degeneration: Gait impairment, tremor in the arms, dysarthria, intermittent diplopia, or blurred vision.

Ventricular enlargement w/ cog dysfxn.

Neuromuscular compl: Peripheral neuropathy, acute/chronic myopathy.

Dx: Bedside glucose (hypoglycemia very common in alcoholics). Serum ethanol level (BAL); serum methanol & ethylene glycol levels. Suspect DKA if ill-appearing, vomiting, hyperventilating. Beware if pt deteriorating in ED: TBI, hypoglycemia, infection, etc.

Rx: Supportive measures. Thiamine. Szs: treat underlying cause (e.g., hypoglycemia); o/w standard sz management.

Methanol

Oxidized by alcohol & aldehyde dehydrogenase → formate, formaldehyde. Peak serum concentrations w/in 1-2 h (delayed if ETOH coingestion). Pyridoxine & thiamine partially involved metabolite elimination. Zero-order kinetics.

Presentation: Intake of paint solvents, antifreeze, windshield fluid, canned fuel (sterno), gasoline additives, shellac, copy machine fluid, home heating fuels (usually by alcoholic or child). Blurred vision ("snowstorm-like"), blind. ↓ LOC, vision changes, vomiting, abd pain.

Diagnosis: Clinical presentation + AGMA (serum bicarbonate typically < 10 mEq/L). Fundoscopy: Hyperemia, papilledema. Methanol level, serum Osm (calculate Osm gap), ABG.

Management: Fomepizole: Loading dose: 15 mg/kg in 100 mL D5W over 30 min → 10 mg/kg q12h × 48 h → 15 mg/kg q12h until methanol concentration <20 mg/dL (alcohol dehydrogenase inhibitor; EtOH used in past but IV form often not available & has erratic pharmacokinetics [NEJM 2001;344:424]). Folate 50 mg IV q4h or 2 mg/kg IV q6h (cofactor degrading toxic metabolites). Hyperventilation: If pt is intubated, hyperventilating to PCO_2 < 30 reduces acidemia. Sodium bicarbonate: For serum pH < 7.3; start 1-2 mEq/kg IV × 1; maintenance infusion: 133 mEq of sodium bicarbonate in 1 L of D5W. Hemodialysis: for pH < 7.3, Methanol > 16 mmol/L, visual impairment, renal failure.

Ethylene glycol

Oxidized by alcohol & aldehyde dehydrogenase → glycolate, glyoxylate, oxalate. Peak serum concentrations in 1-2 h (delayed if ETOH coingestion).

First-order kinetics. Presentation: Ingestion of antifreeze, paint, polish, coolant, detergent, fire extinguisher foam. Three phases: 0.5-12 h neurologic: Transient inebriation, euphoria (like EtOH effects), n/v, then lethargy, nystagmus, ataxia, ophthalmoplegia, myoclonic jerks, meningismus. Severe intoxication: Coma, hypotonia, hyporeflexia, sz. Fundi usually normal. 12-24 h cardiopulmonary: ↑ HR, RR, BP; SOB. Multiorgan failure → death (2/2 severe AG metab acidosis). 24-72 h renal: Oliguria, flank pain, ATN, ARF (2/2 oxalate crystal deposition).

Dx: UA for calcium oxalate crystals (pathognomonic). Ethylene glycol level, chem10, serum Osm (calculate OG). Woods lamp: Urine/gastric contents may fluoresce; ± neuroimaging (formate may cause basal ganglia ischemia or hemorrhage).

Rx: Similar to methanol poisoning. IVF at 250-500 mL/h IV to enhance renal clearance & limit renal oxalates deposition. Fomepizole: Same as for methanol. Thiamine & pyridoxine 100 mg IV/IM qd (cofactors for metabolite elimination).

Isopropyl alcohol

Metabolized to acetone. Peak concentration ∽4 h.

Presentation: Ingestion of rubbing alcohol, solvents, paint thinner, hair spray, skin cleansers. Same as ethanol, but more severe. Fruity breath (acetone). Hemorrhagic gastritis.

Dx: Serum isopropanol level. Does not produce anion gap. Acetone → falsely ↑ Cr.

Rx: Supportive care. Dialysis for refract hypotension or level > 400 mg/dL.

ETHANOL WITHDRAWAL

Presentation: Discontinuation/significant reduction in EtOH intake, insomnia, anorexia, nausea, vomiting. Tremulousness, anxiety, hallucinations, palpitations; resting tremor; autonomic hyperactivity (tachycardia, HTN, hyperreflexia, irritability, sweating); insomnia, low-grade fever. Onset of si/sx ∽6 h after last use. Resolves over 24—48 h. Szs: GTCs w/in 6-48 h (most 12-18 h), ∽25% pts. SE rare. Halluc: Mostly visual; onset

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first 12-24 h; resolve over 24—48 h. DTs in 1/3 cases if w/d untreated after 2—4 days. Risk factors: Chronic drinking, previous DTs, concurrent illness, >30 yo, withdrawal sx despite high ETOH levels, >2 days b/n last drink & onset of w/d. Disorientation, agitation, sweating, tachycardia, HTN, halluc (usually visual) Mort: 5%, 2/2 arrhyth or failure to dx other underlying med

conditions.

Diagnosis: Clinical, history. Rule out others.

ED Rx: Thiamine 100 mg IV BEFORE glucose 1 amp IV. Sz 2/2 EtOH w/d (no other cause identified): Lorazepam 2 mg IV, significantly reduces risk of more szs; Phénobarbital for SE; Phenytoin often not effective; valproate may be used. Long-acting BZ (e.g., lorazepam 2 mg IV q5-15min, titrate to effect).

In-house Rx: Thiamine 100 mg IV qd indef. MVI & folate 1 mg (thiamine, folate, MVI together as "banana bag") BZ: for agitation & sz prevention. Goal: pt calm but alert. Long-acting benzos preferred, e.g., Diazepam (Valium) or chlordiazepoxide (Librium). Lorazepam (Ativan) or oxazepam (Serax) (shorter acting) useful in pts w/ cirrhosis. If no response to escalating doses of BZs, consider intubation, Phenobarbital 130-260 mg IV q15-20 min, or Propofol. Do not treat psychotic sx w/ phenothiazines or butyrophenones (may precip sz).

Benzodiazepine Management Protocol for Alcohol Withdrawal

Assessment protocol

Initial: Vitals, CIWA-Ar score (helpful to use standard tracking sheet)

Initial CIWA-Ar score ≥ 8 →

CIWA-Ar score & vitals q1h × 8 h, then if stable q2h × 8 h, then if stable q4h.

Initial CIWA-Ar score < 8 → CIWA-Ar & vitals q4h × 72 h.

CIWA-Ar score < 8 × 72 h → discontinue assessments.

CIWA-Ar score ≥ 8 at any time see above.

Administer benzodiazepines according to schedule below.

Consider Rx to ICU if: CIWAS-Ar > 35, q1h required for > 8h, more than 4 mg/h lorazepam × 3 h or 20 mg/h diazepam × 3 h required, or resp distress.

Benzodiazepine prescribing

Choose one drug (diazepam or lorazepam)

Use at least one PRN method ± scheduled method

"PRN" method: All patients (symptom triggered meds only)

"Scheduled" method: If any **HIGH-RISK** factors for severe withdrawal:

- Initial CIWA score 15 or higher
- History of severe alcohol withdrawal
- History of withdrawal-related szs
- Increasing CIWA score while on treatment
- History of heavy, daily drinking

"ICU high dose PRN" method: Limited to ICU patients

Diazepam (Valium) *note—can accumulate; risk prolonged sedation if elderly/liver dz*

PRN: 5-20 mg PO/IV q1h PRN CIWA-Ar score > 8

Scheduled: 10 or 20 mg PO/IV q6h × 4 → q8h × 3 → q12h × 2 → q24h × 1 → stop.

HOLD FOR SEDATION or RR < 12.

ICU dose PRN: 20-100 mg slow IV push q1h PRN CIWA-Ar ≥ 8

Lorazepam (Ativan)

PRN 1-4 mg PO/IV/IM q30min PRN CIWA-Ar ≥ 8

Scheduled: 2-4 mg PO/IV/IM q4h × 6 → q6h × 4 → q8h × 3 → q12h × 2 → stop.

HOLD FOR SEDATION or RR < 12.

ICU Dose PRN: 4-20 mg slow IV push q30min PRN CIWA-Ar ≥ 8

Adjunctive medications (optional) note—risk of arrhythmia, esp w/ low Mg, K, or w/ high dose (>35 mg/24 h).

Haloperidol 2.5-5 mg PO/IV/IM q2h PRN agitation. Check K, Mg wnl before administering.

Atenolol 50 mg PO daily. Hold for HR < 50 or SBP < 100.

MEDICATION OVERDOSES

Aspirin and salicylates

Includes: Acetylsalicylic acid (ASA), methyl-salicylate, bismuth subsalicylate (ingredient in OTC meds, e.g., Pepto-Bismol, Kaopectate). Applied topically or ingested.

Physiology & metabolism: Metab in liver via glucuronidation, oxidation, & glycine conjugation. First-order kinetics at therapeutic doses. ↑ doses/chronic use, zero-order kinetics.

Presentation (not evident until 6-12 h after ingestion): Tinnitus, n/v/d (at 150-300 mg/kg), hyperventilation → resp. alkalosis w/AGMA, MSΔs, szs (>300 mg/kg).

Dx: Clinical, w/ high suspicion if high anion gap acidosis & tinnitus are present. Key labs: CBC, Chem 10 (anion gap), LFTs, coags. Serum: Salicylates, ETOH, ethylene glycol, methanol, iron (coingestions common). UA w/ ketones.

Rx: Supportive measures. Hydration & correction of pH to enhance excretion. UOP monitoring (goal 1-2 mL/kg/h). Endotracheal intubation may be required. If so, maintain respiratory alkalosis. Sodium bicarbonate protocol (even in context of arterial pH as high as 7.55). ABG q2h, stop bicarbonate drip if pH > 7.60. Activated charcoal protocol provide 50 g up to 8 h after intake of >150 mg/kg. Second dose in 4 h if levels continue to increase. HD: Indicated if + CNS toxicity, pulm edema, renal failure, urine alkalinization not possible, or salicylate levels > 100 mg/dL or >60 mg/dL in the elderly. Szs: Bzs.

Lithium

Monovalent cation, used in BPD. Oral; rapidly absorbed. Therapeutic dose 300-2,700 mg/day; target serum levels 0.6-1.2 mEq/L. Peak ˜4 h w/ slow-release preparations, but can be delayed 12 h in OD). Renally excreted. Clearance reduced in hypovolemic hyponatremic states.

Clinical presentation: Acute (pts w/o tissue body burden of Li): n/v, cramping, ± diarrhea → tremulousness, dystonia, hyperreflexia, ataxia; Acute-on-chronic (pts who take lithium regularly & recently took larger dose): GI and neuro si/sx; Chronic (pts w/ large body burden of Li): Triggered by new medication → ↓ renal fxn or hypovolemia. MS Δs → coma, szs. “Syndrome

of irreversible lithium-effectuated neurotoxicity" (SILENT): Impaired cognition, sensorimotor PN, cerebellar dysfxn.

Dx: History, clinical features, serum levels. Key labs: Li serum levels, Chem 10, TSH.

Rx: Replete fluids & Na. Stop Li & concomitant drugs that may interfere w/ its levels, e.g., thiazide diuretics, anticonvulsants, CCBs, NSAIDs, SSRIs. HD: If neurotoxicity & lithium level > 2.5 mmol/L in patients w/ renal failure.

Phenytoin

Na voltage-gated channel blocker, suppresses membrane post-tetanic potentiation & hyperexcitability. Significant albumin binding; displacement can → toxicity w/ high free PHT levels. Liver metab (cytochrome p450). First-order kinetics: In therapeutic range & mild overdoses; zero-order kinetics: At higher concentrations (2/2 enzymatic saturation). Fosphenytoin is safer for rapid intravenous infusion.

Clinical presentation of toxicity: Mild: 20-50 mg/L: Nystagmus, mild ataxia. Severe: 50-100 mg/L: severe ataxia, dysarthria, >100 mg/L: szs & coma.

Rapid IV PHT (& less frequently fos-PHT) can trigger hypotension, bradyarrhythmias, & asystole unless given slowly (<250 mg/min).

Anticonvulsant hypersensitivity syndrome: Idiosyncratic rxn w/ pharyngitis, fever, rash, lymphadenopathy, multiorgan involvement (hepatitis, megaloblastic anemia, rhabdomyolysis, & arteritis). Permanent cerebellar injury after prolonged toxicity. Can also cause: TEN or Stevens-Johnson's syndrome. Leukopenia, PN, gum hypertrophy.

Dx: Clinical plus serum levels. Correct for alb: PHT level = PHT plasma / [(0.02 × alb) + 0.1]

Rx: Supportive. Fall prec. Avoid lidocaine if intubation required. Brady stops when infusion stopped; rarely require pacing. Activated charcoal w/in 4 h of oral overdose. Szs: BZ.

Digoxin

Therapeutic range: 0.5-1 ng/mL. Level > 2 ng/mL toxic; >12 ng/mL potent lethal. Two main causes: ↑ sensitivity: e.g.: Hypoxemia, hypokalemia, hypomagnesemia, hypernatremia, hypercalcemia, acid-base disturbances, aging, coronary ischemia, cor pulmonale). ↑ serum levels: e.g.: Renal insufficiency, antiarrhythmics [quinidine, verapamil, diltiazem), antibiotics (tetracycline, erythromycin, rifampin), immune-modulators (cyclosporine), SSRIs (paroxetine)].

Physiology & metabolism: Inhibits Na-K ATPase, ↓'s conduction at SA & AV

nodes, ↑‘s automaticity. After minimal liver metabolism, is stored in skeletal muscle where conc. correlates w/ therapeutic effect & levels. Renal elim.

Clinical presentation: Nausea, vomiting, diarrhea, abdominal pain; Palpitations, syncope, dyspnea; confusion, somnolence, dizziness, HA, paresthesias, szs (rarely), hallucinations; Visual: Disturbed color vision (often yellow-green coloring), blurred vision, double vision, halos, photophobia, scotomas. Arrhythmia (bradycardia).

Dx: Check plasma levels (at least 6 h after last dose); repeat levels q2h until tox resolved.

Rx: Supportive care; hydration: Optimize clearance; symptomatic bradycardia: Atropine 1 mg. Avoid transcutaneous pacer or β-agonists that could worsen arrhyth. Activated charcoal if ingestion w/in previous 6-8 h. Repeated doses are recommended. Digoxin-fab fragments (Digibind) for dig toxicity w/: Dysrhythmias a/w hemodynamic

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instability, altered MS, hyperK, digoxin level > 10 ng/mL. Correct electrolyte abnls, esp hypo-K & hypo-Mg.

Caution: Beware using Kayexalate concurrently w/ insulin/glucose/bicarbonate and/or Digibind: Risk of → hypokalemia. AVOID giving Ca: can → VT, VF (intracellular Ca).

NEUROTOXINS

Botulism

Clostridium botulinum—spore-forming Gram-positive rod. Toxin destroyed by heat, but the spores which produce the toxin are heat-tolerant.

Pathophysiology: Light chain of toxin: Protease that attacks SNAP-25 (syntaxin or synaptobrevin) at NMJ, preventing vesicular fusion w/ presynaptic membrane & acetylch release → failure of NMJ neuromuscular transmission → flaccid paralysis beginning w/ bulbar muscles & descending over hours-days. Death from resp. failure.

Ddx: GBS, myasthenia gravis, tick paralysis, stroke (brainstem), heavy metal/ organophosphate poisoning.

Dx: Hx, Tensilon test (r/o MG), CSF studies, neuroimaging, EMG w/ rep stim., cxs from serum, stool, & leftover food samples; Mouse bioassay: Inoculate w/ sample, see whether mouse develops Botulism.

Rx: Botulinum toxin works if given early: 50,000 U of types A & B, 5,000 U of type E. Organism is sensitive to benzylpenicillin & metronidazole.

Supportive.

Tetanus

Toxin enters at NMJ & migrates into CNS by retrograde axonal transport.

The A-chain in tetanospasmin inhibits synaptobrevin → inhibits release of GABA & glycine.

Clinical features: Opisthotonos, risus sardonicus, trismus. Any sensory stimulus produces muscle overactivity & tetanic spasm.

Rx: ICU observation, intub if nec. Clean & debride wound. Abx [IV PCN or Metronidazole (1 g q8h for both)] typically given for 1 wk. Control spasms with: IV diazepam (0.05-0.2 mg/kg/h), IM chlorpromazine (0.5 mg/kg/6 h) or IM/IV Phenobarbital (1 mg/kg/h).

Tetrodotoxin

Bacteria consumed by the puffer fish & certain octopus species produce tetrodotoxin (anhydrotetrodotoxin 4-epitetrodotoxin).

Pathophysiology: Tetrodotoxin binds to sodium channels in peripheral nerves.

Clinical features: 15 min-4 h: Paresthesias beginning periorally & progressing to limbs, abdominal pain, diarrhea, n/v, salivation. 4-24 h: Rapid ascending paralysis w/ respiratory failure; DTRs preserved. Bradyarrhythmias, coma (loss of brainstem reflexes) & szs. Death w/in 4-6 h, usually from resp failure. Mort rate ˜50%. Pts who survive acutely (˜24 h) usually survive w/o residual deficits, but recovery takes days.

Rx: No antidote. Supportive. α-adrenergic agonists & IV fluids.

Saxitoxin

Bivalve mollusks & some puffer fish produce Saxitoxin → paralytic shellfish poisoning.

Pathophysiology: Na-channel blocker.

Clinical features: 10-30 min: n/v/diarrhea, abd pain, & tingling/burning of lips, gums, tongue, face, neck, arms, legs, toes; SOB, dry mouth, choking feeling, conf, dysarth, ataxia.

Rx: Similar to tetrodotoxin w/ supportive ventilation & activated charcoal to bind.

Ciguatoxin

Tropical fish may be contaminated w/ ciguatoxin-producing microalgae.

Pathophysiology: Ciguatoxin opens voltage-gated sodium channels in CNS &

PNS.

Clinical features: N/V/diarrhea → HA, myalgias, paresthesias, numbness, ataxia, halluc. Rx: No specific Rx.

PLANT & FUNGAL DERIVATIVES

Ergot: Used to Rx migraine. Severe burning sensation in limbs due to vasoconstrictive effects of ergot alkaloids. Neuropsychiatric SEs: Halluc, irrational behavior, szs.

Nutmeg: 60 g or 12 teaspoons may produce various neuropsychiatric s/sx: convulsions, generalized pain, visual halluc, psychosis.

Strychnine: Highly toxic alkaloid, pesticide; glycine receptor antagonism; severe muscle spasms → death by asphyxia or exhaustion.

Konzo: Cassava insufficiently processed, contains high cyanide levels. Subacute spastic nonprogressive paraparesis, central visual field loss. Chronic: Ataxia, PN.

Lathyrism: Grass pea (Lathyrus sativus). Beta N-oxalylamino-L-alanine; s/sx: Gradual spastic paraparesis; most deficits will self-resolve.

HEAVY METALS

Thallium

Disrupt K-dependent processes; riboflavin sequestration; interference w/ cysteine residues; ribosomal (60S) inhibition; myelin sheath injury; key enzymes: Pyruvate kinase & succinate dehydrogenase, & the sodium-potassium ATPase.

Clinical features: Painful polyneuropathy, alopecia.

Rx: Remove contaminated clothing, avoid self-exposure; activated charcoal 0.5-1 g/kg PO (max dose 100 g); antidote = Prussian Blue. Acute poisoning: 3 g PO/NG, then 250 mg/kg/day div 4×/day; Chronic: 250 mg/kg/day PO div 4×/day; HD controversial.

Arsenic

Inorganic forms, particularly trivalent ones, are more toxic than organic. Inhibits enzymes requiring lipoic acid as cofactor, e.g., pyruvate & α-ketoglutarate dehydrogenase.

Clinical features: GI distress, hypersalivation, dry/tight throat, hoarse, szs, sweating, delirium. Mees lines (discoloration on nails) classic (but can be seen in any heavy metal poisoning). May resemble GBS.

Treatment: Remove source of exposure. Initiate Rx if level >200 µg/L. Recent ingest: Gastric lavage PEG solution at 1 L/h. If does not work, use whole-bowel irrigation. Anticipate & treat cardiac arrhythmias. Maintain high UOP w/ IVF to facilitate excretion. Chelating agents (dimercaprol or succimer) are themselves toxic & only used in severe toxicity. Dimercaprol 3-5 mg/kg deep IM q4h × 2 day, then q12h until recovery or until PO therapy can be started. Succimer 10 mg/kg PO q8h × 5 days, followed by 10 mg/kg PO q12h × 14 days.

Mercury

Organic short-chained methylmercury has worst CNS side-effects (vs. inorganic forms); inhib choline acetyl transferase (last step in acetylcho prod) → motor & cog dysfxn.

Clinical features: Hunter-Russell syndrome: Ataxia, speech dist. & hearing loss. Chisso-Minamata disease: Above sx & numbness in hands & feet, myalgia, constrict visual fields; in extreme cases, paralysis, insanity, coma, & death. Acrodynia (pink disease): Hands & feet pink. Pregnant women exposed → developmental abnormalities.

Rx: Removal of contaminated clothing, washing exposed skin. Aggressive hydration. Gastric lavage. Charcoal. Neostigmine for motor dysfxn. Chelation Rx for acute inorganic mercury poisoning: DMSA: 10 mg/kg PO tid × 5 days, then 10 mg/kg PO bid × 2 wk. D-penicillamine 15—40 mg/kg/day; not to exceed 250-500 mg PO q6h ac (continue 1 wk until decline in urine mercury levels). Dimercaprol 3-5 mg/kg IM q4h for 2 days, followed by 2.5-3 mg/kg IM q6h for 2 days, followed by 2.5-3 mg/kg IM q12h for 1 wk. HD.

Lead

Adults: Nausea, abd pain, irritability, insomnia, lethargy or hyperactivity, headaches, szs; in severe cases, coma & death. Chronic toxicity: Neuropathy, painful arthralgias, bluish line along gums (“Burton line”). Children: Dev delay, cerebral edema. Peripheral blood smear: Basophilic stippling, microcytosis, & hypochromasia.

Pathophysiology: Interfere glutamate, inhibit delta-aminolevulinic acid dehydratase (zinc binding enzyme important in biosynthesis of heme). Inhibits ferrochelatase (catalyzes joining of protoporphyrin IX & Fe^{2+} to form heme).

Rx: Remove the source of contamination. Acute toxicity: Chelation w/ DMSA, EDTA, dimercaprol, or penicillamine. DMSA 10 mg/kg PO q8h × 5days, then 10 mg/kg PO q12h × 9 days. EDTA 50-75 mg/kg/day IV over 8-24 h × 5 days or divided. If given IM in two to six divided doses, mixing w/

lidocaine can ↓ discomfort. Dimercaprol 3-5 mg/kg IM q4h. Penicillamine 25-35 mg/kg PO.

COPPER DEFICIENCY

Poor copper absorption 2/2: Gastric bypass surgery, copper deficient parenteral nutrition, zinc overuse (competes w/ copper absorption; found in denture creams & supplements).

Myelopathy. Copper supplementation does not always reverse. Rx: Stop zinc exp, oral copper Week 1: 8 mg/day, Week 2: 6 mg/day, Week 3: 4 mg/day, Week 4-indefinitely: 2 mg/day

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ORGANOPHOSPHATE POISONING

Pathophysiology: Reversible ACIs act in the synaptic cleft to inhibit the degradation of Ach. Irreversible ACI SE categories: Muscarinic: Bronchorrhea, bronchoconstriction, hypersalivation, sweating, lacrimation, bradycardia, HTN, miosis, micturition. Nicotinic: Fascics, cramps, diaphragmatic paralysis, tachycardia, HTN. CNS: Emotional lability, tremors, slurred speech, Cheyne-Stokes resps, szs, coma. DUMBBELSS: Diarrhea, Urination, Miosis, Bradycardia, Bronchoconstriction, Excitation (Muscle, CNS-Nicotinic effects), Lacrimation, Salivation, Sweating.

Rx: Wear gloves, remove soiled clothes, wash contam skin. Labs: CBC; serum cholinesterase.

Rx: Give both of the following: Atropine 1-2 mg IV bolus, repeat q1-5min prn for desired effects (drying of pulmonary secretions, adequate oxygenation, dry skin, HR > 70, pupils dilated); Pralidoxime 30 mg/kg IV in 100 mL D5NS over 15-30 min. Repeat in 30 min if weakness persists, then q3-8h if si/sx poisoning recur (12 g maximum per 24 h). Alternate dosing: Continuous drip; bolus 25-50 mg/kg, then 10-20 mg/kg/h. Sz ppx: Diazepam.

ORGANIC SOLVENTS & ACRYLAMIDE

No cure. Rx = prevention of chronic exposure. Hexane & m-n-butyl ketone, found in glue; glue sniffers can get GBS-like syndrome. Acrylamide thought to cause Purkinje cell & diffuse axonal injury → ataxia, delayed peripheral neuropathy, & encephalopathy. Acyrlamide is used in labs in protein gels. Important to limit exposure by wearing gloves.

TOXIC GASES

Carbon monoxide

Colorless, odorless, tasteless, nonirritating highly toxic gas produced by

combustion of organic matter under conditions of restricted O_2.

Clinical features: HA, vertigo, flulike sxs. In more acute poisoning: HA, vertigo, confusion, visual & auditory symptoms, convulsions, & unconsciousness. CV effects: Tachycardia, HTN. Severe sequelae occur in 15% who survive acute, include problems w/ STM, dementia, irritability, Parkinson-like syndromes, cortical blindness, & depression.

Pathophysiology: Binding to hemoglobin, myoglobin, & mitochondrial cytochrome oxidase

Rx: Hyperbaric O_2, supportive care.

Cyanide

Inhibitor of metalloenzymes, such as the crucial electron transport chain enzyme cytochrome C oxidase, found in mitochondrial membranes, & once cyanide binds to the iron-containing moiety, aerobic respiration is impaired.

Clinical features: Parkinsonism, severe dystonic reactions, HA, N/V, vertigo, arrhythmias, coma, & death. Parkinsonism can persist even after Rx.

Rx: Antidotes include: Sodium nitrite: 10 mL of 3% solution (300 mg) slow IV push over 2-5 min. Sodium thiosulfite: 12.5 g (50 mL) IV at 3-5 mL/min; may repeat at one-half initial dose after 1 h if sxs persist. Vitamin $B_{12:}$ 70 mg/kg IV over 15 min or 5 g IV over 15 min.

Nitrous oxide

Oxidizes the cobalt core of vitamin B_{12}.

Rx: Stop exposure. IM vitamin B_{12} injections.

VITAMINS

Vitamin A deficiency

Retinoid. Deficiency → blindness.

Clinical features: Xerophthalmia (w/ severe deficiency): Pathological dryness of conjunctiva; Bitôt spots (oval, triangular, or irregular keratin accumulations); cornea becomes cloudy. Untreated → corneal ulceration & blindness.

Rx: Vitamin A 200,000 IU PO qd × 2 days, then repeat in 1 wk. Children <5 yo: ½ dose halved; infants <6 mo old: 1/4 dose. Pregnant women: Vitamin A is teratogenic.

Vitamin A toxicity

Pseudotumor cerebri. Nausea, jaundice, irritability, anorexia, vomiting, blurry vision, HA, muscle & abdominal pain & wkness, drowsiness, & altered MS.

Vitamin B_{12} (Cobalamine) deficiency

B_{12} binds salivary R protein → in duodenum R protein is digested by pancreatic enzymes → B_{12} binds to intrinsic factor (IF, made by gastric parietal cells) → B_{12}-IF absorbed in distal ileum → enters portal circulation bound to transcobalamin II. Cofactor essential for production of proteins, DNA, RNA, & for Krebs cycle; same processes also involve folate, homocysteine (Hcy), MMA. Daily req is small (2 µg/dL).

P.134

Etiologies of Vitamin B_{12} Deficiency

Intrinsic factor deficiency	**Deficient B_{12} intake**
Pernicious anemia (autoimmune gastritis)	Strict veganism (rarely)
Juvenile PA (inability to secrete IF)	Breastfeeding infants of vegan mothers
Gastritis (esp 2/2 *H. pylori*)	Alcoholism
Gastrectomy	Dietary fads
Aging (can → gastric atrophy)	
Terminal ileum disorders	**Achlorhydria**
Tropical sprue	Atrophic gastritis
Celiac disease	Pancreatic deficiency
Enteritis	Proton pump inhibitor use

Crohn disease Exudative enteropathy Intestinal resection Whipple disease Ileal tuberculosis Cublin gene mutation	Zollinger-Ellison's syndrome (in these, pH of distal small intestine too high for cobalamin-IF to bind w/ cublin)
Medications Colchicine Neomycin *p*-Aminosalicylic acid Proton pump inhibitors	**Transport protein abnormalities** Transcobalamin II deficiency R-protein deficiency Nitrous oxide (w/ anesthesia or via recreational use, e.g., "whippets")
Competition for cobalamin Blind loop syndrome Fish tapeworm (*Diphyllobothrium latum*)	**Increased B_{12} requirement** Hyperthyroidism Alpha thalassemia
Defects of intracellular B_{12} metabolism	**HIV/AIDS**

(→ MMA aciduria + homocystinuria in infants)	(Cause likely multifactorial: Poor nutrition, chronic diarrhea, ileal disfunction, exudative enteropathy)
Isolated methylmalonic aciduria	
Isolated homocystinuria	
Methylmalonic aciduria & homocystinuria	

Presentation: Pernicious anemia; Risk factors: White European ancestry, elderly, autoimmune dz (e.g., thyroid dz, vitiligo). “Classic” pernicious anemia: Prematurely gray hair, lemon colored (anemia + icteric), MS slow, shiny tongue, broad shuffling gait.

Other manifestations:

Manifestations of Vitamin B_{12} Deficiency

Hematologic	**Neurologic**
Megaloblastic anemia (↑ MCV, ↓ Hct, ↑ indirect bilirubin, ↑ LDH, hypersegmented neutrophils on smear); Note: 25% cases have no anemia or macrocytosis (e.g., coexisting iron deficiency or homozygous alpha thalassemia-2 can mask macrocytosis)	Paresthesias
Pancytopenia	Peripheral neuropathy
	Subacute combined degeneration (slowly progressive weakness, sensory ataxia, paresthesias → spasticity, paraplegia, incontinence)
	Peripheral Lhermitte syndrome (shock-like sensation w/ neck flexion)
Psychiatric	**Cardiovascular**

Irritability, personality change Dementia Memory impairment (usually mild)	? increased risk of stroke, MI
Skeletal Osteoporosis, hip & spine fractures	**Copper deficiency** Often coexists w/ B_{12} deficiency; can also → myelopathy
Hyperhomocysteinemia (also occurs w/ folate deficiency)	

Diagnosis: Folate, B_{12} serum levels. If folate >4 ng/mL, B_{12} >300 pg/mL → deficiency unlikely (probability 1%-5%). Borderline cases, ↑ suspicion → check MMA, Hcy. Diagnosing pernicious anemia: IF-antibodies (Se 50%-70%, Sp 100%); ? anti-parietal cell abs; serum gastrin; serum pepsinogen levels; Schilling test not available in most of US anymore).

Interpretation of MMA & Hcy values in B_{12} and folate deficiency: MMA↑, Hcy ↑: B_{12} deficiency (94% Se, 99% Sp). MMA nl, Hct ↑: Hcy deficiency (86% Se, 99% Sp).

Rx: R/o treatable causes. PO & IM B_{12} theoretically equally effective (but many prefer IM initially, esp w/ neurological si/sx 2/2 concerns about variable absorption & problems w/ compliance) IM: 1 mg qd × 1 wk → 1 mg qwk × 4 wk → 1 mg qmo indefinitely. PO: 1-2 mg qday × 1-2 wk → 1 mg qday indefinitely.

Monitoring on therapy: Fe, LFTs, K, reticulocyte count at 1 week (if hypo-K → K suppl); HCT at 8 wk (should have normalized); B_{12}, MMA, Hcy: Recheck 1-3 mo.

Prognosis: Recovery is most rapid first 3 mo; may continue over 6-12 mo.

Vitamin B_9 (Folate) deficiency:

Nucleotide synthesis & remethylation of Hcy. Pregnancy: Protects against neural tube defects (esp important in those on AEDs). Pts on methotrexate

may develop deficiency; can be reversed w/ leucovorin rescue.

Clinical features & pathophysiology: See Vitamin B_{12}.

Rx: Folate 5 mg PO qday. Note: Folate suppl can mask B_{12} def by preventing anemia.

Vitamin B_1 (Thiamine) deficiency

Wernicke encephalopathy (described in "Alcohol" section). Wet beriberi: CHF & peripheral edema can be fatal. Dry beriberi (aka endemic neuritis): Wasting & partial paralysis 2/2 PN damage (axon & myelin). Can be complication of gastric bypass/TPN.

Rx: See discussion of Rx for Wernicke encephalopathy in "Alcohol" section.

Vitamin B_3 (Niacin/Nicotinamide) deficiency

Pellagra: Clinical triad of: dementia, diarrhea, & dermatitis. Other CNS: PN, szs, depression, insomnia, tremor, rigidity, ataxia. Early dx may prevent irreversible damage. Causes: carcinoid syndrome, Tb meds.

Rx: Nicotinamide IV 100 mg q6h until acute sx resolve, then 50 mg PO q8-12 h until all skin lesions heal. Pediatric dosing: Nicotinamide 10-50 mg PO q8-12 h until sx resolve.

Vitamin B_3 (Niacin) toxicity

Flushing: Prostaglandin-mediated; more common w/ immediate-release preparations. More intense after EtOH, exercise, sun exp, spicy foods. Minimized if taken after meals or if aspirin taken 30-45 min prior. Severe flushing ↓'d by starting immed.-release niacin at low dose (e.g., 50 mg tid) and increasing slowly. Other SEs: N/v, pruritis, hives, constipation, myopathy; rarely, hepatotoxicity (s/sx: jaundice, abd pain, blurred vision, hyperglycemia), precipitation of preexisting gout.

Rx/precautions: Reduce/stop niacin. Hepatotoxicity more common w/ sustained release. Monitor serum uric acid, blood glucose, LFTs q6-8 wk while titrating dose.

Vitamin B_6 (Pyridoxine) deficiency

At risk: Elderly, alcoholics, HD pts. Bioavailability can be ↓'d by steroids or anticonvulsants.

Pathophysiology: Neurotransmitter synthesis: Serotonin, epi, norepi, & GABA. B_6 also involved in: Amino acid, glucose & lipid metab, histamine syn, Hg syn & fxn, gene expression.

Clinical features: Seborrheic dermatitis, angular chelitis, atrophic glossitis w/ ulceration, somnolence, confusion, PN, szs, intertrigo, & conjunctivitis.

Rx: Improving dietary intake. Pyridoxine 100 mg/day.

Vitamin B_6 (Pyridoxime) toxicity

Excess consumption (>200 mg/day) can → sensory neuropathy or neuronopathy.

Vitamin D deficiency

RFs: Poor intake, lack of sun, endocrine d/o's (1° or 3° hyperparathyroidism, thyrotoxicosis).

Pathophysiology: Prohormones converted in liver to 25-OH-vitamin D; Second hydroxyl group added in kidney, forming 1, 25-OH-vitamin D (biologically active agent).

Clinical features: Proximal myopathy a/w osteomalacia. Severe deficiency: Hypo-Ca (s/sx: Paresthesias, hyperreflexia, tetany, carpopedal spasm, tetany; Trousseau sign—inflating blood pressure cuff & maintaining above systolic BP → carpal spasm; Chvostek's sign (tapping inferior zygoma → facial spasm).

Rx: Vit D 1,000 IU/day.

Vitamin E (Tocopherol) deficiency

May mimic Friedreich ataxia. Other: Myopathy, PN, ophthalmoplegia, nystagmus, pigmentary retinopathy.

Rx: USRDA is 15 mg daily.

Biotin deficiency

Essential component of several enzyme complexes (acetyl-CoA carboxylase, pyruvate carboxylase, proprionyl CoA carboxylase, & beta-methylcrotonyl CoA carboxylase).

Etiology: Can occur w/ consumption of raw egg whites. 2° deficiency: Absent biotinidase, multiple carboxylase deficiency.

Clinical features: Altered MS, myalgias, paresthesias, nausea, anorexia. May lead to long-chain fatty acid def w/ alopecia, seborrheic dermatitis.

Rx: Unclear, ˜30 µg/day.

Summary of Primary Neurological Signs a/w Vitamins

Vitamin deficiency	Clinical sign
A, B_1, folate, B_{12}, E	Optic neuropathy & other ocular signs
B_1, B_6, folate, B_{12}, E	Neuropathy
Folate, B_{12}, E	Myelopathy
D, E	Myopathy
B_1, B_3, folate, B_{12}	Encephalopathy
B_6	Sz

Meningitis, Encephalitis, and Brain Abscesses

Meningitis: Inflammation of the meninges. Encephalitis: Inflammation of the brain.

Menigoencephalitis: Inflammation of brain & meninges. Aseptic meningitis: Meningitis w/(˜) routine bacterial cx (misnomer—causes include infectious & noninfectious agents, excluding causes of acute bacterial meningitis). Chronic meningitis: Meningitis > 1 mo. Recurrent (Mollaret's) meningitis: >1 episode, nl CSF b/n.

Leptomeningitis: Primarily arachnoid + pia (usual meaning of "meningitis"). Pachymeningitis: Involves primarily dura (much rarer).

OVERLAPPING CLINICAL SYNDROMES

Bacterial & aseptic meningitis, meningoencephalitis, & brain abscess

Roughly four acute clinical syndromes, generally merit different w/u & mgt:

• **Acute bacterial meningitis**:	(+)meningeal, (±)cortical si/sx
• **Acute aseptic meningitis**:	(+)meningeal, (−)cortical si/sx
• **Acute encephalitis**:	(±)meningeal, (+)cortical si/sx (multifocal > focal)
• **Brain abscess**:	(±)meningeal, (+)cortical si/sx (focal > multifocal)

Syndromes of bacterial meningitis & encephalitis overlap, hence "meningoencephalitis."

In practice, all four frequently present similarly

Common in all four: HA, fever, nuchal rigidity, photophobia, n/v.

Acute bacterial meningitis: Fever (77%), nuchal rigidity (83%), AMS (69%), sz (5%). At least 2/4 of these + in 95% cases. Elderly pts can be "atypical": Lethargy, AMS, no fever

Encephalitis: Fever, HA, AMS, sz, focal signs, mvmt d/os.

Aseptic meningitis: Neg routine CSF cx, CSF pleocytosis (usu lymphocytic, but not always); discomfort, lethargy, HA, f/n/v, but preserved mentation.

Brain abscess: Confusion, drowsiness, szs. Distinguish from meningoencephalitis by imaging.

Distinguishing at presentation: Sometimes clear initial distinction possible (frequent exceptions). "Classical" CSF profile can help (beware wide variability in CSF for bacterial meningitis). Decision tools may aid early triage, e.g., Bacterial Meningitis Score (BMS) (Pediatrics 2002;110:712; JAMA 2007;297:52; Curr Opin Neurol 2009;22:288).

Bacterial Meningitis Score (*Pediatrics* 2002;110:712)

Predictor	**Points**
Positive Gram stain	2
CSF protein ≥ 80 mg/dL	1
Peripheral ANC ≥ 10,000 cells/mm^3	1
Seizure at or before presentation	1
CSF ANC ≥ 1,000 cells/mm^3	1

Interpretation of score (*possible scores range from 0 to 6*)

BMS = 0: strongly suggests aseptic meningitis (Se 74%, Sp 100%)

BMS = 1: won't miss bacterial meningitis, but nonspecific (Se >99%, Sp 37%—73%)

BMS ≥ 2: strongly suggests bacterial meningitis (Se > 99%, Sp 97%)

Rev Med Liege 2006; 61:581; *Pediatrics* 2002;110:712; *Curr Opin Neurol* 2009;22:288.

Caveats: Derived based on pedi population. Valid if inclusion/exclusion criteria are met: *Inclusion criteria: CSF WBC > 10 cells/mm^3*

Exclusion criteria: H/o neurosurgery; immunosuppression; CSF RBC > 10,000/mL; pretreated w/ antibiotics within 48 h; septic shock; presence of purpura.

Pathways for Initial Management of Acute Meningitis & Encephalitis

Meningeal si/sx only	→	Bacterial	→	admit, w/u ABM
			→	admit, w/u AAM
	→	"Aseptic"	→	home w/ f/u
Cortical ± meningeal si/sx	→	Clue(s) to etiology	→	admit, core + focused w/u AME
	→	No specific clues	→	admit, core + broad w/u AME

(ABM = acute bacterial men., AAM = acute aseptic men., AME = acute meningoencephalitis.)

Typical CSF Findings in Meningitis & Encephalitis

	Glucose (mg/dL)		**Protein (mg/dL)**	
	<10	**10-45**	**>250**	**50-250**
More common	BM	BM	BM	VM, NS, Lyme dz
Less common	TBM, FM	NS, VM (e.g., mumps, LCMV)	TBM	
	Total white blood cell count (cells/µL)			
	>1,000	**100-1,000**	**5-100**	

More common	Bacterial meningitis	BM, VM	Early BM; TBM, NS
Less common	Mumps, LCMV	Encephalitis	Encephalitis

(BM = bacterial men, VM = viral men, TBM = Tuberculous men., NS = neurosyphilis, FM = fungal meningitis. Adapted from UpTo Date 2009, "Cerebrospinal fluid: Physiology & utility of an exam in dz states".)

TRIAGE IN THE EMERGENCY DEPARTMENT

Admit & emergently treat if: Suspect acute bacterial meningitis or encephalitis. Tailor w/u & Rx to clinical situation; general rules of thumb by best-fitting syndrome:

• AME → broad spectrum bacterial abx + acyclovir

• ABM → dexamethasone + empiric bacterial abx + acyclovir

Admit for observation + further w/u, ± Rx: In selected cases of aseptic meningitis. Most admissions for supportive care (IVF, antiemetics, pain control). Broad ddx w/ few treatable causes (˜ same ddx as encephalitis—see below); clinical suspicion for specific causes & illness severity must determine w/u scope.

Consider discharge home from ED: In selected pts w/ aseptic meningitis, no universally accepted criteria currently exist, reasonable to d/c pts meeting the following criteria: (1) "Nontoxic" clinical appearance. (2) BMS = 0 (neggram stain, CSF ANC < 1,000, CSF protein < 80, peripheral ANC < 10). (3) Normal serum WBC. (4) No sz during illness (5) No cortical signs on neurological examination. (6) Adequate control of sx (e.g., n/v). (7) Able to arrange f/u w/ PCP in 1-3 days. (8) Advise return to ED immediately in case of any clinical worsening.

ETIOLOGIES OF ASEPTIC MENINGITIS & ENCEPHALITIS

Ddx of Aseptic Meningitis & Encephalitis

Infectious

Viruses: Enteroviruses (polio, coxsackie, ECHO)

Herpes viruses (HSV-1,2, VZV, CMV, EBV, HHV-6, simian herpes B virus)

Resp viruses: Adenovirus, rhinovirus, influenza types A, B, parainfluenza viruses, RSV

Arboviruses: EEE, WEE, VEE, SLE, WNV, LA, California EV, CTFV, powassan virus mumps, measles, rubella

HIV, HTCLV-I & II, LCMV, rotavirus, encephalomyocarditis virus, vaccinia, rabies virus hepatitis A, B, parvovirus, smallpox, vesicular stomatitis virus

Bacteria: Partially Rx'd meningitis, parameningeal infxn, Endocarditis *Mycoplasma pneumonia*, *Mycoplasma hominis*, *Mycob. tuberculosis* Ehrlichiosis, brucella, *Bartonella henselae*, *Francisella tularensis*, *Actinomyces listeria*, *Nocardia*, *Chlamydia*, rat-bite fever/sodoku, *Strep. moniliformis Spirillum minus, Coxiella burnetii* (Q fever), *Whipples bacillus*

Spirochetes: *Borrelia burgdorferi* (Lyme), *T. pallidum* (syphilis), leptospirosis

Rickettsiae: RMSF, typhus

Fungi: Crypto, Histo, *Coccidioides*, *Sporothrix*, *Blastomyces*, *Candida*, *Aspergillus*, zygomycosis (=mucormycosis), *Pseudallescheria*, *Paracoccidioides*, dematiaceous mold

Parasites: *Toxoplasma*, cysticercosis (*Taenia solium*), trichinosis (*Trichinella spiralis*), *Angiostrongylus*, *Strongyloides stercoralis*, *schistosomiasis*, Amoebae (*Naegleria*, *Acanthamoeba*, *Balamuthia*), *Trypanosoma* sp., Malaria sp., *Baylisascaris procyonis*

Noninfectious

Drugs: TMP-SMX, NSAIDs (esp ibuprofen), amoxicillin, OKT3 (muromonab, CD3), IVIg, INH, azathioprine, intrathecal(IT)-MTX, IT-cystine arabinoside, allopurinol, carbamazepine, sulfasalazine, pyridium (phenazopyridine),

Demyelinating dz: MS, ADEM, NMO, transverse myelitis

Systemic dz: Collagen vascular dz, SLE, Sjögren syndrome, Wegener, PAN, CNS vasculitis, Behçet dz, sarcoidosis, Vogt-Koyanagi-Harada syndrome, Fabry dz

Neoplastic: Leptomeningeal cancer, leukemia, lymphoma, carcinomatous meningitis, post-transplantation lymphoproliferative disorder

Vascular: Infarctions (brain, cord), CNS vasculitis (primary or secondary)

Post-infxn/vaccine: Rubeola, rubella, varicella, variola; vaccines: Rabies, pertussis, influenza, vaccinia, yellow fever

Chemical: Blood leak from brain, cord, meninges due to e.g., angioma, AVM; can cause superficial hemosiderosis; Cholesterol leak from: craniopharyngioma, teratoma, epidermoid cyst

Other: HaNDL syndrome ("headache w/ neurologic deficits & CSF lymphocytosis"—?viral)

ACUTE ASEPTIC MENINGITIS & ENCEPHALITIS

WORKUP & EMPIRIC TREATMENT

General points: (1) Distinguish primary vs. post- or parainfectious; (2) Mosquito & tick born illnesses have regional & seasonal variation; (3) WNV occurs mainly during mosquito season, affects elderly most; (4) Enterovirus, influenza, varicella: Incidence varies seasonally; (5) HSV: No significant variation by season or geography; (6) Identification of etiologic agents only possible in ˜1/3 cases even w/ "aggressive" w/u.

History: Onset/pace/progression, travel, pets/animal/insect exposures/bites/scratches, sick contacts, PPD/HIV/immune status, prior similar illness, transfusion hx, recent illness, recent abx, new meds, sexual hx, rash, mouth/genital sores, arthritis, dry mouth/eyes.

Exam: See suggestions at beg of chapter. (1) Gen si/sx: HA, fever, stiff neck, photophobia, n/v; sz, MSΔs, focal si/sx, mvmt d/os. (2) Focal vs. diffuse brain involvement (by exam or imaging)—can point to etiology, (e.g. Arboviral infection: Diffuse, w/ early, rapid, HA, fever/n/v/AMS/focal signs, coma; HSV: Focal; fever/HA progress for days; then szs, obtundation). (3) Useful clues on exam (Table 16.1): Enlarged liver, lymphadenopathy, parotitis, rash, respiratory sx, retinitis, cerebellar ataxia, CN palsies, dementia, myorhythmia,

Parkinsonism, paralysis, CN palsies, ulcers of mouth & genitals, joint inflammation, dry eyes or mouth, iridocyclitis, rash, blisters/vesicles (including on genitalia), hydrophobia, aerophobia, pharyngeal spasm, hyperactivity, tremors (eyelids, tongue, lips, limbs).

Empiric abx (while confirmatory tests are pending)

1. Empiric coverage for ABM × 48 h if: Bacterial meningitis suspected (see below) or elderly, immunocompromised, or received abx recently (even if viral meningitis more likely).

2. Suspect encephalitis: Acyclovir 10 mg/kg q8h × 14days (until r/o HSV; see chapter “Neurologic Infectious Diseases”).

3. Rickettsial or Ehrlichial dz: During appropriate season, treat those w/ suggestive clinical picture w/ doxycycline 100 mg q12 for 10 days or until afebrile for at least 3 days.

4. ADEM: Steroids, ± IVIg or plasma phoresis (see chapter “Demyelinating Diseases of the central Nervous system”.

5. Other causes of aseptic meningitis & encephalitis less common or not treatable— target any therapies toward treatable causes for which there exist reasonable grounds for suspicion.

Diagnostic Tests: Labs: Vast ddx. Use “two-step” approach: (1) Initial w/u for dangerous/common/treatable causes (see Table 16.3), (2) Further w/u focused based on: Pace & temporal pattern of illness (acute, subacute/chronic/recurrent), clinical clues (see Table 16.1), epidemiology & risk factors (Table 16.2), initial lab results (Table 16.3). MRI w/ gado: If suspect encephalitis (may help narrow ddx). EEG: If pt is confused/ obtunded/comatose to r/o nonconvulsive status epilepticus.

Table 16.1 Possible Etiologies Based on Clinical Findings

Hepatitis: *C. burnetii*

Lymphadenopathy: HIV, EBV, CMV, measles, rubella, WNV, *Toxoplasma pallidum*, *Bartonella* sp., *TB, Toxo, Trypanosoma brucei gambiense*

Parotitis: Mumps virus

Rash: HIV,VZV, HHV-6, B virus, WNV, some enteroviruses, *Rickettsia rickettsii, Mycoplasma pneumoniae, B. burgdorferi, T. pallidum, Ehrlichia, Anaplasma phagocytophilum*

Respiratory sx: VEE, Nipah virus, Hendra virus, influenza, adenovirus, *M. pneumoniae, C. burnetii, M. tuberculosis, Histo*

Retinitis: CMV, VZV, HSV, WNV, *B. henselae, T. pallidum*

Urinary symptoms: St. Louis encephalitis virus (early)

Cerebellar ataxia: VZV (children), EBV, mumps, SLE, *T. whipplei, T. brucei gambiense*

Cranial nerve palsies: HSV, EBV, *Listeria, TB, T. pallidum, B. burgdorferi, T. whipplei, Cryptococcus, Histo, Coccidioides* sp., sarcoid, HIV, Lyme, VZV, CMV, HSV

Dementia: HIV, sCJD & vCJD, measles virus (SSPE), *T. pallidum, T. whipplei*

Myorhythmia: *T. whipplei* (oculomasticatory)

Parkinsonism: JEV, SLEV, WNV, Nipah virus, *T. gondii, T. brucei gambiense*

Flaccid paralysis: JEV, WNV, tickborne encephalitis virus; enteroviruses, (enterovirus-71, coxsackieviruses), poliovirus

Rhombencephalitis: HSV, WNV, enterovirus 71, *Listeria*

Malignancy, CN or spinal nerve palsies: Neoplastic meningitis

Intractable HA + mild meningeal signs: Granulomatous CNS angiitis

Ulcers of mouth & genitals, serositis, arthritis, dry eyes & mouth, uveitis, rash: Behcet's, Sjögren's, SLE, sarcoid

Vesicles in dermatomal pattern: VZV

Genital vesicles & ulcers: HSV-2, Behcet's

Hydrophobia, aerophobia, pharyngeal spasm, hyperactivity: Rabies

Tremors of eyelids, tongue, lips, extremities: SLE, WNV

Temporal lobe preference: HSV > VZV, EBV, HHV6, syphilis

Hydrocephalus: Bacterial, fungal, parasitic agents

Very low CSF glucose: Tuberculosis, cryptococcus

Skin rash, aphthous ulcers: HIV, VZV, HSV, EBV, CMV, JCV, Behcet's

P.140

Age	
Neonates	HSV-2, CMV, rubella virus, *Listeria, T. Pallidum* (*syphilis*), *Toxoplasma*
Infants & children	EEE, JEV, Murray valley EV, influenza virus, La Crosse v.
Elderly	EEE, SLE, WNV, sporadic CJD, *Listeria*
Animal contact	
Bats	Rabies virus, Nipah virus
Birds	WNV, EEE, WEV, VEE, SLE, Murray EV, JEV, *Cryptococcus*
Cats	Rabies v., *C. burnetii, B. henselae, T. gondii*

Dogs	Rabies virus
Horses	EEE, WEE, VEE, Hendra v.
Old World primates	B virus
Raccoons	Rabies v., *B. procyonis*
Rodents	EEE, VEE, tickborne EV, Powassan v. (woodchucks), La Crosse v. (chipmunks, squirrels), *Bartonella Q, LCMV*
Sheep & goats	*C. burnetii*
Skunks	Rabies virus
Swine	JEV, Nipah virus
White-tailed deer	*B. burgdorferi*
Immunocompromised	VZV, CMV, HHV-6, WNV, HIV, JCV, TB, *Listeria, Crypto, Histo, Toxo, Coccidioides*
Agammaglobulinemia	Enteroviruses, *M. pneumoniae*
Ingested items	
Undercooked meat	*T. gondii*
Raw meat, fish, reptiles	*Gnanthostoma* species
Unpasteurized milk	Tickborne EV, *Listeria, C. burnetii*
Insect contact	
Mosquitoes	EEE, WEE, VEE, SLE, Murray Valley EV, JEV, WNV, La Crosse v., *Plasmodium falciparum*

Sandflies	*Bartonella bacilliformis*
Ticks	Tickborne EV, Powassan v, *R. rickettsii, Ehrlichia, A. phagocytophilum, C. burnetii, B. burgdorferi*
Tsetse flies	*T. brucei (gambiense & rhodesiense)*
Occupation	
Exposure to animals	Rabies virus, *C. burnetii, Bartonella* sp.
Exposure to horses	Hendra virus
Work w/ primates	B virus
Laboratory workers	WNV, HIV, *C. burnetii, Coccidioides* sp.
Health care workers	VZV, HIV, influenza v, HIV, measles, TB
Person-to-person transmission	HSV (neonatal), HHV-6, VZV, EBV, VEE (rare), poliovirus, MMR, enteroviruses, Nipah v, B virus, WNV (transfusion/transplant/breast feeding), HIV, rabies v. (transplant), influenza v, *M. pneumoniae, TB, T. pallidum* (syphilis)
Recent vaccination	ADEM
Recreational activities	
Camping/hunting	Mosquito, tick agents (see above)
Sexual contact	HIV, *T. pallidum*
Spelunking	Rabies virus, *H. capsulatum*
Swimming	Enteroviruses, *Naegleria fowleri*

Season

Late summer/early fall	Mosquito, tick agents (see above), enteroviruses
Winter	Influenza virus
Transfusion & transplantation	CMV, EBV, HIV, tickborne EV, rabies, CJD, *T. pallidum, A. phagocytophilum, R. rickettsii, crypto, Histo, Coccidioides*

Travel

American northwest & northern midwest	Borrelia
American SW & Mexico	Coccidioides
Africa	Rabies, WNV, *P. falciparum, T. brucei (gamb., rhod.)*
Australia	Murray Valley EV, JEV, Hendra virus
Central America	Rabies, EEE, WEE, VEE, SLE, *R. rickettsii, P. falciparum, T. solium*
Europe	WNV, tickborne EV, *A. phagocytophilum, B. burgdorferi*
India, Nepal	Rabies virus, JEV, *P. falciparum*
Middle East	WNV, *P. falciparum*
Russia	Tickborne encephalitis virus
South America	Rabies, EEE, WEE, VEE, SLE, *R. rickettsii, B. bacilliformis* (Andes mountains), *P. falciparum, T. solium*
Southeast Asia, China, Pacific Rim	JEV, tickborne *EV*, Nipah virus, *P. falciparum, Gnanthostoma sp, T. solium*

Unvaccinated status	VZV, JEV, polio v, measles, mumps, rubella

Table 16.3 Laboratory Workup for Encephalitis & Aseptic Meningitis

General

Serum: CBC w/ differential, ESR, CRP, ACE; RPR & FTA-ABS, cryptococcal antigen

Cx: Bacterial, fungal; serologies: EBV, HIV (if Ab neg but high suspicion → plasma HIV RNA testing); *B. henselae* IgG, *Mycoplasma* IgM, ELISA + Western blot for *B. burgdorferi.* Acute & convalescent phase serologic testing for: HSV-2, EBV.

CSF: Cell count + diff, protein, glucose, opening pressure.

Cx: Bacterial, fungal, viral, mycobacteria

FTA-ABS (Se, not Sp; nonreactive test excludes dx; reactive nondiagnostic), AFB smear

PCR for: HSV-1, HSV-2, VZV, EBV, enteroviruses, mycoplasma, *M. tuberculosis*

VZV IgM & IgG; VDRL (Sp, not Se), cryptococcal antigen

B. burgdorferi serology (ELISA & Western blot); EIA capture, calculate IgG index

Respiratory/sputum: Cx for mycobacteria, DFA for respiratory viruses, PCR for mycobacteria, PCR for mycoplasma, viral isolation throat & nasopharynx swabs, viral cx.

Nasopharynx: Swab for viral cx. **Throat:** Swab for viral cx. **Stool:** Rectal swab viral cx.

Skin: Cx &/or DFA of skin lesions (if present) for HSV, VZV; PPD

DFA & PCR of skin bx specimen (if rash present) for *R. rickettsiae.*

Imaging: CXR, MRI brain w/ & w/o gadolinium.

Additional Workup as Indicated

Immunocompromised: *T. gondii* serum IgG, CSF PCR: CMV, JCV, HHV-6, WNV

Travel to endemic area: Blood: Serum complement fixing or immunodiffusion abs for *Coccidioides;* **CSF:** Complement fixing or immunodiffusion abs for *Coccidioides* sp.; Histoplasma antigen. **Urine:** Histoplasma antigen.

Approp. time of yr & geography: Serum: Acute & convalescent phase serologic testing for: SLE, EEE, VEE, HSV-2, EBV, La Crosse virus, LCMV, WNV, enteroviruses, adenoviruses, *M. pneumoniae, R. rickettsi*, *Ehrlichia chaffeensis, A. phagocytophilum.* WNV IgM. LaCrosse virus IgM.

Whole blood specimen: Smears for *Ehrlichia morulae*, PCR for *Ehrlichia, Anaplasma* species, PCR for *Anaplasma* species.

CSF: IgM for WNV & SLE, PCR for *Ehrlichia*, PCR for *Anaplasma* species.

(DFA = Direct fluorescent antibody. *Clinical Infectious Diseases* 2008:47:303.)

CHRONIC MENINGITIS

Def: Persistence of clinical meningitis ± abnl CSF, for >4 wk. Called recurrent meningitis if clinical episodes are separated by asymptomatic periods.

Sx: Nonspecific; variable combinations of fever, HA, stiff neck, focal

neurological signs.

Ddx

- Idiopathic: No cause identified in ~ 1/3 cases.
- Infectious:

  Bacterial: Partially treated bacterial; TB, syphilis, Borrelia, leptospirosis, listeriosis, brucellosis, M. pneumoniae.

  Fungal: Cryptococcus, coccidiomycosis, histoplasmosis, blastomycosis.

  Parasites: Cysticercosis, acanthamoeba, Angiostrongylus cantenensis, toxoplasma.

  Viral: EBV, HSV, HIV; enterovirus (in pts w/ agammaglobulinemia,"chronic enteroviral meningitis associated with agammaglobulinemia (CEMA)").
- Noninfectious/nonmalignant
- Sarcoidosis, Sjögren, Behcet's, SLE, Wegener's, Vogt-Koyanagi-Harada, other vasculitis
    - Drugs: NSAIDs, abx, IVIg, immunosuppressants, allopurinol, vaccination, intrathecal Rx
- Neoplastic: Lymphoma, leukemia, adenocarcinoma.
- Other rare causes: Hereditary auto-inflammatory periodic fever syndromes, cholesterol embolization, Fabry dz, SAH, migraine (mild), CSF leak.

Next several subsections cover specific causes of chronic meningitis. Others covered in Neurological ID (e.g., TB, Syhphilitic, Lyme, Cryptococcal, HIV), Neuro-Rheum (Behcets, Sjogren, Wegeners, SLE), & Neuro-Onc (Neoplastic meningitis).

HISTOPLASMA MENINGITIS

Endemic fungal infection in US, Central America, & South America. Typically self-limiting respiratory illness. Progressive disseminated histoplasmosis in the immunocompromised can present w/ severe meningoencephalitis or chronic basilar meningitis.

Dx: CSF cx often neg (despite large vol). Detection of CSF Abs by complement fixation establish dx (but high false + rate due to cross reactivity).

Rx: Liposomal amphotericin B 5.0 mg/kg daily for a total of 175 mg/kg given over 4-6 wk then itraconazole 200 mg bid for at least 12 mo, ART (for AIDS).

COCCIDIOIDES MENINGITIS

Soil fungus (Coccidioides immitis) endemic in SW US & Mexico. Usu self-limiting respiratory illness. Disseminated dz in genetically susceptible or immunocompromised can p/w meningitis (e.g., basilar, meningoencephalitis, mass lesion, hydrocephalus) months after primary infxn. Vasculitis with infarcts also occurs.

Dx: CSF shows chronic mononuclear pleocytosis (w/ eosinophilia), ↓ glucose, ↑ protein, & complement fixation antibody titer.

Rx: Fluconazole 400 mg/d for life, ± intrathecal amphoteracin B initially.

TOXOCARIASIS MENINGOENCEPHALITIS

Very rare helminth infxn (roundworm) of human w/ Toxocara canis (dog) or T catis (cat) via geophagia or exposure to contaminated soil. P/w meningitis/meningoencephalitis/

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myelitis w/ ocular lesion & hepatomegaly. Dx: ↑eos & + abs in serum or CSF, MRI w/ enhancing subcortical white matter lesions (˜ADEM). Rx: Antihelmintic therapy & corticosteroids.

EASTERN EQUINE ENCEPHALITIS

Most neuropathogenic arbovirus in US; most endemic in eastern N. America (July-October).

Clinical: Incubation: Mosquito bites causing cutaneous lesions; Prodrome: Fever, HA, flu-like sxs. Acute: Sz, CN palsies; HoNa, ↑ WBC. Chronic: Severe neuro sequelae in survivors.

Dx: CSF: Neutrophil-predominant pleocytosis & ↑ protein, normal glucose. EEG: Generalized slowing followed by lateralizing epileptiform discharges. MRI: Asymmetric or unilateral hyperintensity in the basal ganglia & thalamus. CSF & serum IgM confirms dx. Serum plaque-reduction neutralization test (PRNT) may be useful.

Rx: None available. High mortality.

VOGT-KOYANAGI-HARADA SYNDROME

Def: Idiopathic T-cell mediated autoimmune activation against melanocytes.

Features: (1) Aseptic meningitis: HA, fever, meningismus, fluctuating encephalopathy, & focal deficit (cranial neuropathy, hemiparesis, ataxia,

transverse myelitis). (2) Ocular: Chronic, bilateral panuveitis w/ retinal detachments & hyperemia of the optic disc, depigmentation of choroid (mottled “sunset glow” fundus, pale lesions [Dalen-Fuchs nodules] in inferior retina). (3) Auditory: Tinnitus, sensorineural hearing loss, & vertigo. (4) Cutaneous: Vitiligo, alopecia, poliosis of lashes, eyebrows, & scalp. Often seen in darkly pigmented young adults (Asian, Hispanic).

Dx: Granulomatous panuveitis w/ exudative retinal detachment. Fluorescein angiography. LP & neuroimaging not as helpful in establishing diagnosis.

Rx: Early high dose systemic steroids (1-2 mg/kg daily) w/ gradual taper over 6 mos lead to favorable prognosis. NSAIDs for maintenance. Immunomodulatory Rx for recurrent uveitis.

SARCOIDOSIS

Features: Noncaseating granulomatous inflammation of the lungs, skin, joints, eye, & CNS. Clinical recurrent meningitis uncommon. Asymptomatic chronic basal granulomatous leptomeningitis or arachnoiditis common. Other CNS manifestations include cranial neuropathies, obstructive hydrocephalus, chronic hypertrophic pachymeningitis manifesting as HA, granulomatous anterior uveitis, retinal vasculitis, hypothalamic inflammation, myelopathy, & mononeuropathies.

Dx: Tissue diagnosis (conjunctiva, bronchial, lymph node) is more reliable.

Ddx: Exclude opportunistic infections w/ immunosuppressive therapy.

Rx: Oral corticosteroids w/ duration depending on symptomatic response & the duration of the meningitis. Methotrexate might be adjunct therapy.

HYPERTROPHIC PACHYMENINGITIS

Def: Progressive thickening & fibrosis of the dura mater due to localized or diffuse inflammation. Usu idiopathic but can be a/w infections (TB, syphilis, Borrelia, fungal infection, HTLV1) & systemic inflammatory disorders (sarcoidosis, Wegener granulomatosis, Sjögren, giant cell arteritis, rheumatoid arthritis).

Clinical features: Middle age to elderly; male predominance. Typically p/w severe HA. Subacute optic neuropathy, ophthalmoparesis, deafness. Mass lesions are a/w focal neuro si/sx & sz. Spinal meningeal involvement a/w myelopathy.

Dx: ↑ ESR. CSF: ↑ Protein, few cells, nl gluc, nl OP. MRI: Enhancement of meninges (tentorium, falx, middle cranial fossa near the cavernous sinus). Pathology: Infiltration of inflammatory cells (granulomatous, lymphocytic, plasma cells); sparing pia & arachnoid.

Rx: HA & meningeal enhancement resolve w/ corticosteroid. Recurrence w/ steroid taper.

DRUG-INDUCED MENINGITIS

Uncommon. Usu 2/2 repeated exposure e.g., IVIg (>2g/kg dose, >6g/h infusion rate, w/o prehydration), NSAIDs, abx (e.g., trimethoprim, bactrim, PCN), Immunosuppressants (infliximab, MTX, cytarabine, azathiprine), Vaccination (MMR). Others: Allopurinol.

Clinical: Similar to other aseptic meningitis; often +systemic features (myalgia, arthritis, lymphadenopathy, rashes). Dx: CSF nonspecific but w/ pleocytosis (hundreds to thousands of WBCs w/ polymorph or eosinophilic predominance), mildly elevated protein, normal glucose. Rx: Rapid recovery after drug withdrawal.

RECURRENT MENINGITIS

RECURRENT PYOGENIC MENINGITIS

Risk factors: (1) Immunodeficiency: Agammaglobulinemia, complement deficiency. (2) Anatomical communication between subarachnoid space & skin or nonsterile cavity: Congenital defect: Meningocele, encephalocele, lesion in skull base or middle ear, persistent dermal sinuses of vertebral column, neural tube defect, neurenteric fistula; Acquired defect: Trauma (fracture of cribriform plate of the ethmoid), neurosurgery.

Rx: Abx, correction of anatomical or immunological d/o.

RECURRENT ASEPTIC MENINGITIS

Ddx: (1) Chronic inflammatory dzs: Sarcoidosis, Behcet, Wegener granulomatosis, Vogt-Koyanagi-Harada, Sjögren, SLE, vasculitis; (2) Drugs: NSAIDs, antimicrobials, IVIg, immunosuppressants, allopurinol, vaccination, intrathecal agents; (3) Structural lesions: Craniopharyngioma, epidermoid cyst, glioma; (4) Chronic infections manifesting as recurrent clinical episodes: syphilis, Lyme, brucellosis, fungal, HIV; (5) Reactivation of latent infection: HSV, EBV, Toxoplasma (Mollaret meningitis).

Mollaret meningitis

Recurrent self-limiting episodes of fever, HA, & meningismus (±sz & focal signs); abrupt onset, lasting 2-5 days, separated by asymptomatic intervals of variable duration, resolving after several episodes. ± a/w prior/concomitant genital herpes.

Dx: CSF in first HSV meningitis: Pleocytosis (PMN → lymphs, Mollaret

cells, ↑ protein & nl gluc; +HSV-2 cx 75% (not used in practice); +HSV-2 PCR. (Mollaret cells — large, multilobulated, mononuclear cells w/ faintly stained vacuolated cytoplasm, thought to be activated macrophages, also found in WNV, sarcoid, Behcet). CSF in recurrent episodes of HSV meningitis: Lower cell count, less protein, higher glucose; neg HSV-2 culture.

Rx: For severe recurrent episode, acyclovir (5-10 mg/kg q8h × 10 days). Long-term ppx not recommended; if freq episodes consider intermittent ppx (w/ valacyclovir 500-1,000 mg daily).

Benign recurrent lymphocytic meningitis

Similar to Mollaret (probably semantics—just a milder version of the same process). CSF: Lymphocytic pleocytosis from onset (no initial PMN), mildly ↑ protein, normal glucose, no Mollaret cells.

ACUTE BACTERIAL MENINGITIS

Definition: Inflammation of the leptomeninges (pia+arachnoid mater), due to bacterial infxn of CSF & arachnoid mater (in subarachnoid space & ventricles).

Epidemiology (NEJM 2006;354:44-53): 5/100,000 adults (>16 yo). Major causes (in adults, in developed countries): (1) Community acquired (CA-ABM): Streptococcus pneumoniae, Neisseria meningitidis; also Listeria monocytogenes if >50 yo or deficiency in cell-mediated immunity; (2) Healthcare-associated (HA-ABM): Staphylococci, aerobic Gram-neg bacilli, neurosurgery (depending on antimicrobial ppx), internal or external ventricular drains, after trauma (e.g., skull fracture w/ CSF leak).

Clinical features: Patients usu appear ill. Fever: Most have T > ~38°C (100.4°F); some are hypothermic. HA: Common, usu severe, generalized. Statistics from 279 cases of CA-ABM (NEJM 1993;328:21): Fever: 95% at presentation, 99% w/in 24 h; for many lasted >10 days. Nuchal rigidity: 88% on initial exam; often lasted >7days. MS Δ: 78% (most confused/lethargic, but ~1/4 responsive to pain only or unresponsive). “Classic triad”: fever, nuchal rigidity, MSΔ (NEJM 2004;351:1849) (Full triad present in ~60% w/ pneumococcal vs. ~30% w/ meningococcal meningitis.). 95% have at least two of these four: fever, nuchal rigidity, MSΔ, HA; 99% have at least one of these→ absence of all three makes ABM unlikely. Exception: Elderly, chronically ill may have no si/sx except lethargy.

Clues to etiology on exam: (1) Listeria: ↑ risk of sz; often p/w rhombencephalitis (ataxia, CN palsies, nystagmus). (2) N. meningiditis: Rash (64%; of these, ~90% are petechial; can be maculopapular). (3) Arthritis: in ~7% cases; most common w/ N. meningiditis. Requires joint aspiration. (4)

Infections elsewhere in body: “Seed areas”, e.g., otitis, sinusitis, sepsis.

Physical exam: (1) Vital signs. (2) “Meningeal signs” (nuchal rigidity/neck stiffness, Brudzkinski & Kernig signs, jolt accentuation of HA); focal deficits including CN palsies; rash, arthritis, signs of other infections (e.g., sinus infection). (3) Careful standard neurological exam (e.g., for mental status, CN palsies, etc.), otorrhachia.

P.144

Diagnostic value of classic meningitis signs: Low Se, moderate-high Sp (Clin Infect Dis 2002;35:46); Se & Sp defined w.r.t. predicting CSF pleocytosis:

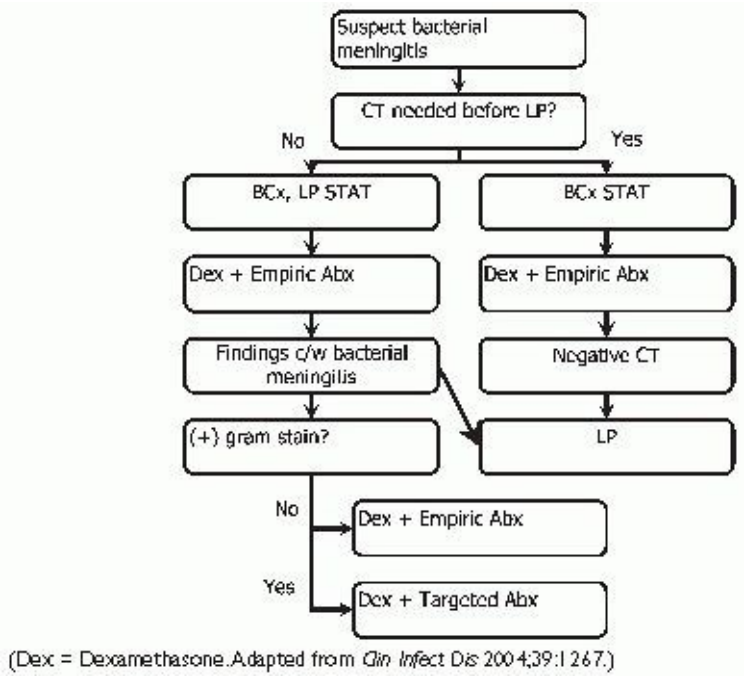
Nuchal rigidity: Pain w/ touching chin to chest (actively or passively): Se 30%, ˜70%

Brudzinski sign (passive neck flexion → hip flexion): Se 5%, Sp 95%

Kernig sign (w/ hip flexed, extend the knee → pain): Se 5%, Sp 95%

Jolt accentuation of HA (rotate head horizontally @ ˜3 Hz→ ↑ HA): Se 90%, Sp 60% (Headache 1991;3:167).

MANAGEMENT OF ACUTE BACTERIAL MENINGITIS



(Dex = Dexamethasone. Adapted from Clin Infect Dis 2004;39:1267.)

WORKUP

DO NOT DELAY INITIATION OF ANTIBIOTICS FOR IMAGING OR

LP!

If LP is delayed by CT: Before CT: Draw BCx × 2, start dexamethasone, start abx.

Who needs CT before LP? (ISDA Guidelines: Clin Infect Dis 2004;39:1267): Immunocompromised (HIV/AIDS, s/p transplant, immunosuppressive meds);h/o CNS dz (mass lesion, stroke, focal infection); new onset sz (<1 wk before presentation); seizure >30 min (rationale: sz → brain swelling → ↑ ICP); papilledema; ↓ LOC; focal deficit.

Serum: CBC, PT, PTT, CRP, chem7.

CSF: Routinely send: Gram stain & cultures, cell count & differential, protein & glucose. Further studies if +cortical si/sx or if Gram stain/c&s neg (see encephalitis w/u).

TREATMENT FOR SUSPECTED BACTERIAL MENINGITIS

- Initial abx based on local epidemiology & comorbidities (e.g., age, skull fracture, neurosurgical hx, immune status, coexisting infections; see Table 16.4
- Consider changing abx when pathogen & sensitivities avail: see Table 16.5
- Abx dosing: See Table 16.6. Abx duration: See Table 16.7
- When can treatment be completed at home? See Table 16.8

Table 16.4 Empiric Abx for ABM (Clin Infect Dis 2004;39:1267)

Risk factor, antibiotics (first line)	Probable pathogens
2-50 yo	
Vancomycin + ceftriaxone OR cefotaxime	*N. meningitidis, S. pneumoniae*
<50 yo	
Vancomycin + ceftriaxone	*S. pneumoniae*, *N. meningitidis*, *L.*

OR cefotaxime + ampicillin	*monocytogenes*, aerobic GN bacilli
Basilar skull fracture	
Vancomycin + ceftriaxone OR cefotaxime	*S. pneumoniae*, *Haemophilus influenzae*, group A b-hemolytic streptococci
Penetrating head trauma	
Vancomycin + cefepime, vancomycin + ceftazidime, OR vancomycin + meropenem	*Staphylococcus* aureus, coag-neg staph (esp *Staph epidermidis*), aerobic GN bacilli (including pseudomonas)
Post-neurosurgery	
Vancomycin + cefepime, OR vancomycin + ceftazidime, OR vancomycin + meropenem	Aerobic GN bacilli (incl *Pseudomonas aeruginosa*), *S. aureus*, coag-neg staph (esp *S. epidermidis*)
CSF shunt	
Vancomycin + cefepime, OR vancomycin + ceftazidime, OR vancomycin + meropenem	Coag-neg staph (esp *S. epidermidis*), *S. aureus*, aerobic GN bacilli (incl *P. aeruginosa*), *Propionibacterium acnes*
Impaired cellular immunity	
Vanco + ceftriax. OR cefotaxime + ampicillin	*L. monocytogenes*, Gram-neg bacilli
Dosing	
Vancomycin	1 g q12h (or 30-45 mg/kg/day div bid-tid)
Ceftriaxone	2 g q12h
Cefotaxime	2 g q4-6h

Ampicillin	2 g q4h
Cefepime	2 g q8h
Dexamethasone	0.15 mg/kg q6h × 2-4day, first dose ˜15 min before (or w/) first abx dose

Table 16.5 Specific Abx in ABM by Pathogen (Clin Infect Dis 2004;39:1267)

Organism	Standard therapy	Alternatives
S. pneumoniae		
Penicillin MIC		
<0.1 µg/mL	Penicillin G or ampicillin	Third-gen cephalosporin[a], chloramphenicol
0.1-1.0 µg/mL[b]	Third-gen cephalosporin[a]	Cefepime, meropenem
≥2.0 µg/mL	Vanco + third-gen cephalosporin[a],[c]	Fluoroquinolone[d]
Cefotaxime or ceftriaxone MIC >1.0 µg/mL.	Vanco + third-gen cephalosporin[a],[c]	Fluoroquinolone[d]
N. meningitidis		
Penicillin MIC		

<0.1 µg/mL	Penicillin G or ampicillin	Third-gen cephalosporin[a], chloramphenicol
0.1-1.0 µg/mL	Third-gen cephalosporin[a]	Chloramphenicol, fluoroquinolone, meropenem
L. monocytogenes	Ampicillin or penicillin G[e]	Trimethoprim-sulfamethoxazole, meropenem
Streptococcus agalactiae	Ampicillin or penicillin G[e]	Third-gen cephalosporin”
Escherichia coli & other Enterobacteriaceae[f]	Third-gen cephalosporin	Aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole, ampicillin
P. aeruginosa[f]	Cefepime[e] or ceftazidime[e]	Aztreonam[e], ciprofloxacin[e], meropenem[e]
H. influenzae		
β-Lactamase neg	Ampicillin	Third-gen cephalosporin[a], cefepime, chloramphenicol, fluoroquinolone
β-Lactamase positive	Third-gen cephalosporin	Cefepime, chloramphenicol, fluoroquinolone
S. aureus		
Methicillin susceptible	Nafcillin or oxacillin	Vancomycin, meropenem
Methicillin resistant	Vancomycin[g]	TMP/SMX, linezolid
S. epidermidis	Vancomycin[g]	Linezolid

***Enterococcus* species**

Ampicillin susceptible	Ampicillin plus gentamicin	—
Ampicillin resistant	Vancomycin plus gentamicin	—
Amp & vanco resistant	Linezolid	—

[a] Ceftriaxone or cefotaxime.

[b] Ceftriaxone/cefotaxime-susceptible isolates.[c] Consider addition of rifampin if the MIC of ceftriaxone is >2 µg/mL.[d] Moxifloxacin.[e] Addition of an aminoglycoside should be considered.[f] Choice of a specific antimicrobial agent must be guided by in vitro susceptibility test results.[g] Consider addition of rifampin.

Table 16.6 IV Abx Dosages for Adults w/ABM [Total daily, (Interval in h)]

Amikacin[a]	15 mg/kg (8)	**Meropenem**	6 g (8)
Ampicillin	12 g (4)	**Moxifloxacin**	400 mg (24)[b]
Aztreonam	6-8 g (6-8)	**Nafcillin**	9-12 g (4)
Cefepime	6 g (8)	**Oxacillin**	9-12 g (4)
Cefotaxime	8-12 g (4-6)	**Penicillin G**	24 MU (4)
			600

Ceftazidime	6 g (8)	**Rifampin**	mg (24)
Ceftriaxone	4 g (12)	**Tobramycin**[a]	5 mg/kg (8)
Chloramphenicol	4-6 g (6)[c]	**TMP-SMX**[d]	10-20 mg/kg (612)
Ciprofloxacin	800-1,200 mg (8-12)	**Vancomycin**[e]	30-45 mg/kg (8-12)
Gentamicin[a]	5 mg/kg (8)		

Total daily dose must be divided by dosing interval. [a] Based on ideal body wt in absence of obesity. Adjust to get peak serum conc 7-9 mg/L & trough < 1-2 mg/L for gentamicin or tobramycin & peak of 25-40 mg/L & trough < 4-8 mg/L for amikacin.

[b] No data on optimal dosage.[c] Higher dose rec'd for pneumococcal meningitis.[d] Dose based on TMP component.[e] Maintain serum trough conc of 15-20 µg/mL.

(Adapted from *Clin Infect Dis* 2004;39:1267.)

Table 16.7 Duration of Abx for ABM Based on Pathogen*

Neisseria meningitides	7
Haemophilus influenza	7
S. pneumonia	10-14
S. agalactiae	14-21
Aerobic *Gram-neg bacilli*	21

L. monocytogenes	≥21

*Not rigid—modify as clinically indicated. *Clin Infect Dis* 2004;39:1267.

Table 16.8 Criteria for Outpt Abx in Pts w/ Bacterial Meningitis

- Inpatient abx for >6 days
- Absence of fever for at least 24-48 h prior to initiation of outpatient therapy
- No significant neurologic dysfunction, focal findings, or seizure activity
- Clinical stability or improving condition
- Ability to take fluids by mouth
- Access to home health nursing for antimicrobial administration
- Reliable intravenous line & infusion device (if needed)
- Daily availability of a physician
- Established plan for physician visits, nurse visits, lab monitoring, & emergencies
- Patient and/or family compliance w/ the program
- Safe environment w/ access to a telephone, utilities, food, & refrigerator

(Adapted from *Clin Infect Dis* 2004;39:1267.)

Early prognosis/triage to ICU vs. ward: See %‘s complications/outcomes

above. Model based on retrospective analysis 269 cases ABM dx'd w/in 24 h of ED arrival (Ann Intern Med 1998;129:862). Three indep predictors: HoTN, AMS, szs. Outcome prediction: No. of factors at first abx dose → ˜ % death/sign. neuro deficit at discharge: 1 → 9%, 2 → 30%, 3 → 60%. Delay in abx → worse prognosis (untreated→ higher risk category). Worse prognosis w/ ↑age. Pts w/ higher risk category probably best served in ICU.

COMPLICATIONS OF BACTERIAL MENINGITIS

(NEJM 2006;354:44). %s for pts not routinely treated w/ dexamethasone therapy.

Systemic complications: Cardiopulm failure (29%), hyponatremia (26%), DIC (8%), arthritis (2-6%), endocarditis/myocarditis (<1%).

Deterioration of consciousness: Cortical involvement (15-20%), szs (15-23%), brain edema (6-10%), hydrocephalus (3-8%).

Neurological complications: Cerebrovascular (˜20%), arterial infarct/vasculitis (˜15%), venous infarct (˜4%), ICH (<1%), ↓ hearing (˜15%), brain abscess (<1%), myelitis (<1%).

Specific focal deficits: CN palsies: (CN:VIII → 14%, VI → 3%, III → 1%, VII → 1%), aphasia (2%), hemiparesis (4%), quadriparesis (1%).

Long-term outcomes: Death: 21%, vegetative state, <1%, severe disability (dependent for ADLs) 3%, moderate disability (perform ADLs but cannot resume premorbid activities) 10%, mild/no disability (resume premorbid activities) 66%. Long-term cognitive Δs 10%.

BRAIN ABSCESS

Definition: Focal infectious collection within the brain parenchyma.

Etiology: Bacteria invade brain by direct spread (˜40%) or hematogenous seeding. Direct spread: Usu single abscess; Sources: Subacute & chronic otitis media, mastoiditis (spread to inferior TL & cerebellum), frontal or ethmoid sinuses (spread to the FL), dental infection (usu → FL). Hematogenous spread: Usu multiple abscesses; location: distribution of MCA, grey-white jxn (due to microinfarction → BBB breakdown). Common associated infxns: Chronic pulmonary (e.g., lung abscess or empyema); skin, pelvic infxns, intra-abdominal; bacterial endocarditis, esophageal dilation & endoscopic sclerosis of esophageal varices, cyanotic congenital heart dz (mostly children). Trauma: Bullet wounds, other foreign objects; abscess sometimes develops yrs later. Neurosurgery: Abscess formation can be delayed. Idiopathic: No cause identified in ˜40% cases (Surg Neurol 1993;39:290).

Pathology: Depends on age of infection. 1-2 wk: “Cerebritis”: Poorly demarcated lesion + surrounding edema. 2-3 wk: Necrosis & liquefaction w/ fibrotic capsule around lesion.

Organisms: Most are bacterial and polymicrobial; in immunocompromised pts must also consider fungi. Vary w/ site of primary infection (see table below), age, immune status.

Immunocompromised patients: Wide range of organisms, including the above. Also: T. gondii, Listeria: esp in pts on steroids, Nocardia asteroides (common soil organism); airborne—enters via lungs, Fungi: Aspergillus, Cryptococcus, Coccidioides; Candida; Cladosporium trichoides & Curvularia spp. (cause mucormycosis).

Immigrants: Parasites are a frequent cause. Cysticercosis (T. solium): 85% of brain abscess in Mexico City (Ann Trop Med Parasitol 1999;93:69). Less common: Entamoeba histolytica, Schistosoma japonicum, Paragonimus species.

Organisms Commonly Causing Brain Abscesses (*NEJM* 2003;348:2125)

Source of infection	**Pathogens**
Paranasal sinuses	*Streptococcus* (especially *S. milleri*), *Haemophilus*, *Bacteroides*, *Fusobacterium*
Odontogenic sources	*Streptococcus*, *Bacteroides*, *Prevotella*, *Fusobacterium*, *Haemophilus*
Otogenic sources	*Enterobacteriaceae*, *Streptococcus*, *Pseudomonas*, *Bacteroides*
Lungs	*Streptococcus*, *Fusobacterium*, *Actinomyces*
Urinary tract	*Pseudomonas*, *Enterobacter*
Penetrating head trauma	*S. aureus*, *Enterobacter*, *Clostridium*
Neurosurgical procedure	*Staph*, *Strep*, *Pseudomonas*, *Enterobacter*

Endocarditis	*Viridans streptococcus, S. aureus*
Congenital cardiac malf.	*Streptococcus* (esp R → L shunts)

Presentation: Often nonspecific → delays in dx. General syndrome: HA (usu on side of abscess, gradual onset, severe, persistent). Confusion or drowsiness, focal or generalized szs (25%). Focal motor, sensory, speech deficits (50%)—days-weeks after HA onset. Behavioral si/sx. Fever, ↑ WBC, neck stiffness (15%). Vomiting, CN 3,6 palsies, papilledema (↑ ICP).

Ddx: Epidural or subdural empyema, septic dural sinus thrombosis, septic emboli, bacterial meningitis, mycotic aneurysm, necrotizing encephalitis (e.g., HSV encephalitis), brain tumor.

WORKUP & MANAGEMENT OF BRAIN ABSCESSES

Management: (1) Imaging + other diagnostic testing (usu NOT LP). (2) Emergent neurosurgical aspiration or excision (before starting antibiotics if possible). (3) Empiric abx. (4) Tailor management based on culture results & follow-up imaging.

Testing: (1) Blood cultures (draw immediately) (2) CT w/ contrast—fast, but less sensitive than MRI. Early: Irregular hypodensity w/o enhancement; +surrounding edema. Later: Ring enhancing lesion + surrounding edema (2) MRI w/ gado: Similar findings to CT, but more sensitive. Compare T1 pre & post-contrast; classic finding ring enhancing lesion. DWI: Helps distinguish ring enhancing lesions due to neoplasm vs. abscess. Abscesses: hyperintense on DWI (=restricted diffusion of pus); neoplasm hypointense or variable hyperintensity (but less than w/ abscess). (3) LP: Contraindicated if focal sx (e.g., unilateral HA) or signs ↑ ICP. If not contraindicated, pattern is variable; mean (range) for parameters: ↑ protein 250 mg/dL (90-425 mg/dL), ↓ glucose 39 mg/dL (11-58 mg/dL), ↑ WBC: 4,400/µL (80-5,000). Rarely resembles bacterial meningitis: indicates rupture intro ventricle. (4) Aspiration (stereotactic CT-guided or surgical), & cultures: Gram stain, aerobic, anaerobic, mycobacterial, & fungal cultures; special stains: acid-fast stain (for mycobacteria), modified acid-fast stain (for Nocardia), fungal stains. (5) Serology: Blood anti-Toxo IgG Ab, serum anticysticercal abs. (6) ± Brain bx + histopathology: Sometimes necessary.

Imaging findings: Depend on age of abscess.

- Early cerebritis: Poorly demarcated lesion, no necrotic center, surrounding edema
- Late cerebritis: Discrete lesion, necrotic center w/ early ring enhancement, surr. edema
- Encapsulation: Discrete w/ well developed capsule (ring enhancing), necrotic center, edema

Antibiotics: (1) Do NOT use: aminoglycosides, erythromycin, tetracycline, clindamycin, first generation cephalosporins: poor crossing of blood brain barrier. (2) Initial empiric antibiotic therapy (see table below): Taylor initial regimen based on presumptive & Gram stain results if available. Further tailor Rx after sensitivities are determined. (3) Steroids: Indicated in case of substantial mass effect on imaging (see table below). Reasons to avoid steroids unless indicated: ↑ risk abscess rupture into ventricle, ↓ abx penetration, confounds imaging findings (reduces contrast enhancement), slows abscess capsule formation. (4) Duration of antibiotics: Aspirated lesions: 6-8 wk (but depends on clinical course & f/u imaging. Sometimes can shorten course to 2-4 wk for surgically excised abscesses. Contrast enhancement can last for mos; alone is not indication for continued abx.

Initial Empiric Antibiotics for Brain Abscesses

Oral, otogenic, or sinus source	Metronidazole 15 mg/kg IV loading dose, then 7.5 mg/kg IV q8h **PLUS either:** *If suspected oral focus:* Penicillin G (4 MU/day IV q4h, **or** *if suspected sinus or otogenic source:* ceftriaxone 2 g IV q12h **or** cefotaxime 2 g IV q4-6h
Hematogenous	Vancomycin 15 mg/kg IV q12h* **PLUS** metronidazole (see above)
Neurosurg or penetrating TBI	Vancomycin 15 mg/kg IV q12h* **PLUS either** ceftazidime 2 g IV q8h **or** cefepime 2 g IV q8h

Steroids

Sx mass effect	Dexamethasone 10 mg IV ×1, then 4 mg IV q6h

* Adjust for renal fxn as approp.

Adapted from *UpToDate* “Treatment & prognosis of brain abscess”, Southwick et al., June 2009.

Prognosis (Clin Infect Dis 1992;15:394): Complications: Mass effect, hydrocephalus, focal deficits, szs, vent rupture. Szs: 30-60% cases (esp w/ frontal brain abscess).

Mortality: Most die if untreated; w/ Rx: ˜ 10-30% (Am J Med 2003;115:143). Predictors of higher morbidity & mortality: Rapid neurodeterioration or severe MSΔs before hospitalization, coma (>60% mortality), rupture into ventricle (>80% mortality).

NEUROSURGICAL MANAGEMENT OF BRAIN ABSCESSES

Indications for neurosurgery (drainage vs. excision): Dangerous mass effect; Relieve hydrocephalus; Definitive dx by stereotactic bx or excision; Rx by drainage or excision.

Timing: Early cerebritis: Abx, imaging, observe for encapsulation. Late cerebritis: Aspiration. Encapsulated: Excision or aspiration. Multiple: Drain or excise large lesions.

Stereotactic drainage vs. excision: Drainage generally preferred b/c less morbidity.

Needle aspiration: Best w/ CT guidance. If possible do prior to initiation of empiric abx (exception: w/ bacteremia, may start empirically based on BCx results if available).

Circumstances where drainage may be delayed or not done: (1) Early cerebritis w/o cerebral necrosis. (2) Inaccessible location (technical difficulty or eloquent area).

Follow-up imaging: Crucial: Usu at 48 h & 1 wk (sooner for neuro status Δ).

Excision: ↑ up-front morbidity vs. aspiration. May be preferred to aspiration if: trauma (e.g., remove foreign bodies/bone chips), encapsulated fungal abscess, multiloculated, no clinical improvement w/in 1 wk of aspiration, ↑ size after aspiration, signs of ↑ ICP. Abx course often shortened for excised lesions (2—4 wk). Excised lesions ↓ relapse rate vs. drained lesions.

Table 16.2 Possible Etiologies Based on Risk Factors & Epidemiology

Neurologic Infectious Diseases

NERVOUS SYSTEM LYME DZ

Definition: Tick-borne spirochete infxn caused by Borrelia burgdorferi (Borrelia garinii or afzelii in Europe/Asia). Most common tick-borne infxn in US & Europe.

Epidemiology: Endemic to NE corridor & parts of midwest; >90% cases occur in CT, DE, MD, MA, MN, NJ, NY, PA, RI, WI (MMWR Wkly Report 2007;56:573). 9/100,000 cases nationally; 35/100,000 in max affected states. In endemic areas 5%-10% have + serology (most asymptomatic). Peak incidence of Lyme infxn is late spring & summer.

General non-neuro presentation (NEJM 2001;345:115): Stage I: Early localized (weeks after infxn): Fatigue, malaise, HA, arthralgia/myalgias, fever, lymphadenopathy. Erythema migrans (EM). Stage II: Early disseminated (weeks-months after infxn): Persistent flu-like illness, dissem. EM rash, arthritis (60% untreated pts), heart block, myocarditis (in 5% untreated pts). Stage III: Late persistent (months-years): Acrodermatitis chronicum atrophicans, recurrent arthritis (large joints). Note: stages often clinically indistinct.

Specific presentations that support Lyme dx

Non-neurologic: (1) Derm: EM; ˜70% cases, usu early; painless, single erythematous lesion w/ central clearing (5—40 cm) at bite site or multiple disseminated lesions; Borrelia lymphocytoma; common in Europe; lymphoreticular proliferation of earlobe or breast areola 6-12 mo after infxn; Acrodermatitis chronicum atrophicans: esp in Europe; bluish red discoloration of distal extremities ˜1 yr after infxn → years later atrophic skin + prominent blood vessels. (2) Cardiac: Acute 2°-3° AV block; usu weeks-months after infxn. (3) Rheum: Recurrent brief mono-/oligoarthritis + swelling; usu weeks-years after infxn.

Neurologic presentations of Lyme dz: (Neurology 1996;46:619). Neuro involvement in ˜15% untreated cases, typically in stage II-III. Even untreated, most cases of acute CNS Lyme improve or completely resolve in weeks-months; ˜5% untreated pts → chronic neurologic dz. (1) Meningitis ± cranial neuritis or acute radiculoneuritis: up to 15% cases (si/sx: HA, neck stiffness, cranial neuropathies (esp CN VII palsy), painful radiculoneuritis w/ motor & sensory involvement). CSF antibodies & CSF PCR almost always positive. (2) Peripheral neuropathy/chronic radiculoneuropathy: ˜30% cases.

Mononeuritis multiplex. Unlike early radiculoneuritis, not a/w meningitis, cranial neuropathy, or CSF abs. (3) Chronic axonal polyneuropathy w/ radicular pain, distal paresthesias. (4) Encephalomyelitis: Rare, 0.1%-5% cases; most reported in Europe. Cognitive decline. Usu slowly progressive dz of white matter. (5) Encephalopathy: Mild cog. dysfxn. If exam, brain MRI & CSF nl likely 2/2 systemic infxn. (6) Transverse myelitis. (7) Optic neuritis in pedi population 2/2 infl. or ↑ ICP. (8) Chronic encephalomyelitis w/ spastic paraparesis, CN palsy, cognitive Δs, persistent CSF abs (seen in Europe w/ B. garinii infxn). Subtle cognitive dysfxn w/o inflammatory Δs in CSF but w/ + CSF abs.

Diagnostic eval: CLINICAL dx w/ lab data as supportive. High suspicion if h/o tick exposure & typical skin lesion. LP: do if e/o CNS involvement, incl severe, prolonged HA, nuchal rigidity, AMS, or subacute meningoradiculitis. Pts w/ isolated neuropathy (e.g., Bell palsy) do not automatically require LP.

Diagnosis of CNS Lyme: Need (1) & (2) & one of (3): (1) One of the neurologic entities described above & (2) Possible tick exposure in endemic area & (3a) EM (or histopathologically proven Borrelia lymphocytoma or acrodermatitis) OR (3b) + immunologic e/o exposure in serum OR (3c) + isolation of B. burgdorferi from cx,

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histology or PCR. Ideally also find immunologic e/o exposure in CSF (unless strictly PNS involvement or chronic dz). Definite dx of CNS Lyme difficult (low Se of cx from specimens other than skin lesions).

Laboratory Dx of Lyme Dz

	Comments	Sensitivity/Specificity
Serologic ab detection (must request specific species if European/ Asian Lyme suspected)	Often undetectable post-exposure after 2-6 wk; false+ in mononucleosis, AI dz, syphilis; false- 2/2 early abx; >1 mo most pts IgG +, suspect false+ if only IgM+; after abx, IgM & IgG titers slowly ↓ (but may remain ↑)	Se 20%—30% in first weeks (IgM) but >80% after 6 wk; Sp > 95%
Western blot	Confirmatory, usu not helpful if seroneg; IgG blot + if 5/10 bands present; IgM blot +	CDC recs: “two tier” test w/ ELISA & Western blot 56%-100% Se, 100%

	if 2/3 bands present	Sp; Se lower during acute period (<6 wk)
CSF ab detection	Less useful in nonacute presentation of CNS Lyme	Sensitivity ranges from 50%-100%, often near 90% for meningitis; up to 95% specific
Culture	Difficult to cx; low sensitivity of specimens other than skin	Skin cx: Se 80%, Sp 100% CSF cx: Se 10%, Sp 100%
PCR (serum, CSF or synovial fluid)	High rate of false +s; useful mainly if classic clinical presentation in endemic area & serum Lyme ab is neg	Se, Sp not well established; may be ˜100% but clinical signif. +PCR unclear; may detect DNA from dead bacteria
Cell-mediated immunoassay	Useful if suspicion high in seroneg pt (due to antibiotic use around time of exposure)	

AI = autoimmune.

Treatment: Approp abx can → dramatic improvements even w/ severe forms of meningoradiculitis. Consider repeat LP after 2 wk to eval response of pleocytosis, protein, & antibodies to Rx. IgG ab in CSF often persists for years after Rx. No known benefit of concurrent steroid administration. Vaccine 76% effective in preventing Lyme infxn. Prophylactic doxycycline 200 mg recommended if can be given w/in 72 h of removing tick that can be identified as Ixodes scapularis & is attached for >36 h (NEJM 2001;345:79).

Prognosis: Good Rx response in 90% of appropriate pts. No proven benefit of additional abx for “post-Lyme syndrome” (chronic fatigue, diffuse pain, cognitive impairment).

Treatment of Lyme Dz

	Antibiotic	**Dose**	**Side effects**
CNS Lyme w/ e/o infxn	IV ceftriaxone (first line)	2 g/day × 2-4	Rash, n/v/d, pseudomemb. colitis,

crossing blood brain barrier[a]	IV cefotaxime	wk	↑ LFTs
	IV PCN G	6 g/day 18-24 MU/day div q4h	Rash, n/v/d, HA, pseudomembranous colitis GI upset, n/v/d, black or hairy tongue
Peripheral neuropathy, isolated cranial neuropathies	Oral doxycycline (children >8 yo, nonpregnant F)	200 mg/day × 14-21 d	Photosensitivity rash in sun, pseudomembranous colitis
	Oral amoxicillin (children <8 yr & pregnant F)	500 mg tid × 14-21 d	Rash, diarrhea, pseudomembranous colitis, hemolytic anemia
Early localized or disseminated infxn	Same as for periph. neuropathy/ isolated cranial neuropathy, Alt: cefuroxime 500 mg bid × 14-21 days		Same as above
Serious cardiac or joint involvement	Same as for CNS Lyme		Same as above

[a] In Europe, oral doxycycline may be sufficient for CNS Lyme (*Lancet Neurol* 2008;7:690).

EHRLICHIOSIS

Presentation (J Vector Borne Dis 2008;45:273): 1-2 wk post-tick exposure, develop malaise, low-back pain, fever, HA, N/V, myalgias/arthralgias. Can also p/w pharyngitis, lymphadenopathy, encephalopathy.

Etiology: Ehrlichia chaffeensis = obligatory intracellular tick-transmitted bacterium. Vector: Most commonly A. americanum (lone star tick); can be other ticks (e.g., Ixodes). Reservoirs: White-tailed deer. Most infxns occur in S. central, SE, & mid-Atlantic states.

Dx: IFA ab titer to E. Chaffeensis, or + PCR (blood, CSF) & confirmation of

E. chaffeensis DNA, or immunostain + for E. chaffeensis Ag in bx, or +Cx (blood, CSF).

Rx: Doxycycline 100 mg bid PO or IV × 7-14 days; tetracycline 500 mg PO qid × 7-14 days.

NEUROSYPHILIS

Definition: Spirochete, Treponema pallidum, infxn. Varied presentation: "great imitator."

Epidemiology: Historically highest rates in southern states & in blacks. After decades of decline, rates of 1° & 2° syphilis on the rise, esp in HIV+ MSM.

Special considerations in HIV (Clin Infect Dis 2007;44:1222): (1) 1° syphilis infxn facilitates transmission & acquisition of HIV. (2) May see multiple, more persistent, or larger/deeper chancres, concurrent 1° & 2° stages at presentation, earlier development of gummas & more frequent CSF abnlities w/ higher cell count, higher elevation of protein, lower glucose. (3) Transient ↑ in viral load & ↓ CD4 count w/ syphilis infxn. (4) Neurologic dz seen earlier—HIV pts may be at ↑ risk for developing neurosyphilis. (5) Risk of neurosyphilis in HIV pts after adequate Rx for syphilis unknown. (6) More likely to have persistently + serologic & CSF tests despite Rx (unclear clin. significance). (7) If CD4 count ≤350 cells/mL or RPR titer ≥1:32 → need LP (Clin Infect Dis 2009;48:816).

Clinical Presentation

	Manifestations	**Comments**
1° (weeks after exposure)	**Chancre:** painless, indurated, nonpurulent ulcer	Resolves in 2-6 wk w/ or w/o Rx.
2° (4-8 wk after chancre)	3-10 mm **macular rash** (flanks, shoulders, arms, chest, back); w/o Rx → maculopap. rash (esp palms/soles); malaise, fatigue, HA, lymphadenopathy, sore throat; ± fever, wt ↓, myalgias/arthralgias, **condyloma lata**	Resolves w/o Rx but 25% recur, usu in first year. Rash is most common presenting sx in syphilis (˜90% pts).
Latent	Seroreactivity w/o other e/o	Infectious only via

(Early L: <1 yr postinfxn, Late L: >1 yr post-infxn)	dz	mother → child transmission
Early neurosyphilis (w/in weeks-years)	**Meningitis** (aseptic meningitis); **Cranial neuropathy; Ocular dz** (anterior uveitis, choroiditis, interstitial keratitis, retinitis, scleritis, optic neuritis); **Meningovascular dz w/ strokes:** typically brainstem & cerebral lacunar syndromes, 2/2 propensity for small arterioles; also ACA branch strokes.	25%-60% pts during 1° or 2° syphilis → early neurosyphilis; <5% symptomatic. Enters CNS early (→ CSF pleocytosis, ↑ protein, +CSF-VDRL or PCR). W/o Rx ˜25% do not clear organisms. W/ Rx most immunocompetent pts clear CSF infxn. BUT Rx does not preclude → neurosyphilis.
Tertiary syphilis, incl late neurosyphilis, usu years-decades after infxn	**Cardiovascular syphilis** (10%,˜20-30 y after exposure); **Gummatous dz** (15%, 1-46 y); **General paresis** (˜5%, 2-30 y): chronic dementia w/ prominent behavioral ↓, delusions; **Tabes dorsalis** (˜5%, 3-50 y): chronic spinal cord d/o, sensory gait & limb ataxia & ↓ bowel/bladder fxn; **Rapidly progressive dementia** w/ psychosis (esp HIV pts).	Pts w/ tertiary syphilis are not infectious. 1/3 untreated pts develop late sequelae.

JAMA 2003;290:1510.

Diagnostic Evaluation of Syphilis

Syphilis cannot be cultured. Direct e/o infxn requires darkfield microscopic exam or fluorescent ab stains of genital or mucosal lesions; neither test is sensitive.

Test	Nontreponemal serologic lipid antigen tests	Treponemal serologic tests	CSF tests (non-TP & TP)
	RPR, VDRL	TPPA, FTA-abs	RPR, VDRL, FTA-abs
Se, Sp	Se: 1°: 78%-86%, 2°: 100%, latent: ˜95%; false+ 1%-2% (AI dz, IVDU, TB, vaccinations, pregnancy, HIV, rickettsial infxn mononucleosis, endocarditis, other spirochetal infxns (titers usu <1:8 in false+‘s); false- in HIV; VDRL → +1-2 wk after chancre; rare false- w/ ↑ ↑ ↑ titers (prozone phenomenon)	False+ from other spirochetal infxns, malaria, leprosy; false-in HIV	CSF-VDRL Se 30%-70%, Sp 99% CSF-FTA-abs ˜100% Se, but low Sp
Note	Usu → neg after Rx, although upto 28% w/ 1° syphilis & 44% w/ 2° syphilis still + at 36 mo (*Ann Intern Med* 1991;114:1005)	most + for life despite Rx 10%-25% → neg.	↑ protein, ↑ lymphs (>5) support dx +CSF-VDRL (any titer) = neurosyphilis

(TPPA = Treponema pallidum particle agglutination, FTA-abs = fluorescent treponemal antibodies, Se = sensitive, Sp = specific, AI = autoimmune, TP = treponemal. *JAMA* 2003;290:1510.)

Which syphilis pts need LP? (Clin Infect Dis 2009;48:816): (1) Neuro/ocular sx, (2) Late latent syphilis or ? duration in HIV pt, (3) Active tertiary syphilis, (4) Rx failure (see below), (4) Serum RPR ≥ 1:32 or CD4 count ≤ 350 cells/mm^3 in HIV+ w/ or w/o neuro sx.

Imaging: Variable: nl, ischemic strokes w/ lacunar features, nonspecific WM lesions incl periventricular, mesiotemporal T2-weighted hyperintensities, meningeal enhancement, arteritis/vasculitis on angiography. Cases in recent years w/ mesiotemporal T2-weighted hyperintensities resembling HSV or limbic encephalitis.

Treatment of syphilis (PCN = penicillin; MU = million units, doxy = doxycycline)

1. 1°/2°/early latent dz: Benzathine PCN G IM 2.4 MU × 1. PCN allergic → doxy 100 mg bid × 14 days or tetracycline 500 mg qid × 14 d or ceftriaxone 1 g IV/IM qd × 10 days. Azithromycin may be effective in 1° & 2° syphilis but high % resistance in several major cities.

2. Late latent or nonneurologic tertiary syphilis: Benzathine PCN G IM 2.4 MU wkly for 3 wk. If PCN allergic: doxy 100 mg bid × 28 days or tetracycline 500 mg qid × 28 days.

3. Neurosyphilis, incl ocular or auditory dz: Aqueous crystalline PCN G 3-4 MU q4h × 14 days or 18-24 MU qd in continuous infusion × 10-14 d or procaine PCN 2.4 MU IM qd + probenecid 500 mg PO qid × 14 days; desensitize pts w/ PCN allergy.

Note: Beware Jarisch-Herxheimer reaction (fever/chills, HA, myalgias) from endotoxin release 4-12 h after first injection of PCN.

Follow up: (1) Repeat serologic tests & clinical f/u at 1, 3, 6, & 12 mo (and 24 mo for late latent/tertiary dz or HIV pts). (2) Treatment failure = persistent si/sx & failure of

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nontreponemal tests to ↓ fourfold (two dilutions) w/in 6-12 mo of Rx in early syphilis & 24 mo in late syphilis, or fourfold ↑ at any stage; 5% in non-HIV vs. 20% in HIV pts. (3) Repeat LP: 3-6 mo after Rx & then q6mo until CSF normalizes.

NEUROLEPTOSPIROSIS

General: Neurologic manifestations in 10%-15% of cases of leptospirosis. Consider in pts w/ acute hepato-renal dysfxn & altered MS in or from endemic areas. Consider in ddx of acute aseptic meningitis/meningoencephalitis a/w conjunctival suffusion & often w/ jaundice, although these findings may be absent.

Presentation: Typically fever, chills, HA, vomiting, AMS; szs & focal deficits less common.

Dx: Imaging: nl or may show diffuse cerebral edema. CSF: ↑ lymphs common (<500 cells/ mm^3). Can detect serum & CSF antibodies.

Rx: Options: PCN G, ampicillin & doxycycline for less severe cases.

Prognosis: Significantly altered MS & ↑ ↑ CSF protein are poor prognostic findings.

LEPROSY

Presentation (Microbiol Immunol 2001;45:729): Injury from direct invasion into Schwann cells & from inflammatory response. Magnitude of cell-mediated immunity determines dz extent. Two classic presentations: Tuberculoid (paucibacillary): Macular well-defined lesions w/ sensory loss. Lepromatous (multibacillary): widespread erythematous macules, papules, nodules. Mononeuritis multiplex—Autonomic/sensory/ motor neuropathies.

Etiology: Mycobacterium leprae, an obligate intracellular, acid-fast bacterium. Carriers include mice, armadillos, nonhuman primates.

Workup: Skin bx (full thickness, lesion edge). Serum phenolic glycolipid-1 (Sp for M. leprae)

Classifications: Ridley-Jopling: based on derm, neuro, & histopath findings: indeterminate (I), tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB) borderline lepromatous (BL), lepromatous (LL). WHO: Paucibacillary (PB) ≤ 5 skin lesions & no bacilli in skin smears or multibacillary (MB) w/ ≥6 lesions & may be skin smear +.

Rx: (1) PB: Dapsone 100 mg qd + rifampicin 600 mg qmo × 6 mo. (2) MB: Rifampicin 600 mg qmo + 300 mg clofazimine qmo+100 mg dapsone qd+50 mg clofazimine qd × 12 mo.

Corticosteroids: If leprosy reaction during Rx.

HIV INFECTION OF THE NERVOUS SYSTEM

Epidemiology: >1/2 HIV pts have neuro si/sx;complications include opportunistic infxns, direct effect of HIV virus on nervous system & adverse effects of antiretroviral Rx.

HIV-associated neuropathy (Neurol Clin 2008;26:821): Distal sensory polyneuropathy or antiretroviral toxic neuropathy (often indistinguishable); a/w ↓ CD4 ↑ VL in untreated HIV, age, nadir CD4 count, poor nutrition, DM, neurotoxic meds, ETOH. Sx: asymptomatic, burning pain, dysesthesias, allodynia; distribution typically stocking-glove. ↑ risk for entrapment neuropathy (e.g., carpal tunnel). Common antiretrovirals culprits: didanosine, zalcitabine, stavudine. Exam: ↓ sensation (can be all modalities, esp pain & temp; JPS often ok); ↓ ankle reflexes; strength typically preserved. Ddx for neuropathy in HIV: Mononeuritis multiplex, AIDP/CIDP (often w/ CSF ↑ protein & mild pleocytosis), polyradiculopathy (often 2/2 CMV in late HIV dz, CSF ↑ polys, ↑ protein, ↓ glucose; send CSF for viral PCR; Rx w/ IV ganciclovir, Foscarnet). Diagnosis: Exclude other causes/mimics of axonal sensory polyneuropathy (DM, B_{12} def, renal/liver dz, thyroid dz, syphilis) & concomitant exposure to neurotoxic meds commonly used in HIV pts (e.g.,

antineoplastic drugs, INH, thalidomide). EMG: Axonal, length dependent predominantly sensory polyneuropathy (but can be nl if mostly small unmyelinated fibers affected); uncommonly e/o demyelination/remyelination. ?Nerve bx or skin-punch bx to eval. nociceptive fiber density (↓'d) if unusual features. Treatment: Discontinue specific anti-retroviral if possible. Identify & treat confounding factors such as DM. Symptomatic Rx: TCAs, gabapentin, pregabalin, lamotrigine, duloxetine.

HIV-associated myopathy: (1) Inflammatory myopathy (polymyositis & dermatomyositis): Presentation similar to myopathy in non-HIV pts w/ prox weakness, myalgias, ↑ CPK. EMG c/w necrotizing myopathy. Bx = lymphocytic infiltrate. Polymyositis may be seen in IRIS. Rx: steroids. (2) Zidovudine myopathy: Fatigue, prox muscle weakness & atrophy, myalgias. More common after cumulative dose >200 g. Ragged

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red fibers seen on electron microscopy. Rx: d/c zidovudine; NSAIDs may be helpful. (3) Pyomyositis: Rare. Indurated, tender muscle mass. Dx: nl-high CPK. Ultrasound, CT scan & MRI helpful. Aspirate & culture. Rx: IV abx & surgical drainage as needed. (4) Nemaline rod myopathy: Subacute development of weakness & atrophy. ↑ CPK. Nemaline rods on bx w/ variable muscle necrosis & inflammation. Rx: steroids, ?IVIg. (5) HIV wasting illness: Prox weakness & atrophy w/ diarrhea, fever, cachexia. CPK usu wnl. (6) Diffuse infiltrative lymphocytosis syndrome: B/l salivary gland enlargement or xerostomia. Lymphocytic infiltrate on bx of minor salivary gland. May initially p/w myositis, neuropathy or mononeuritis multiplex. Rx: steroids. (7) Opportunistic infxn or tumor infiltration of muscle.

HIV-associated myelopathy ("vacuolar myelopathy"): ↓ incidence due to ART; ˜5%-10% untreated pts affected; CD4 usu <350/mm^3. Gradual onset weeks-months leg weakness, spasticity, gait ataxia 2/2 ↓ proprioception; urinary incontinence less common. Typically painless & mimics subacute combined degeneration of B_{12} deficiency. Commonly parallels development of HIV-associated dementia (HAD). Exam: Symm. spastic paraparesis; hyperreflexia, often sparing upper extremities; upgoing toes. Less commonly: impaired proprioception in legs less common. Typically no sensory level.

Dx: of exclusion. B_{12} level, serum syphilis & viral testing, CSF analysis w/ syphilis testing & viral PCRs, MRI spinal cord w/ gado. CSF: Few cells. MRI: Of spine often nl or nonspecific hyperintensity; later → cord atrophy. Pathology: Axonal injury, macrophage infiltration, & vacuolation of lateral/dorsal columns; T > C,L spine. Rx: Starting ART after vacuolar myelopathy usu does not improve sx. Symptomatic Rx of spasticity &

neurogenic bladder. Physical therapy.

Other Causes of Myelopathy in HIV

HIV myelitis a/w seroconversion: Self-limited, transient paraparesis. HIV abs may be neg. Send HIV viral load

HTLV I & II: Progressive painful spastic paraparesis, develops over years; common coinfxn w/ HIV in pts from HTLV endemic areas; more rapid decline in HIV+ than in HIV- pts. CSF = significant pleocytosis. Serum & CSF HTLV abs.

Epidural abscess: Fever, back pain, radicular sx. Rapidly → spastic paraparesis. MRI to visualize abscess. IV abx, ± surgical decompression.

VZV myelitis: Usu few weeks after skin eruption. Ipsil. weakness. Spinothalamic/dorsal column impairment. CSF pleocytosis. Dx w/ CSF PCR or cx. MRI: Enhancement at infxn site.

CMV myelitis: Rare (more often causes radiculopathy). CD4 usu $<50/mm^3$.

Rapidly progressive development of spinal cord lesion. CSF w/ marked pleocytosis, ↑ protein & often ↓ glucose. Dx w/ CSF PCR; also r/o retinitis & viremia. MRI: Enhancement of affected area. Rx: IV ganciclovir or Foscarnet.

HSV myelitis: Rare, presentation similar to CMV myelitis. Unlike CMV myelitis, much less marked CSF pleocytosis. Dx w/ CSF PCR & /or cx. Rx: IV high dose acyclovir.

Syphilis: Acute/subacute spastic paraparesis; impaired proprioception; bowel/bladder disturbance & sensory level. CSF: Pleocytosis, ↑ protein; + serum RPR, CSF VDRL or FTA-abs.

Spinal tuberculosis: CD4 count usu $< 250/mm^3$. Often in conjunction w/ TB meningitis.

Other: Vitamin B_{12} deficiency, idiopathic transverse myelitis, multiple sclerosis, lymphoma.

HIV-ASSOCIATED DEMENTIA (HAD)

References: Neurol Clin 2008;26:799; Lancet Neurol 2005;9:543.

Epidemiology: 15%-20% AIDS pts develop HAD; overall incidence ↓ w/ widespread ART. Milder cognitive dysfxn, HIV-assoc. neurocognitive d/o (HAND), w/ milder cognitive dysfxn, in up to 20% HIV+ pts.

Presentation: Progressive cognitive, behavioral, & motor dysfxn, similar to a subcortical dementia. ↓ memory, attention; psychomotor slowing. Agitation, apathy, change in personality; less commonly psychosis & mania. Motor impairment (tremor, gait disturbance, spasticity); may resemble Parkinson dz. Frontal release signs, hyperreflexia. Sx may develop acutely over weeks-months. Milder forms of cognitive motor dysfxn, such as HIV-associated neurocognitive disorder (HAND), may precede HAD.

Risk factors: Low CD4 count, anemia, ↑ age, low BMI, IVDU. CSF & plasma viral load (VL) do not clearly predict progression to HAD (but possible assn b/n CSF VL & severity of HAD). E4 isoform of apolipoprotein E is a/w severity of dementia (Neurology 2004;63:626).

Ddx: CNS lymphoma, CMV encephalitis, progressive multifocal leukoencephalopathy (PML), TB, cryptococcal meningitis, neurosyphilis, depression, vascular dementia, neurodegenerative dementia.

Workup: Imaging: May be nl, esp early on; cerebral/basal ganglia atrophy, ventricular enlargement & diffuse white matter T2 hyperintensities, often isointense on T1. MR spectroscopy: ↑ Choline (astrocytosis) & N-acetyl aspartate (neuronal injury). CSF: Often w/ pleocytosis & ↑ protein & IgG. Neuropsych testing: Psychomotor & memory deficits.

Rx: ART improves neuropsych testing in HAD (J Neurovirol 2000;6:84; Neurology 2006;67:311). In some pts w/ subacute HIV encephalitis, dementia improves markedly w/ ART → should be considered reversible cause of dementia. Controversy re: whether certain regimens superior; stavudine, zidovudine, abacavir, lamivudine, efavirenz, nevirapine, indinavir appear to have best CNS penetration. No clear role currently for neuroprotective agents (e.g., selegiline or minocycline) (Neurology 2007;69:1314).

Prognosis: Both HAD & HAND predict ↓'d survival regardless of whether on ART.

SEIZURES IN HIV

Epidemiology: ˜17% adults w/ HIV, smaller % in those followed regularly in HIV clinic.

Etiology: Opportunistic infxns, meds, metabolic & electrolyte disturbances, substance abuse. Opportunistic infxns most frequently a/w sz: Toxoplasmosis, cryptococcal infxn, & 1° CNS lymphoma (PCNSL). In ˜50% HIV pts w/ sz, no clear cause identified.

Rx: Beware drug-drug interactions w/ ART. Newer AEDS (e.g., levetiracetam, topiramate, gabapentin, lamotrigine) may be safer, although risks of first line agents like phenytoin or carbamazepine (effect on cytochrome p450 system) or valproic acid (previous in vitro studies showing it may induce HIV replication) are likely minimal (Seizure 2008;17:27).

IMMUNE RECONSTITUTION SYNDROME (IRS)

Epidemiology: ˜25% develop some form of IRS, <1% have neuro si/sx. Risk factors: ART-naïve, young age, initiating ART after recent dx of opportunistic infxn, rapid ↓ in HIV viral load.

Presentation: Usu weeks-months after initiating ART (up to 2-3 years). Neuro-IRS usu p/w unexpected new deficits/worsening of prior deficits (e.g., hemiparesis, encephalopathy, szs).

Dx: Mainly clinical. CSF pleocytosis common. MRI: WM & cortex lesions, often enhancing.

Rx: Benefit of steroids controversial; reasonable in pts w/ severe/progressive deterioration.

OPPORTUNISTIC NEUROLOGIC INFECTIONS IN HIV

General: Clinical CNS syndromes in HIV: meningitis, encephalitis, focal lesion(s). AIDS-defining neurologic illnesses include HAD, cryptococcal meningitis, toxoplasmosis, PML, PCNSL, & CMV encephalitis.

Initial eval: (1) Detailed H&P, incl travel, exposures, meds. (2) Eval risk factors for opportunistic infxns. (3) Don’t forget usual infxns seen in non-HIV pts incl CD4 count, VL, current ART, prophylaxis, CBC w/ diff, LFTs, hepatitis serologies, RPR, PPD, chest x-ray, crypto Ag, toxo serology.

Who needs brain imaging prior to LP? (*NEJM* 2001;345:1727)

(1)* *Immunocompromised pts, incl all HIV pts*. (2) ↓ *level of consciousness*. (3) *Focal neuro findings incl papilledema*. (4) *Age* ≥ 60. (*5*) *Known CNS lesion*. (*6*) *sz in past wk.*

MENINGITIS IN HIV PATIENTS

Main causes: Syphilis, Cryptococcosis, HIV & Tuberculosis

SYPHILITIS MENINGITIS

See Neurosyphilis/Syphilis & HIV.

CRYPTOCOCCOSIS

Definition: Infxn w/ Cryptococcus neoformans, an encapsulated yeast transmitted in the environment via respiratory route & not directly from person to person.

Epidemiology: Mainly immunocompromised (HIV/AIDS, immunosuppression after organ transplant). Most common CNS fungal infxn in HIV; previously ˜5%-10% AIDS pts; remains among most common causes of mortality in HIV in developing countries.

Much less common on fluconazole prophylaxis & ART. Typically occurs w/ CD4 < 100 cells/mm^3. C. neoformans var. gattii can → meningitis in immunocompetent hosts. Other risk factors: Pigeon excreta.

Presentation: Usu p/w subacute-chronic meningitis; also form cryptococcomas in dilated perivascular spaces. Can present fulminantly. Typical si/sx: Low-grade fever, HA, n/v, cognitive impairment, ↓ level of arousal. Multiple cranial neuropathies due to basal meningitis, esp optic & acoustic nerves. Rarely p/w focal neuro findings or szs. Neck stiffness & photophobia less common in HIV pts. Extraneurologic: Diffuse pulmonary infiltrates, lobar consolidation or cavitating lesion, rash (papules w/ similar appearance to molluscum contagiosum), UTI.

Workup: Serum cryptococcal antigen ˜94% sensitive but not specific for CNS dz; negative serum test makes cryptococcal meningitis extremely unlikely. CSF: Cryptococcal Ag test ˜91% Se, ˜95% Sp; opening pressure often ↑ ↑ ↑; CSF itself often nl (esp in HIV, despite abundant organisms), but can see ↑ lymphs (>20 cells/mm^3), ↑ protein & ↓ glucose. MRI: often nl; may show leptomeningeal enhancement & thickening but w/ poor sensitivity early in the course & hydrocephalus if left untreated; rarely pseudocysts or cryptococcomas in deep perivascular spaces. Rarely may present as enhancing WM lesions (previously thought to be result of amphotericin toxicity) (Eur J Neurol 2007;14:350). Definitive dx: + CSF cx (Se 75%-95%), + CSF India ink stain (Se 25%-50%), or + CSF cryptococcal Ag (Se 91%).

Treatment: Three stages: induction, consolidation, maintenance.

Induction: (1) Amphotericin B (1 mg/kg/day) w/ flucytosine (100 mg/kg/day) × min. 14 days. Monitor peak levels of flucytosine for adverse effects incl GI & heme toxicity. Amphotericin can → nephrotoxicity, hepatitis, marrow

suppression, pancytopenia. May be a role for amphotericin B w/ high dose fluconazole (800 mg/day) instead of flucytosine given its toxicities & unavailability in developing countries (Clin Infect Dis 2009;48:1775). (2) Serial LP: If OP ≥ 25 cm H_20 remove CSF to ↓ CP by 50% (usu ˜20-30 cc required). Cont. until OP nl × days. Alternatively: Lumbar drain or VPS. (3) ART initiation in ART-naive HIV pts. (4) No role for steroids or acetazolamide for Rx of ↑ ICP (Clin Infect Dis 2000;30:47; Clin Infect Dis 2000;30:710; Clin Infect Dis 2002;35:769).

Consolidation: Stop amphotericin B & flucytosine. Start: Fluconazole 400 mg PO qd for at least 10 wk. Repeat LP 2 wk after induction Rx & before beginning maint Rxonly proceed to maint if CSF is sterile.

Maintenance: Fluconazole 200 PO mg qd. May consider stopping when pt is asymptomatic & sustained CD4 > 100 × >1 yr. Restart maintenance Rx if CD4 ↓ to <100.

Prognosis: Worse outcome a/w high OP, high organism burden, AMS, poor CSF inflammatory response. (NEJM 1992;326:83, Lancet 2004;363:1764. NEJM 1997;337:15). Uniformly fatal w/o Rx. Mortality much improved w/ introduction of amphotericin B but even in developed countries 10-wk mortality still ˜10%-25% (AIDS 2006;20:2183).

CRYPTOCOCCAL MENINGITIS IRS

Recurrent sx of cryptococcal meningitis w/ sterile CSF & lower Ag titer develop in 6%-30% of treated pts after initiating ART. Median time after initiating ART ˜30 days (but may occur months later). Risk ↑ if started on ART <30 days after dx (Clin Infect Dis 2005;40:1049-1052). Much less frequently, pts w/o previously known cryptococcal meningitis p/w sx & reactive CSF Ag but neg CSF cx. Best Rx unclear re: continuing ART, retreating for crypto meningitis, steroids.

HIV ASEPTIC MENINGOENCEPHALITIS

Epidemiology: Aseptic meningitis reported ˜25% 1° HIV infxn (Ann Intern Med 1996;125:257).

Presentation: Acute-subacute, HA ± meningismus, fever, n/v, lymphadenopathy. Often occurs at time of 1° HIV infxn or when CD4 count declining. Pts w/ neuro sx at seroconversion have higher mean CSF viral loads (Clin Infect Dis 2000;30:962). HIV meningoencephalitis also reported in chronic HIV pts, presumably when CNS HIV no longer under good control; typically CSF HIV VL > plasma.

Dx: Test pts w/ clin syndrome c/w meningoencephalitis for HIV (5% pts w/ clin & CSF findings c/w aseptic meningoencephalitis retrospectively found to

be HIV+ but not dx'ed at time of presentation [Clin Infect Dis 2008;47:433]). Typical CSF: Mononuclear pleocytosis >20/mm^3 cells.

Rx: Potential initiation of ART or changing to an ART regimen w/ improved CNS penetration.

P.157

CNS TUBERCULOSIS

Epidemiology: In 2007, >9 mil new TB cases, 1.75 mil deaths (WHO 2009). ˜20% a/w HIV. Most common cause of death worldwide in HIV+ pts. CNS TB ˜1% of TB cases. Risks: Pulm TB, HIV+, young age, malnutrition, alcoholism, malignancy, DM, travel to endemic area.

Pathogenesis: Mycobacterium tuberculosis is an aerobic, nonspore-forming acid fast bacillus, grows very slowly in conventional cx medium. Transmission: Inhalation of droplets. Seeds the brain, spinal cord, & meninges during 1° infxn, forming small foci of infxn, known as "Rich foci," which can erupt into CSF → thick exudate of inflammatory material that encases arteries & cranial nerves primarily in basal meninges. HIV-associated CNS tuberculosis typically from reactivation of prior infxn. Can develop vasculitis affecting circle of Willis, vertebrobasilar system & MCA perforating branches → strokes.

Presentation: Classic (subacute basal meningitis): 2-8 wk of nonspecific prodrome → low-grade fever w/ HA & CN palsy (e.g., VI, III). Specific complications: Endarteritis: → ischemic stroke (base of brain, peri-Sylvian, basal ganglia); Ventriculitis: Obstruction of CSF flow → hydrocephalus ↑ ICP. Tuberculoma (unruptured large tubercles) or TB abscess (rare): mass lesion. Radiculomyelitis: Subacute paraparesis w/ radicular pain & bladder disturbance, adhesive arachnoiditis. May develop fulminant presentation like nonmycobacterial bacterial meningitis. Si/sx in HIV+ similar to HIV- (J Infect Dis 2005;192:2134). Active pulmonary dz in 30%-50% of pts (Infection 2003;31:387).

Ddx: Nontuberculous bacterial meningitis, viral meningitis, parasitic & fungal meningitis, rheumatoid dz, sarcoidosis, idiopathic pachymeningitis, carcinomatosis of meninges.

Workup: PPD+ in 50%-80% pts; false negs more often in HIV+ pts. If PPD neg initially but suspicion is high, repeat PPD in 1-3 wk may ↑ increase sensitivity. CSF: (See table below.) ↑ OP, ↑ lymphs (neutrophil-predom CSF can be seen early & after initiating abx), ↑ protein, ↓ gluc. AFB stain (Se ˜25%; ↑ Se w/ ↑ vol CSF & longer duration of microscopic eval (J Clin Microbiol 2004;42:378)—but should ALWAYS send to attempt determination

of drug sensitivity profile), cx (several weeks, Se 50%-80%), PCR (Se 50%-80%, Sp 90%-100%). CSF in HIV+ pts similar to non-HIV+ pts, although pleocytosis & ↑ protein may be less (J Neurol Sci 2000;181:118). Serum: Enzyme-linked immunospot assay (T-cell based assay of IFN-g release) predicts active TB; when combined w/ PPD overall Se 96%; useful for dx latent TB when PPD is unreliable (anergy, BCG vaccine exposure). CXR: may show military TB; abnl in ˜50% w/ TB meningitis.

CSF Profile in TB Meningitis

WBC (per mm^3)	50-1,000, lymph predominant (but 15% PMN predom early)
Protein	50-500
Glucose	<45 in >80% of pts; progressive decline in CSF glucose on serial LPs is particularly characteristic
+ AFB smear	Se ˜25% but ↑ to >80% w/ repeat smears & using the pellet on the spun specimen of CSF
+ culture	Se 50%-83%; cx + in ˜50% w/ first sample, ↑ to > 80% if 4 large volume (20-45 cc) samples are cultured; culture remains (+) up to 1 wk after initiating anti-mycobacterial therapy
+ PCR	˜100% Sp, but 48%-100% Se; PCR should always be performed w/ culture in order to determine drug sensitivity profile

MRI findings in TB Meningitis: “Classic triad”: Basilar meningeal enhancement, hydrocephalus & infarcts (Eur Radiol 2003;13:1876). >80% have meningeal enhancement, esp of basal cisterns. Hydrocephalus: communicating or obstructive; unlike bacterial meningitis where hydrocephalus is typically transient, in TB meningitis is progressive. Arterial imaging: Focal narrowing, esp distal ICA & prox MCA & ACA. Radiologic appearance usu similar in HIV±; may be ↓ meningeal enhancement w/ HIV (J Neurovl Sci 2000;181:118).

Rx (See table): First line: INH, rifampin, pyrazinamide, ethambutol, & streptomycin 9-12 mo. Second line: Quinolones & amikacin. Consider MDR-TB in any HIV-infected pt, any pt previously treated for TB, any pt from an areas w/ high rates of endemic MDR-TB. ?Steroids: Controversial; may

prevent death & neuro sequelae in non-HIV pts (Cochrane Database Syst Rev 2008;CD002244) but no apparent survival benefit in HIV pts (NEJM 2004;351:1741). TB IRS: Reported; unclear how to treat; after excluding active infxn requiring Rx, unclear whether to continue ART or give steroids.

Standard Regimen for Rx of Tuberculosis

	Dose	Significant adverse effects
Isoniazid	300 mg qd × at least 9 mo (or 6 mo after cx consistently negative)	Peripheral neuropathy, give pyridoxine prophylactically; hepatotoxicity, lupus-like syndrome
PLUS		
Rifampin	600 mg qd × at least 9 mo (or 6 mo after cultures consistently neg)	Orange urine & tears, hepatotoxicity, thrombocytopenia; substitute rifabutin for rifampin in HIV+ pts due to freq interaction w/ ART
PLUS		
Pyrazinamide	15-30 mg/kg (max 2 g) qd; treat for the first 2 mo of therapy	Hepatotoxicity, elevated uric acid
PLUS		
Ethambutol	15-25 mg/kg (max 2.5 g) qd; treat for first 2 mo of therapy	Optic neuritis, rash

(Adapted from *Continuum: Lifelong Learning in Neurology* 2006;12:111.)

Prognosis: 10%-50% fatality; ↑ if delayed treatment. Coma & death in 4-8 wk if untreated. ˜15%-25% w/ long-term morbidity (cognitive & behavioral impairment, focal deficits, CN palsies incl vision or hearing loss, epilepsy). Mortality ↑ in HIV+ pts but no good mortality comparisons in era of ART.

Spinal Cord Involvement of Tuberculosis

Includes radiculomyelitis involving spinal cord & roots, tuberculomas of the spinal cord, epidural abscess, & spinal cord infarction from arteritis of cord vessels

Thoracic & lumbar cord most commonly affected by radiculomyelitis

P/w: Back pain, paresthesias, weakness, & bowel/bladder dysfxn.

MRI: Vertebral body lesions involving disc spaces; paraspinal cord abscess, often in psoas muscles; obliteration of spinal subarachnoid space; thickened clumped nerve roots w/ linear/nodular enhancement; T2 Δs from cord edema, stroke, or myelitis

ENCEPHALITIS IN HIV

CMV ENCEPHALITIS

General: CMV (Herpes family) is most common opportunistic infxn in HIV. CD4 count usu <50 cells/mm^3. Common sites: retina, GI tract, lung, liver, brain, spinal cord, nerve roots

Presentation: Subacute progressive encephalopathy w/ impaired memory, inattention, behavioral Δs, gait disturbance, & HA. Onset typically more rapid than in HIV dementia.

Workup: Imaging: May be nl; commonly: atrophy, vent enlargement, nonspecific T2 hyperintensities. Vent enhancement reflecting CMV ependymitis ˜30% cases (characteristic, but nonspecific) (Neurology 1997;48:A388). Mass lesions rare. CSF: nl or ↑ protein & ↑ lymphs. CMV PCR from CSF in pts w/ HIV: Se 80%-100%, Sp 75%-100%. Culture Se 10%-25%. Extraneurologic clues: CMV viremia, retinitis, HoNa (from adrenal gland involvement).

Rx: Ganciclovir 5 mg/kg IV bid initially then qd or foscarnet 90 mg/kg IV bid

or cidofovir 5 mg/kg qwk × several weeks followed by prolonged 1/2-dose maintenance Rx.

HIV ENCEPHALITIS

See “HIV aseptic meningoencephalitis.”

HIV DEMENTIA

See “HIV-associated dementia.”

FOCAL LESIONS IN HIV

Main causes: Tuberculomas, Toxoplasmosis, Primary CNS Lymphoma (PCNSL) & Progressive multifocal leukoencephalopathy (PML)

Focal Neurologic Lesions in HIV+ Pts

	Cerebral toxoplasmosis	PCNSL	PML
Time course	Rapid, presents w/in days of onset	1-2 wk	Indolent, evolves over wks
Clinical presentation	Focal findings; AMS, HA, fever, constitutional sx	Often focal si/sx incl hemiparesis, aphasia, apraxia, hemisensory Δs, visual filed cut	
Radiologic findings	Ring-enhancing lesions, often multiple, w/ mass effect & edema	Enhancing, diffuse/solitary, lesion, +mass effect & edema	Nonenhancing demyelinating WM lesions w/o mass effect
Location of lesions	Basal ganglia, thalamus, gray-white junction	Deep white matter, periventricular	WM near cortex; no mass effect, nonenhancing. ↑ T2 & ↓ T1 signal

Diagnosis	Serum IgG abs, response to Rx	CSF EBV PCR ± brain bx	CSF PCR for JC virus

(*Lancet* 1996;348:445-452.)

TUBERCULOMAS (see also CNS tuberculosis)

Foci of TB infxn in parenchyma found in 10%-50% CNS TB cases. Grow but do not erupt into subarachnoid space. Tuberculous abscesses (pus-filled encapsulated cavities w/ viable bacilli) rare. Sx depend on location (e.g., focal deficits, szs, e/o increased ICP).

Dx: CSF: wnl or w/ slightly ↑ protein; cx rarely +. Imaging: Variable. (1) Noncaseating granulomas: Usu hypo or isodense on CT, hypointense on T1, & hyperintense on T2 imaging; in CT & MRI enhancement is homogeneous. (2) Caseating tuberculomas w/ solid centers: Ring-enhancing capsule w/ intermediate signal intensity on T1 & T2. (3) Caseating tuberculomas w/ liquid centers: Hypodense w/ rim enhancement on CT & hypointense on T1 & hyperintense on T2 w/ rim-enhancement.

CEREBRAL TOXOPLASMOSIS

General: Most common focal cerebral lesion in HIV+ pts. Caused by Toxoplasma gondii, obligate intracellular protozoan parasite. Transmitted via cat feces & undercooked meat. Symptomatic in ˜10% cases: mononucleosis-like illness w/ prominent lymphadenopathy. IgG seropositivity varies worldwide; IgG abs found in ˜50% Americans & 90% French. HIV pts: typically = reactivation of latent infxn (evidenced by lack of IgM antibodies). Incidence ↓ ↓ in era of ART & toxoplasma/pneumocystis prophylaxis. Risk factors: CD4 count < 200 cells/mm^3, not on ART or toxoplasmosis prophylaxis.

Presentation: Evolves over days-months. ˜50% p/w HA & fever; confusion, lethargy, & szs also common (NEJM 1992;327:1643). Focal findings: hemiparesis, ataxia, & CN palsies; Extrapyramid sx (e.g., hemichorea & hemiballismus) not uncommon due to predilection for BG.

Dx: Serum: IgG abs+ in ˜80% (if neg consider alternative dx). IgM abs of little utility. Imaging: CT: single or multiple contrast-enhancing lesions, often w/ ring or nodular enhancement; common in basal ganglia, thalamus, corticomedullary junction. Definitive dx: Identification of tachyzoites from lesion bx. CSF: ELISA is Se & Sp; CSF IgG ≥1:64 highly specific. CSF PCR is Sp but Se variable. Empiric Rx: trial of pyrimethamine & sulfadiazine to

confirm dx in HIV+ pt w/ + serum IgG, not on toxoplasmosis prophylaxis; avoid coadministration of steroids (may confound clinical & radiologic response). Typically see clinical improvement in 1-2 wk (50% by Day 3, 86% by day 7 & 91% by day 14) & radiologic improvement in 2-3 wk (NEJM 1993;329:995).

Rx: In HIV pts separated into acute Rx, maintenance therapy & 1° prophylaxis.

- Acute: Pyrimethamine: Load 100-200 mg, then 75-100 mg daily AND sulfadiazine 6-8 g div qid OR clindamycin 600-900 mg qid AND folinic acid 10-50 qd. Comments: (1) Rx >6 wk or until enhancing lesions resolve. (2) Dose-limiting effects of pyr & sulf: fever, rash, leukopenia & ↓ plts, renal failure. (3) Clindamycin SEs: Diarrhea, nausea, rash, & granulocytopenia. (4) Alternative regimens: TMP/SMX, pyrimethamine w/ clarithromycin, azithromycin or dapsone, atovaquone.
- Maintenance: 25-50 mg qd AND sulfadiazine 3-4 g total daily dose div qid OR clindamycin 300-450 mg qid AND folinic acid 10-50 mg qd AND appropriate ART regimen. Comments: (1) Consider discontinuing maintenance regimen once CD4

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count sustained at 100-200 cells/mm^3. (2) Toxoplasmosis IRS uncommon but cases have been reported (Ann Int Med 2009;150:656); watch closely for signs of recurrent or worsening infxn after initiation of ART.

- 1° prophylaxis: TMP-SMX DS 1 tab qd OR dapsone 50 mg qd AND pyrimethamine 50 mg wkly AND folinic acid 50 mg wkly. Comments: (1) Recommended for sero+ pts w/ CD4 < 100 cells/mm^3. (2) Seroneg pts advised to avoid undercooked meat & cat feces.

PRIMARY CNS LYMPHOMA (PCNSL)

Epidemiology: Incidence of non-Hodgkin lymphoma, incl PCNSL, ↑'d 100× in HIV+ pts; overall incidence ↓ w/ introduction of ART. At risk: CD4 < 50 cells/mm^3.

Presentation: Focal deficits (e.g., hemiparesis, sensory Δs, homonymous hemianopsia).

Dx: Imaging: Solitary or few large (2-4 cm) lesions, usu contrast-enhancing. Isodense or hypodense on CT; MRI: ↓ T1, ↑ T2 signal w/ significant surrounding edema. Radiologic hallmark is periventricular lesion; lesions also

often found in deep WM. SPECT & FDG-PET may be helpful in distinguishing between infxn & PCNSL. CSF: EBV PCR Se 90%-100%, Sp ˜ 100%. CSF cytology insensitive (<20%). Brain bx: Stereotactic bx of focal lesion, esp if empiric Rx for cerebral toxoplasmosis does not result in clinical and radiologic improvement in 1-3 wk [˜65% lesions that do not respond to empiric toxoplasmosis Rx determined on bx to be PCNSL (J Neurol Sci 1999;163:32)].

Rx: (1) Chemotherapy, incl high dose methotrexate. (2) WBXRT [though ↑ risk of leukoencephalopathy in HIV (Lancet Neurol 2009;8:581)]. (3) ART.

Prognosis: Worse in HIV+PCNSL. Median survival ˜3 mo; <10% live >1yr (Eur J Cancer 2001;37:1296).

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Epidemiology: Incidence has not ↓ in era of ART; ˜5% pts w/ AIDS develop PML.

Pathogenesis: Reactivation of latent infxn w/ JCV, a polyoma virus. Most pts JCV+ by adolescence; latent in bone marrow, kidneys, lymphoid tissue (not CNS). JCV viremia occurs in immunosuppression → hematogenous spread to CNS. JCV infects oligodendrocytes & astrocytes → noninflammatory demyelination & cell death.

Presentation: Slow progressive neurologic decline weeks-months, focal deficits incl ↓ cognition, vision, strength, gait, coordination. Szs rare (Am J Med 1995;99:64).

Dx: Gold standard = brain bx, but characteristic clinical & brain MRI w/ +CSF PCR for JC virus usu sufficient for dx. Imaging: CT: nl or may see hypodense subcortical lesions w/ little or no mass effect. MRI: Asymmetric multifocal subcortical nonenhancing T2 WM abnlities w/ sparing of subcortical U fibers; T1 lesions usu hypo/isointense; less freq affects cortex. CSF: w/ JCV PCR 72%-100% Se, 92%-100% Sp; if ↑ ↑ suspicion should test multiple samples; false neg esp common on ART & early PML. Serum: Useless (80% of gen population sero+ for JCV).

Rx: Initiation of ART is only proven Rx; ˜ 50% improve w/ ART. IFN-α & cidofovir have been tried as therapy. Mirtazapine may be of some benefit (in open pilot case series only thus far) (Arch Neurol 2009;66:255).

Prognosis: Worse w/ ↑ ↑ JCV viral load, lower CD4 count & lack of contrast enhancement.

PML IRS

Can occur weeks after initiating ART. Presentation typically milder than

PML. Often see progression of prior dz or new lesions on imaging. Lesions more likely to enhance in PML IRS compared w/ PML, although lack of enhancement does not preclude dx of PML IRS.

Rx: Steroids generally reserved for pts w/ severe ↓ in neuro status, sig. mass effect or swelling or e/o herniation, ?benefit in less severe cases (Neurology 2009;72:1458).

NEUROLOGIC INFECTIONS IN TRANSPLANT PATIENTS

Initial approach: (1) Detailed H&P incl travel history, animal contacts, food practices & other exposures. (2) Duration & degree of immunosuppression. (3) Current prophylactic therapy. (4) Recipient VZV, HSV, CMV, & toxoplasma IgG serostatus. (5) Donor CMV serostatus. (6) Concomitant systemic sx, incl pulmonary & GI complaints. (7) Time from transplant:

Early (< 1 month): Donor-to-recipient, common bacterial, or nosocomial infxns

Middle (1-6 mo): Opportunistic viral, fungal, or atypical bacterial infxns

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Late (>6 mo): Often in setting of increased immunosuppression for graft rejection

Presentation: Most common si/sx: AMS, HA, szs, & fever. Meningeal signs & AMS may be subtle or absent. Any transplant pt w/ unexplained fever & HA should have brain imaging & LP. Most common causes of opportunistic neurologic infxns: Aspergillus fumigatus, Listeria monocytogenes, C. neoformans (NEJM 1998;338:1741).

Common Neurologic Viral Infections in Transplant Patients

HHV-6: >90% of population is HHV-6 seropositive. Commonly involves mesial temporal lobes w/ T2 hyperintensity. *Presentation*: Similar to HSV encephalitis. *Dx*: CSF HHV-6 PCR. *Rx*: Ganciclovir (5 mg/kg q12h) or foscarnet (90 mg/kg q12h). May require maintenance therapy w/ valganciclovir. *Acyclovir not effective*.

CMV: Seroneg recipients w/ sero+ donors most at risk; p/w meningoencephalitis. Extraneural sites incl retinitis, hepatitis, myocarditis, lung dz. *Imaging*: nonspecific; ± WM abnlities, ventricular enhancement. *Dx*: CSF CMV PCR. May also have CSF ↑ ↑ lymphs. *Rx*: Ganciclovir (5 mg/kg IV bid & then qd), foscarnet (90 mg/kg/ bid), or cidofovir (5 mg/kg qwk); duration: 21 days, then prolonged maint Rx w/ valganciclovir. Recheck CSF

to ensure clearance of (+) PCR before changing to maintenance Rx.

VZV & HSV: Reactivated infxn less common w/ acyclovir ppx. VZV meningoencephalitis uncommon. Can mimic PML or multifocal strokes. HSV encephalitis often involves mesial temporal lobes. *Presentation*: Fever, AMS, szs. Can occur at any point in course post-transplant. *Dx*: CSF PCR. *Rx*: Acyclovir (10 mg/kg) × 14-21 days. Recheck CSF to ensure clearance of (+)PCR before starting maintenance oral Rx.

EBV: Rarely p/w meningoencephalitis; usu as mass lesion a/w systemic or CNS lymphoma or PTLD. Usu occurs middle to late in course post-transplant. *Dx*: Bx & CSF PCR. *Rx*: Stop immunosuppression → resection, XRT, chemo. Antiviral Rx not effective. Prognosis poor.

JC Virus (PML): P/w cognitive impairment, visual loss, weakness, gait disturbance & poor coordination, usu late in course post-transplant. *MRI*: Multifocal subcortical nonenhancing WM T2 ↑ signal w/ hypo or isointense lesions on T1. *CSF* often w/ nl to slightly ↑ protein & mild pleocytosis. *Dx*: Imaging + CSF JCV PCR. *Rx*: Stop immunosuppression.

West Nile Virus: In ddx for any transplant pt p/w meningoencephalitis in summer. *Dx*: CSF WNV PCR or detection of IgM in CSF & blood.

(Adapted from *Continuum*: *Lifelong Learning in Neurology* 2006;12:95; *Neurol Clin* 2003;21:193.]

Neurologic Fungal, Bacterial, & Protozoan Infections in Transplant Patients

Focal CNS Lesions

Aspergillus (incl *A. fumigatus*, Flavus, Terreus, & Niger): Most common cause of focal CNS lesion in transplant pts. Can occur anytime in the post-transplant period. Often accompanied by concurrent pulmonary dz. Angioinvasive, can cause strokes, commonly ICH with SAH if circle of Willis vessels involved.

- *Dx:* Sputum & BAL culture; CSF may show ↑ polys.

  Serum (Se, Sp > 80%) or BAL (Se 76%) galactomannan can support dx (*Transpl Infect Dis* 2003;5:158, *J Clin Microbiol*

2004;42:5517)

- *Rx* (*Clin Infect Dis* 2004;39:797):

  First line: amphotericin (1 mg/kg qd)

  Second line: Voriconazole (6 mg/kg × 1, then 4 mg/kg bid) **or** voriconazole & caspofungin (70 mg on Day 1, then 50 mg qd) for salvage therapy

- High mortality rate even w/ appropriate therapy

Toxoplasmosis: See Focal CNS Lesions in HIV; clinical presentation similar to HIV+ pts. May be either 1° infxn or reactivation of latent infxn.

- BM Tx pts & seronegative pts who receive allograft from sero+ donor at highest risk
- May see ↓ enhancement & perilesional edema depending on degree of immunosuppression
- Rarely causes meningitis or ventriculitis

Nocardia: Gram+ filamentous bacteria, weakly acid-fast. Often a/w chronic steroid use.

- Majority of CNS abscesses a/w pulmonary dz
- Diagnostic evaluation includes sputum or BAL smear & culture or brain bx; smear & culture have low sensitivity; if suspicion high, send repeat specimens
- *Rx:* TMP-SMX 15 mg/kg IV daily for 3-6 wk, then orally for at least 6 mo to a yr
- Alternative regimens include imipenem 500 mg IV q8h or ceftriaxone 1 g IV q12h or cefotaxime 2-3 g IV q6h + amikacin

***Listeria monocytogenes*:**

- Frequently presents as an acute meningitis. Presentation can also resemble a viral encephalitis-like picture or more focal lesion such as an abscess.
- Rhombencephalitis, typical of the infxn seen in healthy adults, is

rare in the immunocompromised

- MRI findings may reveal abnlities noted above but are often nonspecific
- CSF similar to acute bacterial meningitis w/ neutrophilic-predominance & low glucose
- CSF gram stain insensitive given intracellular nature of organism
- Culture & PCR are diagnostic
- Less frequent given prophylaxis w/ TMP-SMX
- Rx: Ampicillin (2 g IV q4h) for 5-6 wk w/ gentamicin (loading dose 2 mg/kg followed by 1.7 mg/kg q8h) for first wk (*Medicine* (*Baltimore*) 1998;77:313)

Molds (incl Rhizopus & Mucor):

- Typically present as mass lesion
- Angioinvasive & thus complicated by cerebral infarcts
- Direct invasion versus hematogenous spread
- Rx: Resection, high dose amphotericin B (1.5 mg/kg/day) or liposomal amphotericin (5-7.5 mg/kg/day)
- Prognosis poor

Meningitis

Candida (incl *Candida albicans, glabrata* & *krusei*):

- Meningitis is most common presentation but can rarely form microabscesses
- Often occurs in setting of severe mucositis
- *C. albicans* typically responds to fluconazole but other species may require Rx w/ amphotericin or caspofungin

***C. neoformans*:** See “Meningitis in HIV Patients”

Histoplasma capsulatum, Coccidioides immitis, Blastomyces

***dermatitidis*:**

(*see Meningitis chapter for additional info*)

- Dimorphic fungi endemic to specific regions of the US
- Histoplasma found in Ohio valley region of the Midwest
- Coccidioides found in Southwestern desert & central California
- Blastomyces found in Mississippi Valley & north central US
- Rx: 2 wk of amphotericin followed by daily fluconazole & maintenance Rx

***L. monocytogenes*:** See above

Tuberculosis: See "Meningitis in HIV Patients." Rare in US transplant pts

(Adapted from *Continuum*: *Lifelong Learning in Neurology* 2006;12:95; *Neurol Clin* 2003;21:193.)

P.162

PARASITIC NEUROLOGIC DZS

NEUROCYSTICERCOSIS

General: Infxn of nervous system w/ larval stage of cestode, Taenia solium. Most common CNS helminthic infxn. Single most common cause of acquired epilepsy in developing world.

Epidemiology: 50 million people infected. Seroprevalence in endemic areas up to 25%.

Pathogenesis: Eating undercooked pork → taeniasis (infxn w/ Taenia solium tapeworm); contamination by feces from person w/ taeniasis → cysticercosis in pigs and humans; no pork consumption required. 15%-25% pts w/ cysticercosis have current tapeworm infxn or documented h/o tapeworm infxn. All pts & close contacts should be screened for taeniasis.

Presentation: 70% w/ intraparenchymal cysts, granulomas, or calcifications; rest w/ subarachnoid, ventricular, or meningeal dz. Szs (usu GTC or SPS). Focal deficits. HA, vomiting, AMS in pts w/ ↑ ICP. Rarely → stroke 2/2 perivascular lesions at base of brain.

Imaging: (1) Viable cysts: CT: Hypodense, well-demarcated nonenhancing lesions w/ thin cyst wall. MRI: Hypointense on T1, hyperintense on T2. (2) Degenerating cysts: CT: Iso- to hyperdense+enhancement & edema. MRI: May see scolex on FLAIR or DWI. (3) Calcified cysts: CT: Punctate hyperdense lesion. MRI: Areas of ↓ signal; not wellvisualized unless a/w perilesional edema or enhancement.

CT vs. MRI: CT advantages: ↑ detection small calcifications, ↓ cost, ↑ availability in developing world. MRI advantages: ↑ detection of small intravent. cysts, cysts close to skull or in p-fossa.

Labs: Enzyme-linked immunoelectrotransfer blot (EITB)= gold standard; detects 7 Ags from Taenia solium larval cysts; can do on serum or CSF. 100% Sp, up to 98% Se (depending on cyst stage) (J Infect Dis 1989;159:50), but may miss pts w/ single lesion or calcifications. Urine Ag detection: noninvasive alternative (Am J Trop Med Hyg 2009;80:379)

Rx: Varies depending on number, location, size, & stage of cysts (see table below). (1) All pts should have a precautionary funduscopic exam to r/o ocular cysts & avoid visual loss due to antiparasitic Rx. (2) ↑ ICP should be treated immediately; may preclude anti-parasitic therapy (3) Szs: Typically well-controlled w/ single AED. Optimal Rx duration unclear. Risk for sz recurrence: calcifications, multiple cysts, recurrent szs prior to Rx. Chronic calcifications are most common finding on imaging. Episodic appearance of perilesional edema at time of sz recurr. Utility of steroids & ppx AEDs in pts w/ perilesional edema unclear.

Recommended Treatment for Neurocysticercosis

Single viable lesion	Albendazole ± steroids ↓'s sz recurrence, improves imaging findings (*NEJM* 2004;350:249)
Multiple viable lesion	Albendazole & steroids
High viable cyst burden	Albendazole & high dose steroids
Single enhancing lesion	Albendazole+steroids vs. no Rx (*Ann Int Med* 2006;145:43)
Mult. enhancing	Albendazole & steroids

lesion

Calcifications	Anti-parasitics not indicated; AEDs for recurrent szs
Encephalitis (massive parasite burden, ↑ ICP)	Anti-parasitic agents contraindicated; treat w/ steroids & hyperosmolar Rx
Giant subarachnoid cysts	Albendazole for >1 mo w/ high dose steroids vs. resection
Meningitis, vasculitis	Typically no antiparasitic therapy, only steroids
Intraventricular cysts	Neuro-endoscopic removal vs. surgery; shunt placement PRN; antiparasitic agent w/ steroids ↓ shunt failure
Intramedullary cysts	Resection; anti-parasitic agents controversial; if used, high dose steroids must be used before, during, & after
Intraocular cysts	Resection
Taeniasis (tapeworm) infxn	Niclosamide, single 2 g dose

Anti-parasitic Agents for Treatment of Neurocysticercosis & Taeniasis

Albendazole, 15 mg/kg/day × 7-15 days: Destroys 85% cysts. Less expensive than praziquantel. Good CSF penetration, useful against ventricular & subarachnoid cysts. Steroids ↑ levels.

Praziquantel, 50 mg/kg/day div tid × 7-15 d. Effective also against taeniasis. Steroids ↓ levels. Destroys 70% of cysts.

Dexamethasone 12-32 mg/day in divided doses

Niclosamide, single dose (2 g for adults) for Rx of taeniasis (tapeworm

infxn)

CEREBRAL ECHINOCOCCUS

General: Two most clinically relevant species are E granulosus & E multilocularis which cause cystic echinococcosis & alveolar echinococcosis, respectively. Transmitted to humans via ingestion of eggs or gravid proglottids shed in feces of infected animals, incl sheep, dogs, & cattle. Incubation period of many months-years.

Presentation: Initial infxn is asymptomatic. Fluid-filled cysts become symptomatic due to rupture, mass effect, or 2° infxn. 1° affected organs: cystic echinococcosis: lungs, liver; alveolar echinococcosis: liver. CNS involved in 2%-8% of cases: brain (hemispheres, cerebellum), & spinal cord. Sx: HA, n/v, szs, CN palsies, other focal deficits.

Dx: Daughter cysts form grape-like multicystic mass; E granulosus cysts usu unilocular while E multilocularis cysts are multilocular. Serum eosinophilia common but CSF often unrevealing given enclosed nature of cysts. Detection of serum abs w/ ELISA, indirect hemagglutination assay, & immunoblot; cross reactivity can occur w/ other cestode infxns.

Rx: Surgical removal of cysts can be curative. Risk of intraoperative rupture & anaphylactic response. Medical Rx: albendazole & praziquantel for months, even after surgery

PARAGONIMIASIS

General: Trematode infxn; transmitted to humans via eating freshwater crustaceans or from cats, dogs, pigs.

Presentation: Initial infxn can cause GI sx & migratory subcutaneous masses. Pulm involvement months after acute infxn. CNS syndromes: meningoencephalitis & myelitis, occur in chronic dz. Ddx includes tuberculosis.

Laboratory findings: Immunologic testing of serum & CSF often yields dx. May detect serum &/or CSF eosinophilia. CSF glucose often low. Definitive dx: identification of eggs in bx or CSF. Imaging: Clusters of ring-enhancing lesions (“soap-bubble” appearance), frequently in occipital & temporal lobes.

Rx: Praziquantel 80%-90% effective. Triclabendazole & mebendazole are less effective alternatives. Consider concurrent steroids.

AMERICAN TRYPANOSOMIASIS (CHAGAS DZ)

General: Infxn w/ Trypanosoma cruzi, a protozoa endemic to S. & Central America. Transmitted via feces of infected reduviid bug, blood transfusions, or organ transplantation.

Presentation: Acute generalized illness w/ fever, HA, & myalgias. Chronic infxn of various organs incl heart, GI tract, & CNS occurs in ˜30% of cases. Meningoencephalitis is most common chronic neuro presentation; focal lesions rare overall but more common in immunosuppressed host. CNS is a frequent site of reactivation in HIV-infected pts. Neuro si/sx: Fever, HA, focal neurologic signs, szs. Embolic strokes common due to cardiomyopathy (Trans R Soc Trop Med Hyg 2007; 101:1075).

Dx: Definitive: detection of intracellular trypomastigotes in CSF & blood. CSF: mild ↑ lymphs/monos, ↑ protein. Imaging: diffuse ring-enhancing lesions. Serum abs Se & Sp for acute & chronic infxn.

Rx: Acute infxn: benzonidazole & nifurtimox. Chronic dz cannot be cured; symptomatic Rx only. Consider long-term maintenance Rx in HIV+ pts (Clin Infect Dis 2005; 40:1005)

AFRICAN TRYPANOSOMIASIS

General: 2/2 two protozoa subspecies, Trypanosoma brucei gambiense (W. & Central Africa) & rhodiense (E. & S. Africa). Endemic: sub-Saharan Africa. Transmitted via Tsetse fly.

Presentation: Gambiense infxn is chronic dz, occurring over months-years; rhodiense infxn more acute, unfolding over weeks-months. Si/sx: Nonsuppurative lesion or chancre at site of fly bite. Early presentation nonspecific w/ fever, malaise, HA, lymphadenopathy (often posterior cervical nodes in gambiense, “Winterbottom’s”) & rash. CNS sx: in late stage (typically <3-4 wk after fly bite in rhodiense infxn vs. months-years after in gambiense) & include irritability, poor concentration, personality Δs, reversal of sleep-wake cycle, abnl gait & speech, weakness, ataxia, extrapyramidal si, fasciculations, sensory Δs (painful limb hyperesthesia, “Kerandel sign”), szs, frontal release signs. If untreated → coma & death.

Workup: CSF: moderate ↑ lymphs, ↑ protein. Serum & CSF PCR sensitive but unclear reproducibility (Ann Neurol 2008;64:116). Imaging: not esp useful in dx; MRI may show hyperdensities in basal ganglia & internal & external capsules (Am J Neuroradiol 2003;24:1383). EEG: typically low volt background or alternating high-volt delta wave bursts w/ periods of lower-voltage delta activity (Ann Neurol 2008;64:116). Card agglutination is good screening test. Definitive dx: identification of trypanosome in serum, CSF, or biopsied tissue.

Ddx includes malaria, some pts may be co-infected.

Rx & prognosis: Without appropriate Rx, case-fatality rate 100%. Follow CSF q6mos × 2 yr after Rx. Selection of agent depends on early versus late stage. (1) Suramin (first line for rhodiense, may use as alternative for gambiense) & pentamidine isethionate (gambiense) adequate for systemic dz but not effective in the CNS (2) Melarprosol for any pt w/ CSF WBC > 5 or if trypanosomes identified in CSF (WHO 1998) ˜10% pts develop postmelarprosol reactive encephalopathy, 50% of whom die. (3) Combination nifurtimox-eflornithine effective first line for gambiense (Lancet 2009;374:56)

NEUROSCHISTOSOMIASIS

General: Trematode infxn, usu transmitted via water contact; also organ transplantation. Three species cause neurologic infxn: Schistosoma mansoni (mainly brain), Schistosoma haematobium (mainly spinal cord), Schistosoma japonicum (mainly brain). Schistosomal eggs enter CNS via hematogenous spread & cause granulomatous inflammatory response.

Epidemiology: Endemic to parts of Caribbean, S. America, Africa, Middle East, & Far East.

Presentation: Acute infxn (Katayama fever) p/w fever, hives, myalgias, eosinophilia, bloody diarrhea. Neurologic complications: myeloradiculopathy w/ cauda equina or conus medullaris syndrome, transverse myelitis, & focal lesions often of p-fossa typically occur weeks-months after acute infxn. si/sx: sz, HA, papilledema, sensory disturbance, lower back or lower extremity pain, bowel/bladder dysfxn, ataxia, & other focal deficits.

Dx: Suspect in any pt w/ focal cerebral lesion or e/o myeloradiculopathy w/ recent travel to endemic area, esp w/ prior water contact. Single or multiple CT hyperdense brain or spine lesions a/w mass effect & edema; hyperintense lesions on MRI comprised of multiple enhancing nodules & branches; spinal cord may be expanded w/ thickening of the cauda equina roots (Am J Radiol 2008;191:582). Definitive dx requires identification of egg from bx specimen. Dx often made by detection of eggs in stool or urine. Evaluate for IgG antibodies in CSF, particularly in pts w/ spinal cord involvement. CSF may reveal lymphocytic pleocytosis & ↑ protein; ↑ CSF eosinophils in ˜50% of pts (Arq Neuropsiquiatr 2003;61:353).

Rx: First line: Praziquantel w/ artemether for synergistic effects & oxamniquine as adjunct. Surgical resection on case-by-case basis. Abs may be + for life. Pts w/ cont’d shedding of eggs in stool should be retreated.

Concurrent steroids for edema (Am J Trop Medi Hyg 1999;61;47).

STRONGYLOIDES

General: Nematode infxn; filariform larvae penetrate skin → lungs → GI tract. Found in tropical & subtropical climates. Autoinfestation allows persistence years after initial infxn

Presentation: Acute infxn: Asymptomatic or pulm/GI sx incl wheezing, abd pain, n/v/d. Maculopapular or urticarial serpiginous rash ("larva currens") often seen in chronic dz. Disseminated dz, incl CNS dz, & hyperinfxn (massive worm burden) more common in immunocompromised hosts, esp on steroids. Meningoencephalitis is most common presentation; may have mycotic aneurysms, vasculitis, & ICH. Enteric bacterial superinfxn, incl meningitis or abscess, can occur in cases of hyperinfxn or disseminated dz.

Dx: Visualization of larvae in stool, serum, CSF; serial samples ↑ Se. Not + in stool until ˜1 mo after infxn (Semin Neurol 2005;25:252). Serum eosinophilia can fluctuate, common at time of initial infxn. IgG Ab detection cannot distinguish recent & prior infxn, may cross react w/ other helminthic infxns & can be neg in disseminated dz (Clin Infect Dis 2001;33:1040).

Rx: Ivermectin 200 µg/kg/day for at least 7-10 days; albendazole, thiabendazole, & mebendazole are effective second-line alternatives. If possible ↓ immunosuppressive regimen. For disseminated dz continue ivermectin daily until sx resolve & stool tests neg × >2 wk. Consider long-term prophylaxis in HIV+ pts.

Prognosis: Disseminated dz mortality 80%.

CEREBRAL MALARIA

General: Vector-borne illness endemic to Africa, Central & South America, & Southeast Asia. In humans caused by one of four species of a protozoan parasite in the Plasmodium genus; cerebral malaria caused by Plasmodium falciparum.

Epidemiology: ˜500 million cases annually w/ ˜3 million deaths.

Presentation: Varies depending on host immune status & infecting species of Plasmodium. Host immune status determined by age, prior exposure, & degree of endemicity. Children & pregnant women at higher risk for more severe dz. Nonspecific sx incl fever, chills, HA, malaise, diarrhea, vomiting, myalgias, decreased level of arousal. Generalized szs in 15%-20% adults & 80% children. Nystagmus, abducens nerve palsy, ocular bobbing, & decorticate or decerebrate posturing less common; e/o raised ICP uncommon in adults.

Dx: Requires high index of suspicion; malaria should be included in ddx in any pt w/ a febrile illness & encephalopathy from or returning from area w/ endemic malaria. In endemic areas, three neg blood smears 8-12 hs apart required to r/o dx. Dx requires impaired consciousness/coma, presence of parasitemia, & exclusion of other causes of encephalopathy. Blood: Thick & thin blood smears for parasitemia. Serologic tests available but low Sp; immunochromatographic detection of P. falciparum histidine rich protein & LDH may be both Se & Sp (Lancet Infect Dis 2006;6:582). CSF: May be nl or mildly ↑ protein & pleocytosis. EEG: May show focal origin of sz. Imaging: CT may show brain swelling which, in combination w/ hypodensities in basal ganglia & cerebellum, suggest worse prognosis (Radiology 2002; 224:811). Brain MRI w/ multifocal, often enhancing WM hyperintensities, cortical infarcts, cerebral swelling, & transtentorial herniation in fatal cases.

Rx: Dictated by Plasmodium species local prevalence & resistance patterns. Options: Quinine w/ doxycycline, mefloquine, & newer antimalarial drugs (e.g., artemisinin derivatives). In pt w/ suspected malaria w/o known resistance patterns, Rx w/ IV quinidine should be started empirically. Steroids & prophylactic AEDs associated w/ worse outcomes.

Prognosis: Neurologic sequelae: upto 10% adult, 30% children survivors of cerebral malaria (e.g., epilepsy, cognitive impairment, visual loss, weakness, ataxia, & extrapyramidal si/sx). Postmalaria neurologic syndrome, w/ szs, tremor, cognitive ↓, psych Δs in absence of active parasitemia described in pts weeks-months after infxn w/ corresponding WM enhancing lesions in the brain & p-fossa; associated w/ Rx w/ mefloquine (Lancet 1996;348:917).

FREE-LIVING AMEBAE

General: Only four known genera of free-living amebae cause human dz: Naegleria fowleri, Acanthameba spp, Balmuthia mandrillaris & Sappinia diploidea.

N. fowleri: Causes 1° amebic meningoencephalitis, an acute fulminant infxn that affects mostly immunocompetent children & young adults after recent fresh water contact. Reaches CNS via direct invasion from nose & olfactory tract. May p/w HA, fever, n/v, meningismus, AMS, szs. CSF typically w/ low glucose & neutrophilic pleocytosis. Amebae extremely difficult to culture or visualize by direct microscopy. Almost uniformly fatal; few cases of survival w/ Rx that included amphotericin B

Acanthameba spp & B. mandrillaris: Causes granulomatous amebic encephalitis, subacute to chronic infxn that affects primarily

immunocompromised pts, Balamuthia can also cause infxn in extremes of age. Transmission: inhalation of cysts via nose & lungs or through contamination of skin lesion. CNS involvement likely through hematogenous spread or directly via olfactory tract. Presentation: HA, fever, n/v, meningismus, AMS, szs, lethargy. Often a/w pulm & skin dz (ulcers, abscesses or erythematous nodules). Diagnostic testing: CSF often w/ moderate lymphocytic pleocytosis, low-nl glucose & ↑ protein. Single or multiple hypodense lesions on CT scan; ring-enhancing on MRI. Acanthamebae may preferentially affect brainstem, cerebellum, & thalamus (Neurology 1980;30;567). Antemortem dx difficult to make as culture from CSF & direct microscopy rarely successful (Clin Microbiol Rev 2003;16:273). PCR assay & immunfluorescence analysis of brain tissue may be helpful. Rx/prognosis: Combinations of pentamidine, sulfadiazine, flucytosine, fluconazole & clarithromycin or albendazole have been tried. Prognosis: poor; few cases of successful Rx.

OTHERVIRAL NEUROLOGIC DISEASES

DENGUE FEVER

General: Arthropod-borne infxn caused by a flavivirus. Occurs in both rural & urban areas of southern hemisphere. Transmitted via Aedes aegypti or Aedes albopictus mosquito. Neuro manifestations relatively rare but often a/w poor prognosis.

Presentation: Sx typically begin w/in one wk of the mosquito bite. (1) Classic "feverarthralgia-rash" syndrome w/ sudden onset of high grade fever, arthralgias, myalgias ("breakbone fever"), & petechial or macular rash; may also have HA, retrobulbar pain, & gastrointestinal distress. (2) "Dengue hemorrhagic fever" in pts w/ prior infxn— bleeding diathesis, thrombocytopenia, & vascular permeability; can → "dengue shock syndrome." (3) Neurologic presentation: spastic paraparesis, transverse myelitis, GBS, mono- or polyneuropathy, szs, encephalopathy, meningoencephalitis, coma, ICH (Lancet 2000;355:1053). (4) Severe complications: HoTN, cerebral edema, hemorrhage, HoNa & fulminant hepatic failure. (5) Postinfectious neurologic sequelae: Common; ˜1/3 w/ neuro sequelae incl transverse myelitis & nerve palsies (Lancet 2000;355:1053).

Workup: IgM & IgG in serum & CSF. Ratio of IgM to IgG helpful in determining 1° vs. 2° infxn. Cross-reactivity b/n dengue & Japanese encephalitis Abs. Dengue viral PCR can also be done on CSF. CSF pleocytosis & ↑ protein common; ± ↑ OP. Imaging may show cerebral edema, meningeal enhancement, or T2/FLAIR hyperintensities.

Rx: Supportive measures. No vaccine available.

JAPANESE ENCEPHALITIS

General: Mosquito-borne flavivirus found in rural Asia & SE Asia. Transmitted via Culex mosquito. In temperate climates, transmission occurs in summer & fall; in tropical regions, transmission may occur year round. Suspect in any pt w/ recent travel to Asia or Southeast Asia presenting w/ meningitis, encephalitis, or acute flaccid paralysis

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Presentation: Mild influenza-like illness w/ HA, cough, gastrointestinal distress, & rigors develops 5-14 days after mosquito bite. Neuro si/sx: HA, sz, ataxia, CN palsies, meningitis, flaccid paralysis. May see parkinsonism (masked facies, tremor, & cogwheel rigidity).

Dx: Combination of central hyperpneic breathing & extrapyramidal sx has 81.3% PPV (Neuroepidemiology 1994;13:97). CSF: Mild ↑ lymphs, moderately ↑ protein, nl glucose. Other findings: IgM Ab detection 75% Se in serum & CSF; dx supported by documented conversion from IgM ↑ IgG Abs (J Neurol Sci 2007;262:165). False+ Western blot may be due to dengue infxn. MRI: May see lenticulate nucleus & thalamic lesions on imaging.

Rx: Supportive measures. Vaccination available.

Prognosis: Fatality ˜25%. Survivors: ˜50% +sequelae (e.g., szs, motor, behavioral).

RABIES

Presentation (J R Soc Med 2002;95:9): Incubation period days-1 yr (usu months). Prodrome: Flu-like. Encephalitic: Pharyngeal spasms, hydrophobia, aerophobia, dysphasia, hyperactivity, hallucinations → progressive encephalopathy, paralysis → coma → death. Paralytic: Rapid onset quadraparesis, w/ few cerebral manifestations early on, then encephalopathy progressing to coma & death.

Etiology: Lyssavirus genus RNA viruses; six rabies virus genotypes cause dz, mainly type 1 (worldwide), & types 5 & 6 (in Europe, usu bats). Most mammals can serve as vector (most: bats & dogs). Vectors also become infected → encephalomyelitis. In N. America, most common vectors are raccoons (40%), skunks (29%), bats (14%), foxes (5.4%)

Dx: Saliva PCR & cx, skin bx, PCR & immunohistochem, serum & CSF Abs.

Rx: ˜100% mortality (only 1 single case report of survival of an nonimmunized individual).

Preventative measures: Pre-exposure: Rabies human diploid cell vaccine (HDCV) SC or IM ×3 doses on Days 0, 7, & 28—given to those at risk for exposure. Postexposure: For nonimmunized, give HDCV vaccine SC or IM on days 0, 3, 7, 14, & 30, plus rabies Ig 20 IU/kg; for previously immunized, give HDCV vaccine days 0 & 3.

Headache

EVALUATION OF HEADACHE

History: Points to Consider

Quality & description of HA: Acuity, frequency, duration, location, severity, age, gender, meds, diet.

Women: Relationship to menstrual cycle, OCP, pre- or postmenopausal or pregnant.

Time of day: Awaken the pt from sleep? Morning or afternoon?

Location: B/l, uni/l, temporal, trigeminal, jaw, occipital, eye, lower face, neck.

Character: Pounding, lancinating, throbbing, pressure, sharp, radiating.

Associated sx/si: Anxiety, stress, aura/prodrome, lacrimation/rhinorrhea, flushing, myalgias, arthralgias, exertional/rest, visual changes, photophobia, phonophobia, n/v, facial tic, trauma/surg.

Exacerbating factors: Valsalva, positions (bending over, lying down), movement.

Past medical history & ROS: Stroke, vasc dz/risk factors, connective tissue d/o, autoimmune d/o, infxns, travel, rashes, trauma.

Family history.

Physical exam: Palpation of the head; auscultate neck, chest; fundus exam; MS, CNs, motor, sensory, coord, gait, DTRs.

Workup: Depends on presentation, consider: Vitals, O_2 saturation; Labs: TSH, ESR, CRP, tox screen (blood/urine), serum infxs serologies, Lyme Ab; LP: OP, xantho, cells, gluc, prot, Gram stain, fungal stain; CT head/cervical spine (?contrast); MRI head/neck (?contrast); angiogram if suspect aneurysm/AVM/vasculitis.

Indications for neuroimaging: Focal finding on exam; HA on exertion or Valsalva; acute onset severe HA; HA awakens patient; change in well-established HA pattern; New-onset HA in patient >35 yo; new-onset HA in HIV or cancer pt; HA w/ stiff neck/fever; papilledema/cognitive deficit; recent trauma w/ change in MS or focal deficit, esp if coagulopathic (Neurol Clin 1998;16:285).

PRIMARY HEADACHE DISORDERS

MIGRAINES

Prevalence ˜12%; 90% pts w/ family history; begin early-late teens around puberty decline in severity & frequency w/ age, especially postmenopause; may present w/ a variety of sx as aura, but acephalgic migraine a dx of exclusion (r/o stroke, TIA, sz). When evaluating pts for migraine, it is important to rule out med overuse HA.

Presentation: Lateralized but can switch sides; mod-severe throbbing pain, worse w/ activity, lasts hours-days; photophobia & phonophobia, N > V; nasal congestion or tearing; aura (motor, sensory, or visual sx).

Common triggers: Changes in homeostasis, sleep patterns, missed or delayed meals, specific foods (cheese, chocolate, red dye, wine, MSG), changes in weather, menstruation or hormonal shifts, stress.

Clinical features: Migraine w/o aura: 4-72 h (untreated); uni/l, pulsating, mod-severe pain, ↑ by activity; N/V, photo/phonophobia.

Migraine w/ aura: Visual sx (flicker lights, spots, lines, visual loss or field deficit), sensory sx, dysarthria; between 5 and 60 min; HA follows w/i 60 min (Cephalalgia 2004;24(Suppl 1):24).

Rx: Nonpharmacological & behavioral interventions: 8-9 h uninterrupted sleep nightly w/ consistent sleeping & awakening times; avoid long work hours or irregular shifts; limit caffeine to <240 mg/day, avoiding skipping meals, avoid smoking; exercise 5×/wk for 30 min; limit rescue/abortive med to 2×/wk; avoid known triggers (foods, alcohol, etc.); keep a detailed HA diary, clarify the efficacy of Rx, help identify triggers.

Acute meds for migraine: Triptans preferred method of acute Rx; mech: inhibit serotonin B/D receptor subtypes in meninges & vasc boundaries of CNs.

Considerations: Early intervention = faster relief; less effective 2-4 h after onset; relief should be w/in 2-4 h, depending on drug; 90% have relief after a second dose; any one Triptan should be tried on three separate occasions before abandoned; failure of one does not mean another will not work; if on propranolol, should receive rizatriptan 5 mg, & total ≥15 mg in 24 h; if HA worsens w/ triptan, reduce the dose by 50%; if nausea, add metoclopramide 10 mg to oral regimen at home; adding NSAID to triptan can improve efficacy & prevent postdrome of lethargy & memory disturb (naproxen sodium 500 mg); concurrent use w/ serotonergic meds should be monitored for serotonin syndrome; Concurrent use w/ MAO inhibitors is contraindicated, except w/ naratriptan & frovatriptan, which both have

substantially longer half lives; migraine w/ aura is not a contraindication to use of a triptan. Coronary & vascular disease is a contraindication.

Common possible side effects: Lethargy, paresthesias, & muscle tightness & stiffness, especially in the neck & chest—must be explained to patients, as can raise anxiety & concerns for anaphylactic reactions & MI. Muscular sx typically pass w/in about 30 min.

Acute Therapies for Migraine

Proven statistical & clinical benefit

Naratriptan po

Rizatriptan po

Sumatriptan po

Zolmitriptan po

Dihydroergotamine (DHE) SC, IM, IV, in

DHE IV+ antiemetic

acetaminophen (APAP), aspirin (ASA) + caffeine po

ASA po

Butorphanol in

Ibuprofen po

Naproxen po

Moderate statistical & clinical benefit

APAP + codeine po

Butalbital, ASA, caffeine + codeine po

Butorphanol IM

Chlorpromazine IM IV

Diclofenac po

Ergotamine + caffeine + pentobarbital + bellafoline po

Flurbiprofen po

Isometheptene po

Ketorolac IM

Meperidine IM IV

Methadone IM

Naproxen po

Prochlorperazine IM, pr

Equivocal or inconsistent evidence

Butalbital ASA + caffeine po

Metoclopramide IM or pr

Ergotamine + caffeine po

Metoclopramide IM or pr

Ineffective failed vs. placebo

APAP po

Chlorpromazine IM

Granisetron IV

Lidocaine IV

Unstudied but used

Dexamethasone IV

Hydrocortisone IV

(Adapted from *Neurology* 2000;55:754.)

P.169

Migraine prophylaxis: Consider starting a prophylactic med if HA-related disability ≥3 days/mo; duration > 48 h; acute meds ineffective, contraindicated, or likely to be overused; attacks → profound disability, prolonged aura, or true migrainous infarction; Attacks occur >2-4×/mo; patient preference (Headache 2005;45(Suppl 1):S34).

Commonly Accepted Rx for Migraine Prophylaxis

Med	Typical dosage	Main adverse effects
Amitriptyline Nortriptyline	10-150 mg/day	
Doxepin	10-100 mg/day, divided in 3-4 doses	Weight gain, dry mouth, sedation, arrhythmias, blurred vision, urinary retention
	25-150 mg qd	
Depakote	250-500 mg bid	Hepatotoxicity, nausea, weight gain, somnolence, tremor, teratogenicity, rash, abdominal pain
Depakote ER	500-1,000 mg qd	
Propranolol	40-240 mg/day, in 3-4 divided doses	
Inderal LA	80-240 mg qd	Fatigue, exercise intolerance, asthma/COPD exacerbation, cold hands,

		bradycardia
Nadolol	20-40 mg qd	
Atenolol	25-50 mg qd	
Timolol	10-15 mg bid	
Topiramate	50 mg bid (titrate from 15-25 mg)	Paresthesias, nausea, somnolence, anorexia, dizziness
Magnesium	600 mg qd	Diarrhea
Riboflavin	200-400 mg qd	Diarrhea, polyuria
Botulinum A injections	10-100 units q3-4mo	Mild pain/bleeding, worsening of HA, ptosis, dry mouth, infection

(*Am Fam Phys* 2006;73:72; *Clin Ther* 2001;23:772.)

MIGRAINE VARIANTS

Status migrainosus: >72 h; need to r/o 2° causes.

Rescue Meds for Status Migrainosus

Drug	**Dose/Route**
Sumatriptan	6 mg SC
Chlorpromazine	12.5 mg slow IV push q20min; max 50 mg
Prochlorperazine	10 mg slow IV push
Valproate IV	300-500 mg IV over 5 min, which can be repeated

Magnesium sulfate	1 gm IV push over one min
DHE45 1 mg + prochlorperazine 10 mg	Mix give 1.5 mL IV push over 1-3 min
Dexamethasone	6-8 mg IV push
Methylprednisolone	250-500 mg IV push
Olanzapine	5-10 mg po

(*Brit J Clin Pharm* 2001;52:69; *Headache* 2000;40:783; *Headache* 2002;42:58.)

Catamenial/menstrual migraine

Women of childbearing age; usually occur right before & during menstruation; Rx: Start NSAID Rx 2-3 days before & continue during menses.

Basilar migraine

Sx include visual sx, vertigo, staggering, decreased coordination of bilateral limbs, dysarthria, tingling in extremities/around mouth; rarely coma/quadriplegia; last 10-30 min, followed by HA w/ possible confusion & stupor for several hours; similar

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to vertebrobasilar stroke presentation; can be very concerning & should prompt stroke w/u w/ vessel imaging. If vascular w/u is neg, Rx is per migraine algorithm.

Opthalmoplegic/Retinal Migraine

Clinical Si/Sx: Recurrent migraine associated w/ plegia of extraocular muscles; transient IIIrd nerve palsy w/ ptosis; ± pupillary involvement; occasionally VIth nerve involvement; more common in children; paresis can last for days-week.

Evaluation: Resembles to retinal artery occlusive d/o’s; stroke workup should be done.

HEADACHE AND PREGNANCY

Some have relief during pregnancy, some have worsening, especially in first trimester. Secondary causes, such as venous thrombosis & pituitary apoplexy,

need to be r/o.

Rx: Most meds used to treat migraine are pregnancy category B, C, D, & toxic to the fetus. First line: Relaxation, ice packs, reassurance. Second line: Aacetaminophen (alone or w/ codeine); narcotics used sparingly. Third line: Antiemetics (trimethobenzamide, chlorpromazine, prochlorperazine, & promethazine PO, IV, or PR). Other: IV Mg - SE: Flushing feeling, lasts <1 min. Note: NSAIDS in the third trimester may prevent ductus closure & should be avoided (Headache 2001;41:171; Am Fam Physician 2009;80:157).

Prophylactic Rx of Migraine in pregnancy: Should be a last resort, risks fully disclosed. Triptan safety appears promising, but data continues to be collected.

When to consider a prophylactic HA med: 3-4 debilitating HAs/mo, recurrent ED visits; HAs that result in dehydration & possible fetal distress; HAs not better w/ Rx above.

Migraines in breast-feeding patients: May use acetaminophen, NSAIDS or narcotics; triptans should be used w/ caution (if used, avoid breast feeding altogether, or pump/feed >4 h after use); ergots contraindicated during lactation.

MIGRAINE AND STROKE RISK

PFO: There is an association of a PFO in pts w/ migraine w/ aura (but not w/o aura); prevalence of PFO ranges from 40.9%-72% (Cephalalgia 2008;28:531). Trials ongoing to determine whether closure is beneficial. No good data yet on ASA in migraine w/ aura.

Imaging & migraine: Commonly, patients w/ h/o migraine have small T2 nonenhancing subcortical WM lesions in the centrum semiovale; very common, should only be worked up for stroke if lesions appear embolic.

Migraine or TIA: Migraineurs can present w/ aura & no resulting or coincident HA, even in people who have not previously had migraine (but a careful hx may elicit one). Any acute neurological change should first be considered stroke/TIA until proven otherwise. Older pts can present w/ aura-like sx despite no h/o migraine. The stroke risk in patients w/ migrainous visual aura was 11.5%, & 29% in those w/ TIA, making the distinction clinically significant (Stroke 1998;29:1539).

Criteria for migrainous aura: Visual sx (scintillating scotoma); gradual “build-up,” expansion, migration of the scintillation; “march” of paresthesias; serial progression from one symptom to another; ≥2 identical spells; when only one spell, dx is on the presence of unequivocal migrainous features; HA w/ the spell (50% of cases); duration 15-25 min, but up to 60 min can occur; benign

course w/o permanent sequelae; exclusion of cerebral thrombosis, embolism, dissection, subclavian steal, epilepsy, thrombocytosis, polycythemia, hyperviscosity syndromes, lupus anticoagulant; nl angiography; recurrence of identical spells.

TENSION HEADACHES

Sx: No age/sex difference; last 30 min-7 days; often bilateral, described as a "tight band" around the head; not worse w/ activity; no n/v, photo/phonophobia, or other associated sx.

Rx (nonmed): Stress release, hot showers, massage, ice packs, heat packs, posture correction, acupuncture, PT.

Rescue meds: NSAIDS (only if episodic), ASA, Tylenol or combinations w/ caffeine, muscle relaxants.

Preventative medications: Tricyclics, dosing as for migraines; muscle relaxants.

CLUSTER AND TRIGEMINAL AUTONOMIC CEPHALGIAS (TACS)

Table of TACS

Prominent autonomic symptoms	Sparse or no autonomic symptoms
Episodic cluster headache	Trigeminal neuralgia
Chronic cluster headache	Idiopathic stabbing headache
Episodic paroxysmal hemicrania	Cough headache
Chronic paroxysmal hemicrania	Benign exertional headache
SUNA and SUNCT syndromes	Headache associated with sexual activity
Cluster-tic syndrome	Hypnic headache

SUNCT = short-lasting unilateral neuralgiform headache attacks with

conjunctival injection and tearing. *Brain* 1997;120:194. SUNCT is classified as a subtype of SUNA (short-lasting unilateral neuralgiform headache with cranial autonomic features) by ICHD. A recent study found SUNCT to actually be more common than SUNA (*Brain* 2006;129:2746).

Cluster headache: Attacks are clustered over a few mos, then abate for mos to yrs.

Evaluation: Can be I to several ×/day, tend to be short (15 min-<3 h); strictly uni/l, periorbital/temporal, must have at least one autonomic disturbance; onset fast, often reaching peak within a few min; debilitatingly severe and should be taken very seriously (people have committed suicide to avoid pain).

Clinical findings: Intense uni/l HA lasting minutes-hours; lancinating, boring pain, accompanied by ptosis, miosis, conjunctival injection, lacrimation, rhinorrhea, facial blushing, or sweating; pt may be restless or agitated; occur in two or more clusters occurring over days-months; can be episodic or chronic (chronic is fewer than 10%-20% of cases) (Cephalalgia 2007;27:824).

Triggers: Alcohol, nitroglycerine, exercise, & increased ambient temperatures.

Rx: Trial of indomethacin first, 25-50 mg/day bid-tid; max 200 mg/24 h; (Black Box Warning: Increased MI/stroke risk); if HA is a SUNA/SUNCT type it will respond to this; SC sumatriptan 6 mg has the best evidence for effective rx, can be given bid on a long-term basis w/o risk of rebound headache (Eur J Neurol 2006;13:1066).

Abortive Therapies for Cluster Headaches

Sumatriptan SC	6 mg SC	Best Rx
Sumatriptan IN	5-20 mg one nostril ×1; repeat in 2 h. Max 40 mg/24 h	Acceptable
Zolmitriptan IN	5 mg one nostril ×1 repeat in 2 h max 10 mg/24 h	Similar to sumatriptan IN
High flow 100% oxygen	8-10 L/min for 15-20 min	Often highly effective

	Lidocaine IN	4% solu IN lidocaine (*JAMA* 1996;276:319)	Adjunct; partial relief
PO	Corticosteroids	1 mg/kg PO; max 60 mg/24 h, 5 days then taper 10 mg q3d	Tendency for rebound; best to start w/ prophylactic med

Prophylactic Meds

PO	Verapamil	Start 80 mg bid, advance 80 mg every 10-14 days. Often effective at 240-960 mg/day in divided doses.	First line preventative. Check EKG before, w/ each increase in dose, & every 6 mo.
PO	Lithium	Start 300 mg bid titrate to therapeutic range of 0.8-1.1 mEq/L	Therapeutic often at 600-1,200 mg/day. Avoid NSAIDS/carbamazepine while on Li, check renal function.

Surgical interventions: Trigeminal nerve ablation; occipital nerve stimulators: some promising early data (Lancet 2007;369:1099); deep brain stimulators (Cephalalgia 2008;28:285).

Paroxysmal hemicrania

Clinical findings: Similar to cluster but attacks much shorter (minutes), more closely spaced; responsive to indomethacin.

Rx: Indomethacin 25-50 mg/day, divided bid-tid; max 200 mg/24 h (Black Box Warning: Increased MI/stroke risk). Any suspected cluster HA should have trial to r/o this.

SUNA/SUNCT

Clinical findings: HA w/ autonomic features. SUNCT (Short-lasting unilateral neuralgiform headaches attacks w/ conjunctival injection & tearing): Ipsi conjunctival injection & tearing. SUNA (Short-lasting unilateral neuralgiform headache attacks w/ cranial autonomic features): Ipsi conjunctival injection or lacrimation, but not both.

Si/Sx: Shorter (seconds-minutes), more freq than hemicrania (up to 30 an hour & 200/day); pain stabbing (variable), can come in various forms: single

stabs or clusters w/o return to baseline.

Triggers: Touching the face, washing, brushing teeth, chewing; variable pains, triggers, should alert to the possibility of SUNA/SUNCT.

Rx: Indomethacin 25-50 mg/day bid-tid; max 200 mg/24 h; second line: Lamotrigine (up to 300 mg/day) (Eur J Neurol 2006;13:1066).

OTHER CAUSES OF PRIMARY HEADACHE

Benign or primary exertional HA: W/ exercise/exertion; b/l, pulsating/throbbing; 5 min to 48 h; ave age of onset: 24; exclude SAH, dissection.

HA associated w/ sexual activity: Occurs during or after sexual activity. Presumed autonomic trigger as HA often occurs at climax when surge of sympathetics; lasts <3 h; can mimic vasospasm (RCVS), SAH or dissection pain; Rx: NSAID 30 min prior to exertion (or sexual activity), e.g., 50 mg indomethacin; Prevention: β-blockers or CCBs.

Hypnic HA: Average onset 63 years, female predom; lasts ˜1 h; assoc w/ REM sleep; 120-480 min after sleep initiation; b/l, diffuse, or frontotemporal; dull, occas throbbing/pulsing, rarely sharp/stabbing; nausea in 20%; rarely photo/phonophobia, lacrimation/ptosis; Rx: Li, ASA, ergots, indomethacin, caffeine, flunarizine.

SECONDARY HEADACHE DISORDERS

Trauma: HA most common w/in 2 wk; most related to muscle tension, most often self-limited tension type HA. Can be migrainous. (Robbins L. Management of HA and HA Meds. 2nd ed. Springer-Verlag; 2000); trauma/surgery can also trigger neuralgias & related pain syndromes (chronic regional pain syndrome); Rx depends on HA type.

HEADACHES SECONDARY TO VASCULAR DISEASE

Stroke: ˜30% w/ acute stroke have a HA (Stroke 1993;24:1621).

SAH: Acute onset, worst HA of life; CT w/o contrast in first 12 h 93% sens; suspected SAH w/ neg CT should have LP (sensitivity nears 100% at 12 h); if CT/LP pos, do CTA; sentinel HA can precede rupture; CTA if clinical suspicion (Ann Emerg Med 2008;51:697).

Vasoconstriction disorders

Etiology: Often thunderclap HA, can have a more gradual crescendo over minutes. Unlike SAH can present as recurrent HAs. Often females age 20-50. HA focal or diffuse, can be assoc w/ stroke-like presentation. May have szs, transient HTN.

Exam: CT & LP if necessary to evaluate SAH; If negative, CTA to evaluate vasculature. ESR/CRP & vasculitis w/u.

Rx: Avoid triggers (esp sympathomimetics); verapamil/nimodipine, but avoid hypotension given constricted vessels, risk for stroke from hypoperfusion.

Conditions Associated w/ Reversible Cerebral Vasoconstriction Syndromes

Pregnancy & puerperium	Early puerperium, late pregnancy, eclampsia, preeclampsia, & delayed postpartum eclampsia
Drugs & blood products	Phenylpropanolamine, pseudoephedrine, ergotamine tartrate, methergine, bromocriptine, lisuride, selective serotonin reuptake inhibitors, sumatriptan, isometheptene, cocaine, ecstasy, amphetamine derivatives, marijuana, lysergic acid diethylamide, tacrolimus (FK-506), cyclophosphamide, erythropoietin, IVIg, RBC tx
Foods	Chocolate, caffeine, & licorice
Miscellaneous	Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal SDH, post-CEA & neurosurgical procedures, exertion, or Valsalva
Idiopathic	No identifiable precipitating factor associated

(Adapted from *Neurocrit Care* 2005;3:91.)

ICH, IPH, SDH, epidural hematoma: HA w/ n/v, disorientation, focal findings; distortion of the meninges; can be uni/l or b/l, deep, constant.

Dx: CT.

Rx: See chapter on “Neurocritical Care.”

Vascular dissections

Clinical findings: High suspicion post-trauma; HA may precede neurological deficits; Ipsi HA/neck pain (occasionally shoulder, jaw or chest); pain often instantaneous, constant, & severe, may have a “tearing” quality; can also be

throbbing, sharp, or dull; may have autonomic features (if carotid artery involved & stretches sympathetics along artery); location of vessel dissected will define the deficits seen & can help target areas of concern; risk factors: severe or benign head/neck trauma, connective tissue disorder.

Exam & workup: CTA: “flame” sign often diagnostic (peaked area of contrast filling collapsed true lumen w/ the false lumen collapsing the vessel space). See chapter on “Stroke & Cerebrovascular Disorders.”

Venous sinus thrombosis

Risk factors: OCPs, dehydration, hypercoaguable, hyperviscous, or hypoproteinemic states, malignancy, extrinsic venous compression (i.e., meningioma or abscess), pregnancy & post-partum, low flow state in sinus.

Clinical history: Usually subacute onset worsening over days, may present as a thunderclap headache. May be assoc w/ neuro deficits, sz, papilledema.

Dx & Rx: See chapter on “Stroke & Cerebrovascular Disorders.”

Hypertensive urgency/emergency

Hypertensive HA occurs typically when SBP ≥200 mm Hg; resolves w/ Rx of the HTN.

Temporal arteritis

Clinical findings: M > F > 50 yo; incidence ↑ w/ age, peaks at 70-80; giant cell arteritis w/ inflam & degradation of internal elastic lamina & occlusion of lumen from hyperplasia; HA in 2/3rds; gradual onset w/ temporal, occipital pain, and/or scalp tenderness; may be assoc w/ jaw claudication, low grade fever, weight loss, visual sx; can lead to blindness if untreated; enlarged thickened vessel may be palpable.

Workup: ESR, CRP, fibrinogen; ESR > 40 in 80%; biopsy is still accurate even after Rx is initiated, but should be done w/in first few days.

Rx: Prednisone 40-60 mg/day. Improvement w/in days. Gradual decrease after 2-4 wk. Guide tx by sx & follow ESR/CRP.

SECONDARY HEADACHES DUE TO NONVASCULAR CAUSES

Tumors: May present as HA worse in morning, w/ lying down, straining, Valsalva, or bending over, new onset HA, persistent uni/l HA (See chapter on “Neuro-Oncology”).

Idiopathic intracranial hypertension (pseudotumor cerebri): Dx of exclusion after other causes of intracranial HTN (IH) have been r/o.

Clinical findings: Women of childbearing age, assoc w/ obesity; n/v, vision

Δs; HA worse w/ Valsalva, lying down, coughing, straining.

Work Up: Look for papilledema; CT to r/o 1° causes of IH; MRV/CTV to r/o venous sinus thrombosis; LP w/ OP; remove mod-large volume & assess response symptomatically.

Rx: Ophtho/neuro-ophtho for visual testing; serial LPs (not ideal); acetazolamide 250 mg PO QID; furosemide can be used if acetazolamide not tolerated, but is not as effective; corticosteroids short-term, can reduce IH to avoid optic nerve damage; avoid opioids; stop any offending meds; weight loss; treat related underlying disorders.

Conditions Mimicking Idiopathic Intracranial Hypertension

Medical disorders	***Meds***
Addison disease	Tetracycline & related compounds
Hypoparathyroidism	Vitamin A & related compounds
COPD	Anabolic steroids
Right heart failure w/ pulmonary HTN	Corticosteroid withdrawal
Sleep apnea	Growth hormone
Renal failure	Chlordecone
Severe iron deficiency anemia	Nalidixic acid
Obstruction to venous drainage	Lithium
Cerebral venous sinus thrombosis	Norplant levonorgestrel implant system
Jugular vein thrombosis	No identifiable precipitating factor associated

(Adapted from *Neurology* 2002;59:1492.)

Headache due to intracranial hypotension

Etiology: Worse w/ standing from seated position; due to over-drainage of CSF via surgically implanted shunt, skull base fractures (otorrhea/rhinorrhea), or spinal dural tear, either spontaneous or post-LP; can affect anyone, especially after trauma; about 4% of CSF leaks are spontaneous; in older patients, causes increased risk of SDH.

Work Up: If fluid can be collected send for beta-trace protein to confirm is CSF; CT can show narrowed lateral ventricles; imaging of area of concern (fine cuts through skull base, MRI spine, etc.); radionucleotide cisternography or myelography (can identify source of CSF leak).

Rx: 50%-85% of traumatic leaks resolve spont w/in 7 days, & almost all w/in 6 mo; ↑ fluid intake; bed rest; caffeine/sodium benzoate 500 mg IV × 1; can repeat in 4 h; blood patch to epidural space; if conservative rx do not work after 7 days consider surgical intervention.

HA due to infection (see chapter “Neurologic Infectious Diseases”): Meningitis, abscess, otitis media, sinus infxn.

Disturbances of homeostasis: Electrolyte or pH disturbances, sepsis, infxn, UTI; hormonal changes w/ menses, OC, HRT, or pregnancy; toxin exposure; hypoxia. Rx is to correct underlying cause.

HA & psychiatric disorders: Dx that should be given very sparingly only after extensive w/u & trials of meds ineffective.

HEADACHES SECONDARY TO MEDS

Med overuse headache: Careful history; can be tension/migraine in quality, depending on initial HA type; due to almost any med used for acute Rx; caution if on butalbital as abrupt w/d can cause szs; a long-acting NSAID (naproxen) can be used as pt w/d’s.

Drug withdrawal headaches: Often due to caffeine or opiate; HA itself is not dangerous; w/d danger depends on med/drug.

NEURALGIAS

Trigeminal neuralgia: Aka tic douloureux for facial grimace with pain; most common in F > age 50, can occur in children as young as 3; can be presenting feature of MS flair; due to microvasc compression or irritation of CN V by passing vessel; short electrical stabbing pain; volleys of pain on one side of face or mouth, involving one, two, or rarely three divisions of CN V (V2 most common); can be triggered by brushing teeth, chewing, talking, & light

contact w/ the skin; loss of trigeminal sensation is not typical; MRI brain to r/o MS/mass lesion.

Occipital neuralgia: Similar to trigeminal neuralgia but affects C2 on occiput.

Work Up: MRI w/ CISS or FIESTA sequence (thin cuts thru pontine cistern) for vasc compression, tumor, demyelinating lesions.

Rx: Responds well to meds (see table below); b/c condition is episodic, meds should be weaned after pain subsides.

Meds	Doses	Precaution	Side Effects
Carbamazepine	300-2,000 mg/day	Check CBC, lytes, ECG	Sedation, hyponatremia, leukopenia
Phenytoin	300-400 mg/day	Check CBC, ECG	Hirsutism, gingival hypertrophy
Baclofen	15-80 mg/day	None	Sedation
Lamotrigine	25-600 mg/day	Check renal & liver function	Increase slowly to avoid rash
Gabapentin	900-3,600 mg/day	Check renal function	Sedation
Clonazepam	1.5-8 mg/day	None	Sedation
Valproate	500-2,000 mg/day	Check CBC, liver function	Weight gain, hair loss, nausea

Procedures for trigeminal neuralgia: Lidocaine or botox injections. Percutaneous procedures, such as rhizotomy, stereotactic radiosurgery (gamma knife), surgical microvascular decompression.

Central Nervous System Vasculitis

Often considered in ddx of subacute encephalopathy. Difficult to dx. Practically, 1° CNS vasculitis (aka “primary angiitis of the CNS”, PACNS) is dx of exclusion. W/u of suspected CNS vasculitis covered here; material overlaps w/ vasculitidies in the “Neuro-rheumatology” section.

PRIMARY ANGIITIS OF THE CNS

Definition: Inflammation of CNS blood vessels → neurological si/sx related to CNS injury. Stenosis/occlusion → ischemia/infarction &/or aneurysm/hyalinosis/necrosis → hemorrhage. No definitive dx criteria. Pathology: necrotizing/lymphocytic vasculitis, ± granulomatous inflammation of CNS vessels (Leptomeningial/cortical arteries & arterioles > medium size arteries > veins/venules >> large intracranial arteries). Etiology: Idiopathic. Epidemiology: M = F, commonly 30-50 yo. Ddx: Benign angiopathy of CNS/reversible cerebral vasoconstriction syndrome (RCVS), infxn, 2° CNS vasculitis (CTD, malignancy, paraneoplastic, other systemic vasculitides, drugs).

Clinical manifestations (Ann Neurol 2007; 62:442): HA + encephalopathy + multifocal signs. Subacute (sx develop over weeks-months). S/sx: HA (63%), encephalopathy (50%), focal deficit/stroke (40%), sz (16%), ICH (8%), myelopathy. Workup: CBC/diff, BUN/Cr & UA, LFTs. ESR can be normal. Consider EMG, nerve/muscle bx for subclinical dz if systemic involvement suspected.

Minimally Invasive Testing

Serology	R/o underlying processes. ANA, RF, anti-Ro/La, anti-Sm, anti-RNP, anti DS-DNA, ANCA, C3 & C4, cryoglobulins, SPEP/UPEP, quantitative Ig, ACE, infectious serol. (HIV, VDRL, lyme, Hep B/C at minimum).
LP	50%-90% abnormal. ↑ or nl OP, ↑ TP, ↑ WBC (lymph), ↑ IgG, ± OCB, micro neg (send VZV, CMV, VDRL, lyme, others as indicated)
MRI	>90% abnl. Multifocal, bilateral T2/DWI abnormalities ± enhancement involving G/W matter.

Stroke >> ICH.

Rare tumor-like mass lesion.

Combination of neg MRI & LP has high neg predictive value

Invasive Testing

Angiography Suspicion + consistent CSF or MRI → consider conventional angio.

Nonspecific pattern of beading, aneurysm, circumferential/eccentric irregularities, multiple occlusions.

Sensitivity 60% vs. path (CTA/MRA less sensitive).

Pathology Gold standard. Clinical suspicion + prior w/u inconclusive or to confirm dx prior to Rx. Sample leptomeninges + cortex in an affected region. Segmental inflammation = false neg 25% vs. autopsy (*J Neurol* 2001;248:451). Granulomatous, lymphocytic, or necrotizing pattern.

Radiographic mimics: (Curr Opin Rheumatol 2008;20:29; Ann Intern Med 2007;146:34). RCVS most important: Severe, acute, sometimes recurrent HA + w/ (multi)focal deficits (21%). Also consider: Atherosclerosis, fibromuscular dysplasia (FMD), post-XRT.

Characteristics of PACNS vs. RCVS

	RCVS	**PACNS**
Demographics	2:1 female	2:1 male
Acuity	Acute	Subacute
Clinical setting	Defined setting (esp drug exposure, postpartum)	None clear
Reversibility	Days-weeks	Months or longer

SECONDARY ANGIITIS OF THE CNS

Definition: Systemic vasculitis w/CNS involvement or systemic process resulting in CNS vasculitis. Heterogeneous group of d/os. Involves PNS (mononeuropathy multiplex) > CNS.

	Systemic Vasculitidies
Bechet disease	Vasculitis of all sized arteries & veins; oral aphthae, ocular dz; CNS involvement 10%-20%
PAN	Systemic sx & neuropathy >> CNS
ANCA+ vasculitis	PNS >> CNS; *Wegener's*: Pulmonary, renal dz; *Churg-Strauss*: atopy, asthma → eos → vasculitis
GCA	Ophthalmic & ICA/vertebral arteries
Takayasu arteritis	Carotid stenosis
Cryoglobulinemic	CNS dysfunction via vasculitis or hyperviscosity syndrome
	Infections
Treponema pallidum	Any vessel traversing SA space; Favors base of brain
Borrelia burgdorferi	*Lyme neuroborreliosis*: Lymphocytic meningitis, cranial, & radiculoneuritis; CNS vasculitis rare
TB	Gelatinous exudate in SA space at base of brain/prepontine fossa; Meningitis → local vessel inflammation
VZV (or CMV)	*Immunocompetent*: Lg vessel; CN V zoster → c/l deficit; *Immunocompromised*: Sm vessel; HA, ↓ MS, focal deficits

Hep B & C	PAN & cryoglobulinemia
HIV	Vasculopathy ± vasculitis; CNS vascular dz 2/2 HIV or opportunistic infection
Fungi, *Bartonella*, rickettsial	Extremely rare

Connective Tissue Diseases

SLE	Typically small vessel vasculopathy w/ microinfarcts
Sjögren syndrome	Dry eyes/mouth, lymph exocrine infiltration; PNS >> CNS
Rheumatoid arthritis	Vasculitis & pachymeningitis; PNS >> CNS
Scleroderma	Myopathy, trigeminal neuropathy
MCTD	Anti-U1-RNP positive

Misc

Malignancy	Hodgkin's & NHL, hairy-cell leukemia, neoplastic angioendotheliamatosis, premalignant lymphomatoid granulomatosis
Paraneoplastic	PNS; Assoc w/SCLCA & lymphoma ± anti-Hu
Drugs	Cocaine, amphetamines, opioids; RCVS or true vasculitis
Cogan syndrome	↓ Vision (interstitial keratitis) & cochleovestibular dysfxn assoc w/systemic vasculitis
Susac syndrome	Retinopathy, BRAO, hearing loss, encephalopathy; Vasculopathy → microinfarcts

TREATMENT OF CNS-VASCULITIS

Therapy, monitoring, & follow-up for CNS vasculitis: Pts will generally be on high dose steroids & Cytoxan—each w/ specific complications. Close neurological f/u for management of complications of Rx or dz, & med adjustments. Repeat imaging PRN; many recommend repeat CTA or conventional angiogram q6mo. F/u testing & prophylactic meds for expected complications of each Rx discussed below.

STEROIDS

SLOW steroid taper: There is no "validated" schedule. The following is reasonable:

Solumedrol 1 g qday × 3 days, then SLOW steroid taper:

Starting dose: 1 mg/kg qd × 4 weeks, then ↓ 10 mg qwk until 40 mg/day, then ↓ 5 mg qwk until 20 mg/day, then ↓ 2.5 mg qwk until 10 mg/day, then ↓ 1 mg q2wk until 5 mg/day, then ↓ 1 mg qmo until off. Adjust dose PRN based on response.

Prophylactic medications while on steroids: PPI for GI ppx (e.g., omeprazole 20 mg PO qd); Calcium carbonate/vit D (e.g., 250 mg Ca/125 U vit D, 2 tab PO qd); Bisphosphonate (e.g., alendronate 70 mg qwk). Bactrim DS 1 tab qd.

Close PCP involvement: Monitoring labs, side effects (e.g., HTN, DM, weight gain).

CYTOXAN

General considerations: Usually reserved for cases that fail steroids, or with rapidly progressive course & biopsy support or thorough negative w/u. Usually given IV on

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monthly schedule, adjusted according to response (better tolerated & reduced risk for sterility & cystitis compared to daily oral).

Expected duration/schedule of cytoxan therapy: Typically dose monthly. Initial dose often given in hospital, subsequent doses in outpatient infusion center.

Initial frequency: q4wk × 6-12 mo, then gradually ↑ interval between doses. Frequency adjusted based on response—see below (based on MS literature; alternatively continue Cytoxan × 6 mos from time of clinical improvement/stability then switch to azathioprine or cellcept (or methotrexate) for 2-3 yr total, then try tapering those).

Tapering: By end of 3 yr transition to q10-12wk schedule, finally stop by ˜4 yr.

Duration: No clear data on how long to continue beyond 3-4 yr. Sometimes weaning → ↑ dz activity → give 3-5 days IV methylprednisolone & resume prior effective schedule.

Laboratory & other testing while on cytoxan

CBC w/ differential (and ANC): (1) Just prior (<24 h) to initial dose & each maintenance booster; (2) While adjusting regimen: Three CBCs b/n days 8 and 14 after Rx (e.g., days 8, 11, 14); (3) After stable regimen is established: Three CBCs as above for WBC nadir at least q3mo.

Urinalysis (macro & micro) before each treatment.

Chem7, Ca/phos/mag, LFTs, AED levels if applicable: (1) Before initiating CTX. (2) Probably reasonable to monitor these labs 1-2× monthly (before dose & midmonth) while adjusting regimen, then monthly to every 3 mo.

Yearly UA w/ cytology. Cystoscopy q1-2yr.

Initial dosing of cytoxan: Routine labs before & after administration—see below. Methylprednisolone 1g IV, followed by one dose of Cytoxan (same day).

Initial CTX dose: OUTPATIENT: 800 mg/m^2 IV (rounded to the nearest 100 mg), run over 30 min (calculate body surface area using a weight-based nomogram).

INPATIENT: Same initial dose (800 mg/m^2 IV), but give over 4 hr.

Adjunctive Rx (antiemetics, IVF/Mesna for renal protection, etc.)—see protocol below

Dose adjustments (total dose & frequency): Based on two factors: (1) midmonth WBC nadir: determines booster dose, (2) WBC count immediately prior to booster: determines dosing interval. Adjust total dose based on mid-month nadir: ↑ by 200 mg/m^2/month until WBC 1,500-2,000/mm^3 at midmonth nadir (or ANC < 500); If nadir falls below 1,500/mm^3, then ↓ dose by 100-200 mg/m^2; If dose → 1,400 mg/m^2 before criteria are met, then limit increments to 100 mg/m^2; MAX DOSE 1,600 mg/m^2 (even if WBC does not meet criteria). Adjust dosing frequency based on pre-dose WBC: IF/THEN actions based on WBC just prior to maintenance booster: 3,000-4,000/mm^3 → give 75% of established dose; 2,000-3,000/mm^3 → 50% of established dose; <2,000/mm^3 → give NO booster. IF no booster: pt should return 1 wk later for repeat WBC, potential Rx. After schedule is established: Check for

nadir ˜q3ms, adjust regimen PRN.

Suggested Protocol for Cytoxan Administration for CNS Vasculitis

General considerations: Encourage good PO; ideally, drink >3 L/day on day of Rx & following day. Encourage frequent urination. IVF: All treatments should be given w/ prehydration of at least 1 L (e.g., D5-1/2NS, D5W, or NS, depending on clinical comorbidities). Premedicate w/ antinausea medication. Diet as tol, avoid greasy/spicy.

Inpatient considerations/nursing orders: Strict I & Os. Call MD for urine output <50 mL/h, temp > 101 via TA, HR > 100. Robust IV access for high vol IVF (PICC line if nec.) May be adrenally suppressed 2/2 steroids: May need stress steroids. NS @ 150/h, min 500 mL infused before starting Cytoxan & total at least 2 L over 24 h.

Dosing & schedule: Antiemetics: Zofran 8 mg IV 1 h prior to Cytoxan, then Reglan or Zofran PRN. Steroids: Continue at same dose as before starting Cytoxan. Consider: ASA, MVI, thiamine, folate. DVT ppx if bedridden (e.g., LMWH).

Mesna (to prevent hemorrhagic cystitis; dose: 60%-140% of Cytoxan dose total if given IV) (*often not available in outpt setting—in this case hydration is even more critical*).

PO Mesna is ˜50% bioavailable; if given orally doses must be adjusted accordingly): Give 1/3 of entire dose 30-60 min before IV Cytoxan, 1/3 dose 4 h after start of Cytoxan (or immediately after 4 h infusion runs in), 1/3 dose 8 h after start of Cytoxan.

Example dosing schedule: 11 am-IV Mesna 333 mg/12 pm-IV CTX 1,000 mg/4 pm—IV Mesna 333 mg/8 pm—IV Mesna 333 mg.

Cytoxan rate: OUTPATIENT: Run over 30 min. INPATIENT: run over 4 h.

Pain

Characterization: Intensity—can rank on a visual or numerical scale; evoked and/or spontaneous (if evoked, nature of stimulus)? Mitigating factors? Continuous or episodic (and how long episodes last)? Quality of pain (verbal descriptions), localization/radiation, effect on functioning & psychological well-being.

Pain Types: Nociceptive 2/2 ongoing noxious stimulus; Inflammatory: 2/2 ongoing inflammation; Neuropathic: 2/2 lesion in PNS/CNS; persists despite absence of continued stimulus; lancinating, burning, or shock-like.

Abnormal sensory responses: Hypoesthesia—↓ sensory perception; hyperesthesia— ↑ sensory perception; hyperalgesia—↑ pain sensation; paresthesia—abnl sensation; dysethesia—painful paresthesia; allodynia—pain elicited by non-noxious stimulus, e.g., wind, light touch, clothing.

Sensory nerve fiber types

- A-β fibers: Rapidly conducting (40-50 m/s), thickly myelinated: convey vibration, proprioception, touch
- A-δ fibers: Slowly conducting (10-30 m/s), thinly myelinated; convey initial pain and temp sensation
- C-fibers: Very slowly conducting (0.7-2.3 m/s), unmyelinated; convey delayed pain and temp

OPIOIDS

- Act via activity at μ, δ, κ, and orphan receptor-like opioid receptors.
- Major effects: Analgesia, resp depression, n/v, cough suppression, miosis, ↓ GI secretions & mobility, ↓ sympathetic CV output.

Opioid Equianalgesic Dose Conversion Table

Drug	PO/PR (mg)	SQ/IV/IM (mg)
Morphine	30	10
Oxycodone	20-30	n/a

Hydrocodone	20-30	n/a
Hydromorphone	7.5	1.5
Fentanyl	n/a	0.1
Oxymorphone	10	1
Meperidine	300	75
Codeine	200	120

Conversion is approx.; wide variation (rates from X to Y not necessarily the same as from Y to X). Modified from The Massachusetts General Hospital Handbook of Pain Management. ed. Ballantyne J. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

Methadone: Metab varies between indiv (2/2 metabolism by N-demethylation vs. glucuronidation); slow β-elimination phase with $t_{1/2}$ = 15-60 h. Risk of resp depression. Sedation can outlast analgesic effects, which follow α-elimination $t_{1/2}$ = 2-8 h. IV methadone has 2× potency. Dose conversion depends on total opioid dose: Higher morphine: methadone ratio for larger chronic dose. Wide range of conversion estimates (use caution). Rough guideline is 4:1 oral morphine: oral methadone, if oral morphine daily dose is 30-90 mg; 8:1 if 90-300 mg; and 12:1 or ↑ if > 300 mg (J Clin Oncol 1998;16:3216).

Responses to medications: Tolerance—need to ↑ dose to maintain analgesia; physical dependence—w/d sxs upon abrupt cessation; addiction—psychological dependence char by preoccupation w obtaining drug, compulsive use despite adverse consequences, loss of control; pseudoaddiction—drug-seeking behav 2/2 inadequate tx.

NEUROPATHIC PAIN MEDICATIONS

Most established for post-herpetic neuralgia & painful diabetic neuropathy; utility inferred in other conditions, e.g. complex regional pain syndrome.

First line: Tricyclic antidepressants (TCA): SEs: Anticholinesterase effects—dry mouth, urinary reten., const.), orthostatic hypotension. Major risk: Cardiac tox, risk of death w/ OD. Consider screening EKG if age > 40. Amitriptyline → ↑antichol SE; 2° amine derivatives such as nortriptyline or desipramine have less.

Selective serotonin & norepinephrine reuptake inhibitors (SSNRI):

Duloxetine, venlafaxine.

Common SEs: Nausea, drowsiness, appetite change. Less sexual SEs than TCAs.

Gabapentin and pregabalin: Generally well tol., min drug-drug interactions; common

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P.179

SEs: Somnolence, dizziness; can be minimized by slow up-titration. Efficacy less than TCAs, but better SE profile.

Second line: Opioids: Similar efficacy to TCAs, but higher risk of abuse.

Third line: Oth AEDs: Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid.

Drug Dosing for Oral Neuropathic Pain Treatment

Drug	Initial Dose	Typical Maintenance Dose	Maximum Dose
TCAs	10-25 mg qhs	50-100 mg/day	150-250 mg/ day
Duloxetine	30 mg qd	30 mg bid/ 60 mg qd	120 mg/day
Venlafaxine	37.5 mg qd-bid	75 mg qd	225 mg qd
Gabapentin	100-300 mg tid	600-900 mg tid	3600 mg/day
Pregabalin	25-50 mg tid	50-100 mg tid/75-100 mg bid	600 mg/day
Lamotrigine	25-50 mg qd	200-400 mg/day	500 mg/day
Topiramate	25 mg qd	100-200 bid	400 mg/day
Carbamazepine	100 mg	200-400 mg bid	1600

	bid		mg/day
Oxcarbazepine	300 mg bid	600 mg bid	2400 mg/day

(Modified from *Pain* 2007;122:237.)

PAINFUL DIABETIC NEUROPATHY

Epidemiology: 25%-30% pts w/ DM have distal symmetric sensory or sensorimotor polyneuropathy (DSP); 8%-26% have neuropathic pain (Curr Opin Neurol 2008;21:527)

Tx: TCAs, AEDs, gabapentin, pregabalin, opioids, topical lidocaine. TCAs have lower NNT than AEDs, less dependence/addiction than opioids.

ZOSTER PAIN AND POST-HERPETIC NEURALGIA

Key features: Painful prodrome in up to 75%; uni/l dermatomal dist. of grouped vesicles or papules; history of prior rash in same location suggests herpes simplex, not zoster; pain and allodynia in area of rash.

Three phases of pain (based on temporal patterns of improvement): (1) herpes zoster acute pain: resolves within 30 days of rash onset; (2) subacute herpetic neuralgia: abates within 30-90 days after rash onset; (3) postherpetic neuralgia—persists > 120 days.

Tx: TCAs, gabapentin, pregabalin, opioids, topical lidocaine. Acute treatment with antivirals: was thought to ↓ risk of postherpetic neuralgia; recent Cochrane review does not support this (Cochrane Dat Systemic Rev 2009;2:1; J Pain 2008;9:S37).

COMPLEX REGIONAL PAIN SYNDROME

Definition: Continuing pain disproportionate to inciting event (usually injury, can be immobilization or structural lesion); Type I (reflex sympathetic dystrophy)—without major nerve damage; Type II (causalgia)—with major nerve damage.

Si/Sx: Sensory (hyperesthesia and/or allodynia), vasomotor (temp/color asymmetry), sudomotor (sweating changes)/edema, motor/trophic (wkness, tremor, dystonia, and/or nail or skin thickness Δs) dysfxn.

Tx: Same as for neuropathic pain. Calcitonin and bisphosphonates. PT is key. Procedures to interfere w/ sympathetic innervation (stellate ganglion block, lumbar sympathetic block, Bier block) widely used, without strong evidence (Harden RH. Reflex Sympathetic Dystrophy Syndrome Association

Treatment Guidelines, 2006, http://www.rsds.org/3/clinical/guidelines/index.html).

LOW BACK PAIN

Epidemiology: 15 million physician visits; fifth most common complaint. 90% of acute episodes (duration < 3 mo) recover; after that becomes less likely. Return to work rate after 6 mo off <50%; after 2 yr close to 0%.

Approach: Distinguish between axial LBP, radicular pain, or pain in legs. Predominantly axial/pain: Usually degen Δs of discs and facet joints. Radicular pain: Impingement of nerve roots centrally or at neural foraminae 2/2 disc herniation, facet joint hypertrophy, & enlargement + calcification of ligaments. Red flags: Si/sx conus medullaris or cauda equina compression—bowel or bladder retention or incontinence, groin paresthesias, progressive wkness, worsening pain. Pos straight leg raise is 91% sens for disc herniation

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but not spec (26%); cross straight leg raise (raising the opposite leg causes pain) is 88% spec but only 29% sens. (Spine 2000;25:1140); straight leg-raise, abnormal cold sens, and ↓ pinprick most discriminating tests (PLoS Med 2009; 6: e1000047).

Tx:

Pain	Initial therapy	Rx for persistent pain
Acute radicular	Course of NSAID or acetaminophen; add muscle relaxant if spasm present. If severe, add an opioid analgesic for a short period	Epidural steroid injection 2-6 wk after onset can ↓ duration of pain but does not affect long-term outcome
Chronic radicular	Neuropathic pain med. Min chronic opioid tx, esp for neuropathic pain	Consider a trial of a spinal cord stimulator
Acute axial	Course of NSAIDs or acetaminophen + muscle relaxant if spasm present	Physical therapy
Chronic axial	Local anesthetic blocks of the innervation to facet joint (medial	Consider a multidisciplinary pain

	branch blocks). If successful, radiofrequency ablation of the media → >6 mo of relief	treatment program, including medical, rehabilitation, and behavioral treatments

(Modified from *JAMA* 2008;299:2066.)

TRIGEMINAL NEURALGIA

Definition: Unilateral lancinating brief (<1s) stereotyped paroxysmal attacks of severe pain in trigeminal distribution.

Epidemiology: ˜4.5/100,000/yr F>M, slightly. Most common >50 yo.

Dx: Most common in second and third CN V divisions (rare in first); precipitated by light mechanical stimulation to small areas of face/oral mucosa (trigger zones) by light touch or wind, as well as eating, drinking, or speaking; may cause ipsi muscle spasm (tic douloureux). “Classic TN” (idiopathic or 2/2 vascular compression of CN V): Clinical sensory exam is normal; pts are asx between attacks. “Symptomatic” TN: Identifiable nonvascular structural lesion responsible (e.g., cerebello-pontine angle tumor compressing the CN5 root, MS, odontogenic).

Tx: Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:527.

Pharmacological: Maj pts respond well to med tx; best studied is carbamazepine; some evidence for oxcarbazepine, baclofen, lamictal, gabapentin, phenytoin.

Surgical: Three main options; choose based on age, concern for SEs. (1) Percutaneous ablative procedures directed toward gasserian ganglion (thermal, mech, or chem disruption); (2) microvasc decompression of the trigeminal root; (3) gamma knife XRT to trigeminal root.

CERVICOGENIC HEADACHE AND OCCIPITAL NEURALGIA

Definition: Head/face pain from bone, nerve, or soft tissue structures of neck/C-spine. 0.4%-2.5% in general pop, much higher in pts w/ chronic HA. F > M (4:1). Cross-talk b/n CN V nucleus & upper cervical level sensory fibers → head and face pain.

Presentation: Triggers: Neck movement, sustained/awkward neck postures, Valsalva, cough/sneeze; may be reproduced by pressure over suboccipital, C2-4 regions or greater occip nerve; restricted active/passive neck ROM, stiffness. Typically u/l w/o shifting sides; can be b/l; localized to occip, frontal, temporal, or orbital regions; intermittent × hours-days or constant, or constant + superimposed attacks; usually deep, nonthrobbing; may throb

when migraine superimposed; assoc si/sx: n/v, photo/phonophobia; dizziness, blurred vision, lacrimation, conjunctival injection, ipsi neck, shoulder, or arm pain.

Occipital neuralgia: Isolated to sensory fields of greater/lesser occip nerves; usu deep/burning pain w/ brief episodes of shock-like pains; paresthesias or numbness over the affected scalp; due to occip nerve entrapment but can be referred from C2 spinal root, or C1-2 or C2-3 facet joints.

Eval: R/o post-fossa tumor, Arnold-Chiari malf, abnl vasc structure (e.g., AVM/dural fistula) or injury (e.g., vert dissection).

Treatment: NSAIDs, trial of neuropathic pain treatments; PT; occip nerve block can be beneficial but may falsely identify the occip nerve as the source of the pain;

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if diagnostic blocks of cervical nerve or medial branch (which innervates the facet joints) are pos, radiofrequency ablation can provide longer relief (J Am Osteopath Assoc 2005;105:S16).

PHANTOM LIMB PAIN

Distinct from phantom limb awareness, phantom sensations, and stump pain. Occurs in 50%-80% of amputees regardless of reason for amputation. Failure to block by local anesthetic to stump suggests that central mech involved. Neuropathic pain meds have not been found to be effective. Myoelectric prosthesis or sensory discrimination testing may help min. cortical reorganization and ↓ pain (Nat Rev Neurosci 2006;7:873).

CENTRAL POST-STROKE PAIN (DEJERINE-ROUSSY SYNDROME)

General: Usually 2/2 thalamic stroke, but also 2/2 lesions throughout spinothalamoc-ortical pathway; pain develops usu 1-2 mo after ischemic stroke/ICH. Can be spont or evoked.

Tx: Amitriptyline and lamotrigine first line. Alternatives: Mexiletine, fluvoxamine, gabapentin (Anesth Analg 2009;108:1645).

DYNIAS

(Sem Neurol 1996;16:63.)

Definition: Poorly understood focal, often chronic pain syndromes. Usually tx'd w/ neuropathic pain meds, espc TCAs.

Glossodynia: Painful tongue, synonymous with "burning mouth syndrome." Must r/o: Rxns to dental materials/implants, vit def (B_{12}, other B vitamins, Fe,

folate, and zinc), endocrine causes (myxedema, DM), psych causes.

Carotidynia: Pain over carotid that may project to ipsi head; self-limited <2 wk duration. Controversial dx; recently removed from International Classification of Headache Disorders. Vascular lesions of carotid, lesions of soft tissues of neck must be r/o.

Vulvodynia: Pain at vaginal introitus; usually h/o dyspareunia, pain w/ tampon insertion; constant pain can also occur. Exam: Exclude vulvar dermatoses/malignancy. Psych support often nec. component of tx.

Orchidynia: testicular dynia, orchialgia; 1° or 2/2 infection, malig, trauma, surgery, torsion, other structural lesion (varicocele, hydrocele, spermatocele). Pain referred from hip, ureter (e.g., nephrolithiasis), or 2/2 entrapment of genitofemoral/ilioinguinal nerves.

Prostatodynia: Persistent lower urinary tract symptoms (urgency, dysuria), prostatic discomfort w/o evidence of bacteria or purulence in prostate fluid. May localize to perineum, suprapubic area & groin, low back; ± pain w/ ejaculation.

Coccygodynia: Osteoarthritis of sacrococcygeal & coccygeal joints, 2/2 trauma or chronic pressure. Pain commonly 2/2 anorectal infxns, anal fissures or hemorrhoids, rarely tumors. Pain can be improved by sitting on a doughnut-shaped pillow to remove pressure.

Proctodynia: Anorectal area; may be 2/2 local dz of anus or rectum, or referred from urogenital tract or lower spine. Includes proctalgia fugax, sudden brief spasms of pain.

PAIN SYNDROMES FROM SODIUM CHANNEL MUTATIONS

(Adv Genet 2008;63:85.)

Rare pain syndromes a/w mutations in voltage-gated sodium channel Na_V 1.7.

Erythromyalgia: Prominent features: Erythema, swelling, burning pain, predom of distal extrem. 1° and 2° forms exist. 1° form: Most of the characterized mutations cause channel activation at less depolarized voltages. Secondary causes include PN, mushroom or mercury poisoning, hypercholesterolemia, myeloproliferative disease, and autoimmune conditions.

Paroxysmal extreme pain disorder (familial rectal pain syndrome): Pain in the ocular, mandibular, and rectal areas. Associated mutations impair channel inactivation.

Congenital insensitivity to pain: Extremely rare condition in which

nociception is impaired but other sensory modalities are preserved. Pts often suffer damage to oral cavity and limbs due to absent pain sens. Mutations have completely elim. measurable current.

Dizziness and Deafness

Vestibular system: Otolith organs composed of cilia embedded in crystals (called otoliths), floating w/in endolymph (viscous fluid). Mvmt of head causes endolymph to move in opp direction, forcing the cilia to travel w/ it. Direction of mvmt is encoded by one or more otolith organs; amplitude is encoded by firing rate of the cilia (proportional to degree of bending). Otolith organs sense linear (saccule & utricle) & rotational (semicircular canals) acceleration.

Auditory system: Sound waves → vibrates TM → vibrates middle ear ossicles → fluid wave of endolymph in cochlea → vibrates basilar membrane of organ of Corti → hair cells bend → activation of cochlear/auditory nerve → dorsal + ventral cochlear nuclei → superior olivary n. → inferior n. → medical geniculate n. → auditory cortex (transverse temporal gyri of Heschl).

APPROACH TO DIAGNOSIS OF DIZZINESS

Tables below adapted from Medical Clinic North America 2003;87:609.

History: Key questions: Tempo, meaning of "dizzy," circumstances of sxs (positional v. constant), assoc sxs (N, V, visual changes), previous h/o similar sxs, affect pt's life, meds (Δs or new additions), pt's best guess of cause of dizziness.

Elements of History

D/o	Tempo	Sxs	Circumstances
Vestibular neuritis	Acute dizziness	Vertigo, dysequilibrium, N/V, oscillopsia	Spontaneous, exacerbated by head movements
Labyrinthitis		Vertigo, dysequilibrium, N/V, oscillopsia, hearing loss, & tinnitus	
Wallenberg's syndrome (dorsal		Vertigo, dysequilibrium,	

medullary infarct)		N/V, tilt, lateropulsion, ataxia, crossed sensory loss, oscillopsia	
B/l vestibular deficit or >3 days from a uni/l vestibular defect		Dizzy, dysequilibrium, occasionally oscillopsia	Induced by head mvmts, worsened when walking in dark or on uneven surfaces
Mal de debarquement	Chronic dizziness	Rocking or swaying as if on a boat	Spontaneous while lying or sitting. Rarely occurs while in motion
Oscillopsia		Subjective illusion of visual motion	Spontaneous w/ eyes open
Anxiety/depression		Lightheaded, floating, or rocking	Induced by eye movements w/ head still
Benign paroxysmal positional vertigo	Spells: seconds	Vertigo, lightheaded, N	Positional: Lying down, sitting up or turning over in bed, bending forward
Orthostatic hypotension		Lightheaded	Positional: Standing up
Transient ischemic attacks		Vertigo, lightheaded, dysequilibrium	Spontaneous
Migraine	Spells:	Vertigo, dizziness, motion	Usually movement induced

	minutes	sickness	
Panic attack		Dizzy, N, diaphoresis, fear, palpitations, paresthesias	Spontaneous or situational
Motion sickness		N, diaphoresis, dizzy	Movement induced, usually visual-vestibular mismatch
Meniere disease	Spells: hours	Vertigo, dysequilibrium, ear fullness, hearing loss, & tinnitus	Spontaneous, exacerbated by head movements

Central vs. Peripheral features[a]

	Central	**Peripheral**
Nausea	None/mild	Severe
Positional	No	Yes
Neurologic signs/Sx	Common	Rare
Imbalance	Severe	Mild/moderate
Hearing loss	Rare	Common
Oscillopsia	Severe	Mild
Caloric test	Hyperexcitability	Canal paresis

Recovery	Mos	Days-weeks
Nystagmus	Pure vertical or torsional, multidirectional, can change direction w/gaze, dysconjugate, no suppression w/ fixation	Torsional and/or horizontal, unidirectional in all gazes, conjugate, suppresses w/ fixation

[a] Classic features—central lesions can mimic peripheral features.

Sxs	**Mechanism**
Dysequilibrium: Imbalance or unsteadiness while standing or walking	Loss of vestibulospinal, proprioception, visual, motor fxn, joint pain/instability, & psych factors
Lightheadedness or presyncope	Decreased blood flow to the brain
Sense of rocking or swaying as if on a ship (mal de debarquement)	Vestib syst adapts to continous passive motion, must readapt once envir stable. Anxiety.
Motion sickness	Visual-vestibular mismatch
N & V	Stimulation of medulla
Oscillopsia: Illusion of visual motion	Spontaneous: Acquired nystagmus headinduced: severe, b/l loss of the VOR
Floating, swimming, rocking, & spinning inside of head (psychologically induced)	Anxiety, depression, & somatoform d/os
Vertical diplopia	Skew deviation
Vertigo: Rotation, linear movement, or tilt	Imbalance of tonic neural activity to vestib cerebral cortex

Physical examination: Key elements: General exam (spontaneous movement, N, V), visual acuity, eye movements (spontaneous, pursuits, saccades), vestibular-ocular reflex testing, position testing, coordination (ataxia in

cerebellar lesions) gait.

Physical finding	Pathology
Spontaneous nystagmus present	Acute UVL, or brainstem/cerebellum abnormality
Skew deviation (comitant vertical eye misalignment)	Disruption of peripheral or central utricle pathway
Decreased VOR	Chronic vestibular hypofunction
Eye movements & vertigo elicited only during maneuvers	Usu inner ear debris w/ BPPV. Rarely central pos vertigo/nystagmus, perilymphatic fist., hypermobile stapes, Meniere dz, sup SCC dehiscence
Visual tracking impaired	Brainstem abnormality
Imbalance while standing/walking	Any of the above

(Adapted from *Medical Clinic North Am* 2003;87:609.)

Vestibülar-Ocular Reflex Testing

Test	Procedure	Result
Vestibular dynamic visual acuity	Static, distant visual acuity is determined w/ the head still. Dynamic visual acuity determined while pt's head oscillated manually at 2 Hz	A dynamic visual acuity of 3 or more lines above static visual acuity indicates a vestibular defect
Head thrust	Pts fixate on a distant visual target, & eye position is observed immediately after a small thrust of the head to the left & right	A refixation saccade & oscillopsia after head thrust toward dysfxnal canal indicates decreased VOR

Head-shaking nystagmus	Pitch the pt's head down 30 degrees & oscillate the head horizontally 20×	Elicitation of jerk nystagmus indicates a vestibular imbalance

Bedside Positional Maneuvers

Maneuver	Description	D/o
Dix-Hallpike	See below under "BPPV" for details	BPPV, central positional nystagmus, central positional vertigo, dehiscence of superior SCC, perilymphatic fistula
Pressure testing	Nystagmus/drift of eyes w/ pos + neg pressure directed to ext auditory canal	Dehiscence of superior SCC, Meniere disease, perilymphatic fistula
Tullio sign	Nystagmus or drift of eyes w/ loud noise	

(Adapted from *Medical Clinic North Am* 2003;87:609.)

Stance

Maneuver	Description	D/o
Romberg	Stand w/ feet slightly apart + arms by side w/ eyes open for 30 s & then eyes closed for 30 s; Romberg present when pt is stable w/ eyes open but loses balance w/ eyes closed	Acute vestibular lesion; peripheral neuropathy; some aged >65; functional d/o w/ exaggerated sway or rock on heels but not fall
Fukuda stepping	Step in place for 50 steps w/ arms extended & eyes closed; pos w/ turning to one side >30 degrees	Uni/l vestibular lesion

Retropulsion	Stand w/ feet slightly spread apart & instruct them to take just one step backward if they are pulled backward by the hips by a mild force; pos test if ≥3 steps backwards or falls backwards	PSP, PD, NPH

Imaging: CT/MRI: Stroke/ICH.

Neurophysiology: Electronystagmography or videonystagmography—eval of saccades, pursuit, gaze stabilization, nystagmus, extraocular mvmts w/ caloric irrigation testing.

CENTRAL CAUSES OF DIZZINESS

DDx of central dizziness: Cerebrovasc d/os, migraine, central pos. vertigo, MS, szs, CP angle tumors, cerebellar degen/cerebellitis, hereditary ataxias, craniocervical jxn d/os, psych.

Cerebrovascular D/os

Vertebrobasilar TIA	Episodic Concurrent diplopia, dysarthria, drop attacks, ataxia Consider subclavian steal syndrome	
PICA stroke	Wallenberg syndrome	
AICA stroke	Cerebellar ± brainstem stroke or direct infarction of inner ear (peripheral)	
SCA stroke	Ipsi dysmetria Full SCA syndrome (rare) includes: Horner's, contralateral CN VI palsy, contralateral pain/temp loss	
Insular stroke	Rarely can cause tilting, lateropulsion, N, unsteady gait	
Posterior fossa hemorrhage	Any combination of above + HA/MS changes	

Presyncopal dizziness	Global hypoperfusion

Migraine: Dizziness common; basilar migraine; HA often occipital; aura Sx localize to basilar; triptans contraindicated 2/2 risk stroke. Benign paroxysmal vertigo of childhood: Age 1-4 yr, paroxysms of vertigo & imbalance + N/V usually w/o HA lasting 1-20 min w/o permanent sequelae; felt to be subtype of migraine, often responds to migraine Ppx. Migranous vertigo: Migranous sx + intermittent vestibular sx; often responds to migraine PPx.

Central positional vertigo: ˜ 10% of positional vertigo/nystagmus is central; lesions can be near fourth ventricle, dorsal vermis, vestibular nuclei; felt to be a disinhibition of vestib reflexes; can be imposs. to differentiate from BPPV w/o imaging or specialized vestib testing.

Multiple sclerosis: Can mimic peripheral dz if plaque in root entry zone of vestibular nerve; heavily myelinated middle cerebellar peduncle common site; look for INO, pendular nystagmus; vertigo & dizziness can be a SE of MS tx.

Epilepsy: Rare. Vertiginous epilepsy: Recurrent vestibular sx alone or w/other sz/sx. Rotatory sz: Rotation of the body >180 degrees w/ speech arrest & 2° generalization. Vestibulogenic sz: Sz induced by vestib stimulation (caloric testing). Dizziness/vertigo/nystagmus all SEs of AEDs.

Cerebellopontine Angle Tumors

Vestibular schwannoma (acoustic neuroma)	Benign vestibular nerve Schwann cell tumor Most common CP angle tumor Uni/l hearing loss, tinnitus, & ataxia first Sx Can impact cerebellum, pons, CN V & VII Assoc w/NF-2
CP angle meningioma	Second most common CPA tumor CN V, VII, VIII equally likely to be affected
Cerebellar tumors	Metastasis most common in adults

	Medulloblastoma most common in children
	Also astrocytoma, ependymoma, hemangioblastoma
	Occipital HA common

Cerebellar Degeneration/Cerebellitis

Paraneoplastic	Anti-Yo, anti-Ri: Breast & gyn CA
	Anti-Hu, Zic 1, Zic 4, PKCγ: Lung
	Anti-Tr, anti-mGluR1: Hodgkin dz
Infectious/post-infectious/post-vaccination	Generally age < 6
	Parainfectious/post-vaccine pathology is demyelination
	Bact & viral causes, incl VZV, HSV, Lyme
	Can be assoc w/cerebellar swelling in severe cases
	Steroids ± EVD or suboccipital decompression may be indicated
	Recovery is the norm
Alcohol-related	Especially vermian
Other	Vitamin deficiencies (thiamine, vit E)
	Toxins (AEDs, chemotherapeutics)
	MF-GBS
	GAD- or Gliadin-assoc cerebellar ataxia

Hereditary ataxias: SCA1-SCA28: Autosomal dominant; 6 are CAG repeat (SCA1-3, 6, 7, 17); Freidreich ataxia: Autosomal recessive GAA repeat; familial episodic ataxias: autosomal dominant channelopathies.

Craniocervical junction D/Os: Sx worsen w/neck extension & cough; spontaneous & positional vertigo, tinnitus, hearing loss, dysarthria/dysphonia,

ataxia, shortness of neck, low neck hair line, limited neck ROM, lower CN signs, sometimes hydrocephalus.

Craniocervical Junction D/os

Atlas-foramen magnum congenital fusion	Most common anomaly Signs of cervical cord compression
Atlantoaxial dislocation	Instability of C1 (atlas) on C2 (axis) Assoc w/ RA & Down syndrome
Platybasia & basilar invagination	Platybasia: Flattening skull base Basilar invagination: Upward bulging of occipital condyles Characteristic shortness of neck w/cerebellar/spinal signs
Chiari type-1 malformation	>5 mm cerebellar tonsillar herniation through foramen magnum Progressive dizziness or gait instability ± positional vertigo, tinnitus, hearing loss, lower CN signs May worsen w/ neck extension

Psychiatric dizziness: Panic d/o, gen anxiety, depression, personality d/o common in dizzy pts; look for stimuli inv social events; no nystagmus helps in dx; vestibular d/o can also induce psych sx; phobic postural vertigo; subjective sx gen w/o falls assoc w/spec stimuli/positions/social situations; nl testing; avoidance behavior.

PERIPHERAL CAUSES OF DIZZINESS

Vestibular neuritis: Vertigo, N, nystagmus, tendency to fall toward lesion w/o hearing loss or other neuro sx; often post- or para-infectious; some e/o latent HSV infxn similar to Bell’s; subsides in weeks due to habituation & some return of fxn (often not complete); uni/l hearing loss may implicate labyrinthitis; image if any vasc RF or central si’s (CN VIII enhancement may be seen). TX: Steroids if ≤3 days from onset for faster recovery (no clear

long-term benefit); short-term anti-emetics & vestibular suppressants (meclizine, bz); vestib rehab.

Ménière disease: Recurrent attacks of vertigo lasting >20 min w/horiz rotatory nystagmus; hearing loss (may not be episodic); aural fullness and/or tinnitus; vertigo often severe w/days of disequilibrium/N/V; often becomes b/l; caused by endolymphatic hydrops. TX: Low-Na diet, avoid caffeine/chocolate/EtOH/tobacco; diuretics may be helpful; for acute attacks, oral steroids (prednisone 1 mg/kg × 10-14 days; 2 wk taper); if unsuccessful consider IM or intratympanic methylpred/dexamethasone; Menitt device (noninvasive pulse-pressure tx); endolymphatic sac enhancement surgery; if intractable consider destructive tx: gentamycin transtympanic perfusion, vestib neurectomy, labyrinthectomy.

Benign paroxysmal positional vertigo: Most common cause of vertigo; brief (<1 min) spells provoked by Δs in position; central findings absent; canalithiasis: debris trapped in canal causes abnl cupula stim w/ head mvmt; post canal BPPV 85%-95%, lateral BPPV 5%-15% (ant, multiple, b/l rare); dx w/ Dix-Hallpike maneuver. Recovery often spont after wks-mos of sx, but may recur; TX: Canalith repositioning maneuvers (e.g., Epley), habituation exercises (e.g., Brandt-Daroff), meds, surgery for refractory cases.

Dix-Hallpike Maneuver

Procedure	Pt sitting upright w/ legs extended
	Rotate head 45 degrees
	Lie pt down quickly keeping head at 45 degrees lowering head off back of table ˜20 degrees below horiz
	Observe eyes for 45 s
Pos results	Latency: 5-10 s
	Direction: Rotational-upbeat nystagmus toward affected ear (sx more severe w/affected side down)
	Duration: 30-60 s
	Reversal: Direction reverses when sitting up
	Fatigability: Effect diminishes w/ repeated tests

Rx BPPV

Epley	Pt sitting upright w/ legs extended

maneuver • Only effective for posterior canal dz • Multiple studies demonstrate effectiveness	Rotate head 45 degrees toward affected side Lie down quickly w/ head at 45 degrees, lowering head off back of table ˜20 degrees below horiz (affected side ↓) & hold 30 secs Turn head 90 degrees toward nonaffected side & hold 30 secs Turn head & body an additional 90 degrees toward nonaffected side & hold 30 secs (pt now lying on side w/face pointed nearly ↓) & hold 30 secs Bring pt to upright sitting position Pt often asked to remain in upright position ×24 h (sleep in chair; not validated)
Other maneuvers	CRP: Lempert supine roll maneuver & Gufoni method for horiz BPPV Habituation: Semont maneuver
Brandt-Daroff exercises • Less effective than Epley • Often used in conjunction	While sitting up, pt turns head 45 degrees to L Quickly lie to R w/head held in position (looking up) & hold 30 secs or until dizziness subsides Return to upright position w/head neutral position & hold 30 secs Turn head 45 degrees to R & quickly lie to L w/head held in position (looking ↑) & hold 30 secs or until dizziness subsides Return to ↑ position w/head neutral position & hold 30 secs Repeat 5× for 1 set; repeat 3 sets/day
Meds	Anti-emetics, meclizine, BZs, scopolamine
Surgery	Posterior semicircular canal occl. & singular neurectomy Reported effective only in unblinded, retrospective studies

APPROACH TO DIAGNOSIS OF HEARING LOSS

History: Tempo, trauma, infxn (otitis externa/media, measles, mumps, CMV, syphilis, Lyme), si's/sxs dizziness, recent HEENT surg, meds (aminogylcosides, quinine, salicylates, cisplatin).

Exam: Exam of outer & middle ear; otoscopic exam; Weber test: Place 512 Hz tuning fork at the middle of the head; in uni/l conductive hearing loss, sound heard loudest in affected ear; Rinne test: Place 512 Hz tuning fork on mastoid process until no longer heard, then next to external ear; in conductive hearing loss, sound heard longer on mastoid than ear; audiometry.

CAUSES OF HEARING LOSS

Conductive Hearing Loss

History	Physical findings	Etiology
Sudden painless hearing loss	Cerumen	Complete canal occl
Sudden painful hearing loss	Narrow canal w/ debris	Otitis externa
	Nl canal; red, immobile tymp memb	Chronic otitis media
Gradual painless loss of hearing	Immobile tympanic membrane	Middle ear effusion
	Nl mobile tympanic membrane	Otosclerosis
	Reddish-blue pulsating mass behind intact tympanic membrane	Glomus tumor or vascular anomaly
	Retracted or perforated tympanic membrane, w/ chronic drainage	Cholesteatoma

(Adapted from *Am Fam Physician* 2003; 68:1125-1132.)

Sensorineural Hearing Loss

History	PE	Audiogram	Etiology
Gradual hearing loss, noise/tobacco exposure	Elderly pt; nl TM	B/l, symmetric high-frequency loss	Presbycusis
Gradual hearing loss, noise/tobacco exposure	Nl TM	B/l, sym loss at 4,000 Hz	Noise-induced hearing loss
Rapidly progressive, b/l hearing loss ± fluctuation	Nl TM ± vertigo or disequilibrium Nl TM; vertigo & nystagmus	Any abnl pattern w/ poor speech discrimination	Autoimmune hearing loss
Sudden uni/l hearing loss, tinnitus, vertigo, head trauma, straining	Nl TM	Any uni/l abnl pattern	Perilymph fistula
Sudden, fluctuating, uni/l hearing loss, tinnitus, episodic vertigo	Nl TM	Uni/l low-frequency loss	Meniere disease
Gradual uni/l hearing loss, tinnitus	Nl TM, ± CN V, VII palsy & disequilibrium	Any uni/l abnl pattern	Acoustic neuroma

(Adapted from *Am Fam Physician* 2003;68:1125.)

Idiopathic sudden sensorineural hearing loss (ISSHL): Sudden deafness of cochlear or retrocochlear origin w/o clear cause (? viral or vascular); spontaneous recovery in 65%; steroids often used but not shown conclusively

to be effective.

Demyelinating Diseases of the Central Nervous System

Major Acute & Chronic Causes of CNS Demyelination

	Acute	Chronic/recurrent
Autoimmune		
Primary demyelinating	MS, ON, NMO, ADEM, AIDP, TM, cerebellitis	MS (RRMS, SPMS,PPMS), recurrent ON, CIDP
Paraneoplastic	Paraneoplastic encephalomyelitis	
Connective tissue dz	SLE, Behcet disease, RA, Sjögren syndrome, anti-phospholipid antibody syndrome (APLAS)	
Granulomatous	Wegener granulomatosis, sarcoidosis, lymphoid granulomatosis	
Vasculitis	CNS and systemic vasculitides	
Other Etiologies		
Infectious	HIV → PML (JCV, usually in HIV)	HIV (→ CIDP), Lyme, neurosyphilis, HTLV1, SSPE, tropical spastic paraparesis/HTLV-1 -ass. myelopathy
Congenital		Adrenoleukodystrophy, Alexander dz, Canavan dz, Krabbe dz Metachromatic leukodystrophy Adrenoleukodystrophy

		Adrenomyeloneuropathy
Toxic metabolic	Central pontine myelinolysis (CPM), toxic leukoencephalopathy	Subacute combined degeneration (B_{12} & IF deficiency), NO poisoning, Marchiafava-Bignami's dz
Hypoxic ischemic	CO poisoning, PRES, delayed hypoxic cerebral demyelination	Radiation-induced necrosis Progressive subcortical ischemic demyelination

MULTIPLE SCLEROSIS (MS)

Definition: Attacks of demyelination, disseminated in time & space → gliotic scars (plaques, scléroses) in the WM of the brain, optic nerve, & spinal cord. First described by Charcot (1868).

Pathophysiology: T lymphocytes attack oligodendrocytes → decreased myelin production + damage to underlying axons. Potentiated by memory B cells.

Epidemiology: Prev: 400,000 US; 1 million worldwide; F:M 2:1; ages 20-40. Genetics: Monozygotic twins 20%-30% concordance; 20% MS pts have a relative w/ MS. Assns: Caucasian, blue eyes, EBV antigen, HLA DRB1, low vitamin D/poor sunlight, exposure, melanocortin receptor, HPA axis stimulation. More severe in African Americans.

DIAGNOSTIC CRITERIA FOR MS

Revised McDonald Criteria (Ann Neurol 2005;58:845)

No. of clinical attacks (time), no. of lesions (space) → additional data needed for dx

- ≥2, ≥2 → None (clinical evidence alone suffices)
- ≥2, 1 → Dissemination in space (DIS) by MRI or ≥2 MRI lesions & +CSF (+OCBs or
- ↑ IgG index) or second clinical attack at new site
- 1, ≥2 → Dissemination in time (DIT) by MRI or second clinical attack 1, 1 → DIS by MRI or ≥2 MRI lesions & +CSF and DIT (by MRI or second clinical attack)
- 0, ≥1 → >1 yr progression & 2/3 of (1) +MRI [9 T2 lesions or ≥ 4 T2

lesions + visual evoked potentials (VEP)], (2) Spinal cord MRI (>2 T2 lesions), (3) +CSF. Likely primary progressive MS.

MRI Analysis for Dx of MS

DIS Criteria	DIT Criteria
• 1 CEL ***or*** 9 T2 hyperintensities (T2H) (brain or spinal cord) • 1 infratentorial ***or*** 1 spinal cord lesion • 1 juxtacortical lesion • 3 periventricular lesions	• 1 CEL @ least 3 mo after last clinical event, not @ site of initial event ***or*** • 1 new T2H any time after reference MRI done ≥30 days after initial event

(CEL = contrast-enhancing lesion, *Brain* 1997;120:2059; *Am J Neuroradiol* 2000;21:702.)

CLINICAL PATTERNS OF MS

(1) Clinically isolated syndrome (CIS) (NEJM 2002;346:158): Initial isolated CNS demyelination event (brain, brainstem, ON, or cord). Risk of → MS after CIS 38% @ 10 yr, 68% @ 14 yr. ↑ risk if initial MRI T2 hyperintense lesions, (T2H): (88% w/ ≥2 T2H vs. 19% if nl MRI,@ 14 yr). If first MRI shows >3 T2H or 1 contrast-enhancing lesion (CEL): rate of new MRI abnls in first few months ˜80%-90%. After CIS repeat brain/spine MRI @ 3 & 6 mo, then annually. If new lesions, initiate Rx. (2) Radiologically isolated syndrome (RIS): +MRI w/ no clinical sx; repeat imaging at 3mo & 6mo; if new lesions, initiate treatment. (3) RRMS: Relapsing remitting MS-85%+90%. (4) PPMS: Primary Progressive MS (older pts, African Americans). (5) SPMS: Secondary Progressive MS (RRMS initially → progressive). (6) “Benign MS”: Low dz burden over >20 yr course (can’t yet dx at onset).

MS attack: Symptomatic inflammatory demyelinating lesion lasting >24 h w/ objective clinical findings, >30 days from prior attack.

Relapse triggers: Seasonal (spring/summer); infxns (GI, influenza, cold), ? stress; peripartum (protective in last trimester, relapses postpartum). Short

term relapse risk correlates w/ enhancing lesions on baseline MRI & w/ relapses over prior 2 yr.

WORKUP FOR MS

DDx broad, MUST r/o MS mimics. Institute w/u early; goal: prevent further attacks.

H&P: Ask about systemic sx (skin involvement, arthralgias); recent infxns, fevers, or vaccinations; prior episodes of motor/visual/sensory loss; recent trauma; family Hx.

Serum: NMO Ab, Lyme, RPR, B_{12}, HIV, ESR, ANA, ACE, HTLV-1 to r/o other etiologies.

CSF: WBC<50; IgG index = (CSF IgG/ CSF albumin)/(serum IgG/serum albumin); nl range 0.34-0.66; (ddx: SSPE, viral encephalitis, CADASIL, HIV, SLE, NMO, ADEM, ALD) Oligoclonal bands (OCB): + in CSF and not serum (ddx: SLE, APLAS, Sjögren, sarcoidosis).

MRI: T1 axial w/ gadolinium, T2/FLAIR axial & sagittal. Brain: Multifocal WM lesions, usually >3 mm. Corpus callosum involvement specific. Dawson fingers: Periventricular ovoid lesions w/ long axis perpendicular to ventricles. T1 hypointensities = "black holes": old plaques; may persist × years; represent axonal loss. Acute plaques = CEL, fade after 4-6 wk. T2 hyperintense lesions (T2H): Stable, shrink or grow. Spinal cord: Lesions in 80% pts, usu cervical, <1 cord segment, peripheral; may be asx.

VEP: Delayed but preserved wave form if h/o optic neuritis (ON).

EMG/NCS: May see peripheral demyelination or axonal damage, usually mild & focal.

Red flags suggestive of possible alternative dx (Neurology 2007;13:13). (1) Hearing loss, especially b/l, (2) Onset <10yo or >50 yo; progressive or stroke-like onset, (3) Serum: ESR >80; CSF: protein >100 mg/dL, WBC > 50 mm^3, + PMNs; or nl CSF, (4) MRI: Negative, u/l lesions, (5) Systemic: Coexisting systemic/autoimmune d/os; + PNS sx, (6) Psych Hx, prominent deficits w/o concurrent objective findings or +MRI, (7) Atypical MRI: Gray matter involvement, anterior temporal lobes, punctate, tumor-like mass lesions, spinal cord lesion extent >3 vertebral segments, diffusion restriction.

COMMON MANIFESTATIONS OF MS & DDX

ON (ddx: NMO, idiopathic, sarcoidosis; mimics: retinal artery occlusion, retinal detachment, acute glaucoma).

Brainstem sx: (1) Internuclear ophthalmoplegia (INO) (ddx: infarcts, e.g.,

CADASIL, lacunes; myasthenia gravis, trauma, syphilis, Lyme, meds (phenothiazines, TCA), SDH, brainstem, & fourth vent tumor); (2) Oculomotor dysfn; diplopia (ddx: Wernicke encephalopathy); (3) Trigeminal neuralgia (ddx: idiopathic; posterior fossa tumor); (4) Facial nerve palsy (ddx: Lyme; sarcoidosis); (5) Generalized brainstem processes (ddx: CPM, Behcet's); (6) Vertigo, nystagmus, oscillopsia (ddx: broad); (7) Cerebellar ataxia (ddx: spinocerebellar ataxia, ADEM, post-VZV cerebellitis, Wernicke's syndrome, vit E deficiency).

Spinal cord sx: Transverse myelitis (TM) (ddx: Acute: NMO, rheumatologic dz, idiopathic, epidural abscess, spinal epidural hematoma, spinal AVM, mycoplasma; Slowly Progressive myelopathy: Structural causes: Cervical stenosis, syrinx, epidural tumor; Others: Spinal AVM, dural venous fistula, HTLV1, HIV myelopathy, Cu or Zn deficiency, hereditary spastic paraparesis, adrenomyeloneuropathy).

Pain syndromes: (1) Trigeminal neuralgia; (2) Lhermitte's sign: Neck flex → electrical sensation; in ˜10% MS pts @ presentation (ddx: cervical stenosis, spinal cavernous angioma or tumor; ↓ B_{12}); (3) Tonic spasms (ddx: NMO, spinal strokes); (4) HA

P.190

(e.g., secondary migraine; ddx broad); (5) Back pain; (6) Dysesthetic limb(s); (7) Brief painful focal szs.

Cognitive changes: Depression, memory loss; aphasia, mania, personality changes (ddx: ADEM, lupus cerebritis, viral encephalitis, HIV, PML, CADASIL, metachromatic leukodystrophy, adrenoleukodystrophy). Many MS pts have functional sx early in dz.

MANAGEMENT OF CLINICAL MANIFESTATIONS OF MS

General guidelines (Neurology 2007;13:181)

- Careful history & exam; pts may conflate sx (e.g., fatigue vs. insomnia 2/2 spasticity)
- Tackle one problem & one intervention at a time to avoid polypharmacy
- Emphasize pt control over individual sx & over overall mindset
- Encourage social support groups; refer to MS Society web site (www.nationalmssociety.org).
- Uthoff phenomenon: Sx ↑ w/ heat (Δs axonal conduction)-cold showers, warm clothes

Visual: ON (see section below): Sx: Acute-subacute u/l or b/l visual loss; retrobulbar pain w/ EOMs or bright light; Findings: ON nerve pale; red desaturation; relative afferent pupillary defect (RAPD); ↓ visual acuity. Mgt: Dilated fundus exam; IV steroids hasten recovery.

Musculoskeletal: Weakness: Worst in hands & hips; Mgt: PT, physiatrist referral for assistive devices (orthotics, canes, walkers), comprehensive rehab programs. Spasticity: Stiffness, cramps, spasms, clonus, pain, impaired mobility, & positioning; Mgt: stretching, PT, orthopedic procedures to release contractures; Rx: muscle relaxants.

Spasticity Rx

Agent	Dosing	Side effects; other
Baclofen (GABA agonist)	5-10 mg po qd to 10-30 mg qid	Sedation, dizziness, wkness, withdrawal sz & encephalopathy, so d/c slowly if taking >30 mg qd Intrathecal avail for refractory spasticity
Tizanidine (α-2 agonist)	2 mg tid to 8 mg qid	Sedation, hypotension, dry mouth, hepatotoxicity
Diazepam (BZD)	2.5 mg qd to 10 mg qid	Sedation, constipation; resp depression
Gabapentin	100 mg tid to 800 mg qid	Sedation, dizziness, edema
Botox		Only for focal spasticity

Tremor: (1) Occupational therapy; (2) Surgery: Thalamotomy, thalamic stimulation— mixed results; (3) No systematically demonstrated effectiveness of: BZD, gabapentin, primidone, propanolol, INH, trazodone, serotonin antagonists, or cannabinoids.

Spinal cord myelitis: PT/OT/rehab.

Sensory disturbances: Positive sx: Dysesthesia, allodynia: Neuropathic pain meds (e.g., gabapentin, pregabalin, duloxetine); Nocturnal dysesthesia: TCAs; trigeminal neuralgia: Carbamazepine, gabapentin; Surgery—unclear benefits:

Rhizotomy, microsurgical decompression, radiosurgery. Negative sx: Hypoesthesia, numbness. Limited interventions.

Genitourinary: (1) Failure to store: Urgency, frequency. Workup: Urodynamic studies. Rx: Scheduled voiding, Self-catheterization, diapers, & condom catheters (pref. to indwelling catheters, unless sacral decubiti present), suprapubic catheter for long-term mgt (limits urethral damage & leakage); Meds: Anticholinergics: LA or SELECTIVE muscarinic antagonists if dry mouth or cognitive S/E occur (Oxybutynin 5 mg qd → 5 mg qid, XR 5 mg qd → 15 mg bid, TD 1 patch twice wkly. Tolterodine 1 mg qd → 2 mg bid, LA (Detrol) 2 mg qd → 4 mg qd. Hyoscyamine 0.125 mg qd → 0.25 mg qd). (2) Failure to void: Urinary retention. Workup: PVR via U/S or catheterization: Abnl if >100 mL or >10% of voided volume. Rx: Scheduled voiding. (3) UTIs: Urologic w/u if frequent despite optimal Rx for retention: r/o foreign bodies, anatomical deformities, uro/nephrolithiasis. Rx: Asymptomatic bacteriuria common w/ indwelling catheters—no Rx as long as no pyuria. For pyuria: Treat aggressively (can exacerbate MS sx, trigger relapses). Encourage voiding, intermittent self-cath; methenamine— nonspecific antimicrobial, minimal SEs, & risk of resistance; Intermittent/alternating nitrofurantoin or TMP/SMX, reserve FQs for resistant infxns.

Gastrointestinal: Constipation: Mgt: R/o or eliminate pharmacologic causes, ↑ fluid & fiber intake; Stool softeners (lactulose, polyethylene glycol, docusate sodium).

Sexual fxn: Anorgasmia, decreased libido: Limit pharmacologic causes (antidepressants, AEDs, bladder Rx). Foreplay. Sexual counseling. F: ↓‘d lubrication— Synthetic lubricants; M: Erectile dysfn—Sildenafil (may also improve lubrication in women).

Systemic: (1) General well being: Yoga, nutrition education, exercise, acupuncture. (2) Fatigue, depression & cognitive complaints: Common. Pts may c/o “brain pain.” When all are present, tackle depression first, then fatigue, then cognitive complaints.

Affective sx: (1) Depression, anxiety: Combined psychotherapy (mood partly 2/2 situational factors) & antidepressants; Nonsedating antidepressants like fluoxetine or bupropion. (2) Pseudobulbar sx (10% pts w/ MS): Low-dose antidepressants. (3) Fatigue: Most common disabling symptom of MS. Identify/Rx causes (e.g., depression, pain, sleep d/o’s, Rx, comorbid conditions). Rx: Amantadine: Beneficial in small RCTs, Modafinil 100-200 mg qam & qnoon; Aspirin: 650 mg bid may provide some benefit according to small study; bleeding risk.

Cognitive sx: Common. W/u: Neuroψ eval. [Tests: Processing Speed/Working Memory: paced Auditory Serial Addition Test; Symbol Digit Modalities Test; Learning & Memory: California Verbal Learning Test (2nd Edition), Brief Visuospatial Memory Test (Revised); Executive Fxn: California Card Sorting Test; Visual Perception/Spatial Processing: Judgment of Line Orientation Test; Verbal Fluency: Controlled Oral Word Assn Test). Rx: Avoid cannabis ↓'s cognition (Neurology 2008;71:164)]; Rx causes: Depression, anxiety, fatigue, meds (sedating/anticholinergic S/E). Compensatory strategies: e.g., notebook, calendar, pill cases, PDA, mnemonics. DMTs may limit dz progression. Donepezil may ↑ verbal memory.

Advanced sequelae (in immobile or bed-bound pts): (1) Osteopenia: From immobility, steroids, possibly inflammatory cytokines. Mgt: Routine bone density assessment. Standard Rx: Calcium/vitamin D, bisphosphonates. (2) Decubitus ulcers: Examine sacrum, ischial tuberosities, greater trochanters, heels. Mgt: Frequent repositioning, padding, improve nutritional status, minimize steroids, specialized bedding, wound care specialist. (3) Aspiration: Speech & language pathology eval of bulbar fxn & dysphagia. Mgt: Mild-moderate → behavioral modifications (eat upright, flex neck before swallowing, small bites), Dietary modifications (thickened liquids). Severe → feeding tube if c/w pt wishes.

MANAGEMENT OF ACUTE MS ATTACKS

Ddx attack: Bladder infxn > tooth infxn > URI; disk herniation; entrapment neuropathy.

Routine w/u (minimal): U/A, ESR, CBC, CXR (looking for trigger).

IV methylprednisolone (Solumedrol) 1 g/day × 3-5 days, (or 1,250 mg PO prednisone), ± 10-14 days PO prednisone taper (J Neurol Neurosurg Psychiatry 1987;50:511). Check PPD. Give Ca/vit D, PPI, insulin SS w/ FS AC + HS while in house & if on taper. Speeds recovery, does not improve long-term outcomes. Plasmapheresis: Fulminant cases refractory to steroids.

DISEASE-MODIFYING THERAPIES (DMTS) IN CIS AND RRMS

Utility: ↓ severity & # relapses, ↓ steroid courses & hospital stays, & alter dz course.

Principles of use: (1) Start early; aggressive w/u of CIS and RIS. (2) Selection based on compliance likelihood, tolerance of side effects. (3) If breakthrough, ↓ dose or switch DMT. (4) Check MRI 6M & 12M after starting DMT, may need to ↓ dose or change Rx. (5) Limited data on safety w/ pregnancy & breastfeeding; usually d/c DMTs & trial of IVIg for relapses.

First Line

Beta INTERFERON: (Beta IFN 1a = Recombinantly produced in Chinese hamster ovary cells; Beta IFN 1b—recombinantly produced in E. coli). MOA: Enhance suppressor T cells, ↓ release of metalloproteinases & proinflammatory cytokines, prevent helper T cell adhesion to BBB, downregulate antigen presentation. S/E: Injection site inflamm, HA; Flu-like sx, rhinitis, fatigue. Rare: Depression, szs, thyroid abnls, suicide, ↓ plts, lymphopenia, ↑ LFTs, symptomatic hepatitis. Monitoring: CBC & LFTs @ baseline, 1M, 3M, 6M; then q3-6M. TFTs q6M. Neutralizing antibody (Nab) formation: A/w more frequent, higher doses; ↑ rate of relapses, & new T2H. Conflicting guidelines: Consider: Test @ 12-24M, if Nab pos, recheck in 3-6M; if still pos, consider switch to alternate DMT. If Nab neg, no further testing.

1. Beta IFN 1a (a) Avonex: Dose: 30 µg IM qwk. Trials: CIS CHAMPS: ↓ RR of CDMS (0.56); ↓ no. of lesions @ 6,12,18 mo (NEJM 2000;343:898); extension

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trials: Benefit of starting early. Evidence (Avonex vs. Rebif): Rebif 44 µg 3×/wk vs. Avonex 30 µg qwk: Avonex ↑ OR of relapse-freedom: 1.9 @ 24 wk, 1.5 @ 48 wk; fewer active MRI lesions (Neurology 2002;59:1496). RRMS MS Collaborative Study Group: @ 104 wk, 22% tx'ed w/Avonex w/ progressive disability vs. 35% w/ placebo; ↓ no. of/vol CELs on MRI. ↓ Yrly exac. rate (0.61 vs. 0.91) (Ann Neurol 1996;39:285). (b) Rebif: Dose: 22 or 44 µg SC 3×/wk (titrate over 4 wk). Trials: CIS ETOMS—↓ risk of CDMS @ 2 yr vs. placeb (34% vs. 45% = ↓ 11%); ↓ no. of new T2H (Lancet 2001a;357:1576). RRMS PRISMS-44 µg vs. 22 µg: ↓ relapse rate @ 2 yr w/ higher dose (27% vs. 33%); ↑ median time (5 vs. 3 mo); ↓ no. of T2H → Dose effect favors 44 µg (Lancet 1998;352:1498-1504). Extension study: Efficacy of higher dose & earlier Rx @ 4 & 8 yr (Neurology 2001;56:1628).

2. Beta IFN 1b: (a) Betaseron: Dose: 8 MIU SC qod (0.25 mg; titrate over 6 wk). Trials: CIS BENEFIT: ↓ risk CDMS to 28% vs. 45% w/ placebo @ 24mo; ↓ no. of MRI lesions (Neurology 2006;67:1242). RRMS IFN Beta MS Study Group: 2 pooled RCTs: Relapse rates 0.84 p.a. in 8 MIU group vs. 1.17 in 1.6 MIU group vs. 1.27 placebo; median 80% ↓ in new MRI lesions (Neurology 1993;43:662). Incoming (Avonex vs. Betaseron): Higher doses given more frequently (Betaseron 8 MIU qod vs. Avonex) → fewer relapses & new MRI lesions @ 2 yr (Lancet 2002;359:1453). (b) Extavia: Similar to Betaseron.

Glatiramer acetate (Copaxone): Dose: 20 µg SC daily. MOA: Acetate salt of synthetic polypeptides. May bind MHCs & cause shift from TH1 to TH2 cells. S/E: Feel "rush." Local injection site Rxn. Localized lipoatrophy. Trials:

CIS Pre-CISe: 25% develop CDMS at 3 yr vs. 43% w/ placebo (Lancet 2009;374:1503-15011). RRMS Copolymer 1 MS Study Group @2 yr, 29% ↓ relapse rate vs. placebo (0.59 vs. 0.84/yr) (Neurology 1995;45:1268); reduces EDSS progression (Neurology 1998;50:701). European/Canadian Glatiramer Acetate Study Group: ↓ no. of CELs, T2H & 33% ↓ relapse rate @ 9M (Ann Neurol 2001;290).

Second Line

Natalizumab (Tysabri): MOA: Ab vs. α-4 integrin, ↓'s T cell crossing BBB. Dose: 300 mg IV qmo. S/E: Hypersensitivity Rxn (d/c if occurs); fatigue, anxiety, pharyngitis, sinus congestion, peripheral edema; PML (risk ˜1/1,000 @ 18M, NEJM 2006;354:924). Abs (6% pts, a/w ↓ clinical effectiveness & ↑ infusion rxns. Test @ 6M if ongoing MS activity or persistent infusion Rxns; if +, retest 3M later & if still +, d/c). Hepatic injury; ↑ risk melanoma. Risk mgt: (1) Reserve for: (a) failed/developed intolerance to initial DMTs (b) aggressive initial dz. (2) Rx via TOUCH (Tysabri Outreach: Unified Commitment to Health)a risk mgt program. (3) D/c steroids & immune modulators prior to Natalizumab initiation. Trials: RRMS: AFFIRM—yrly relapse rate 0.26 vs. 0.81 placebo (↓ 68%); 83% ↓ mean no. of MRI lesions. 17% vs. 29% prob. sustained progression @ 2 yr. (NEJM 2006;354:899). Sentinel: Avonex + Tysabri vs. Avonex + placebo: yrly relapse rate ↓ 54% (0.38 vs. 0.82); ↓ EDSS progression @ 2 yr (23% vs. 29%), ↓ no. of MRI lesions (NEJM 2006;354:911).

Mitoxantrone (Novantrone): MOA: Intercalates w/ DNA; ↓ humoral immunity, ↓ T cell proliferation. Dose: 4-12 mg/m^2 q3mo; Lifetime cumulative dose limit 140 mg/m^2. S/E: Cardiotoxicity (dose limiting); myelosuppression; acute leukemia; amenorrhea; alopecia; nausea; bluish discoloration of sclera & urine. Monitor: LFTs, CBC, BUN/Cr, & LVEF before each dose. Effectiveness: In active RRMS (2 relapses w/ in 12M) & SPMS. Trials: Mitoxantrone in MS study: Mitoxantrone vs. placebo: ↓ EDSS change @ 2 yr (-0.13 vs. 0.23), ↓ % w/ significant ↓ EDSS @ 2 yr (25% vs. 8%); ↓ yrly exacerbation rate (0.35 vs. 1.02); ↑ time to first treated relapse @ 2 yr; ↓ no. of CELs (0% vs. 16%) (Lancet 2002;360:2018).

Additional therapies

Cladribine (Leustatin): Dose: 3.5-5 mg/kg PO daily for 4-5days, 4x/yr. MOA: Purine analog, blocks lymphocyte and monocyte devpt. S/E: HAs, cold sx, vertigo. Lymphopenia. May depress long-term bone marrow fxn. Trial: RRMS: Clarity: @ 2 yr, 80% & 79% w/ no relapse if Rx'ed w/ 3.5 and 5 mg/kg, respectively, vs. 61% w/ placebo; @ least 70% ↓ CELs & T2Hs on MRI; 30% ↓ risk EDSS progression (NEJM 2010;362:416).

FTY 720 (Fingolimod): Dose: 1.25 or 5 mg PO daily. MOA: Sphingosine-1-phosphate receptor modulator may alter lymphocyte migration from lymph nodes. S/E: Cardiovascular: Transient ↓ HR after second dose & sustained ↑ BP. ?PRES, opportunistic infections (disseminated HSV/VZV). Elevated LFTs. Trial: FREEDOMES Phase III RCT @24M. Relative to placebo, for 0.5mg and 1.25mg respectively: RR relapse rate 0.54 and 0.60 vs. placebo; RR of disability progression 0.7 and 0.68 vs. placebo; and fewer MRI lesions (NEJM 2010;362:387-401). Relative to Betaseron, superior efficacy in terms of relapse rate and MRI lesions (NEJM 2010;362:402-415).

Alemtuzumab (Campath-1H): Dose: 12-24 mg/d IV × 5 days initially; then once daily ×3 days annually. MOA: Humanized monoclonal ab causing depletion of T cells, NK cells, monocytes. S/E: ITP (potentially fatal), thyroid autoimmunity. Trial: Early RRMS: CAMMS223: Alemtuzumab a/w 9% disability accumulation @ 36M vs. 26% w/ Rebif; 0.10 vs. 0.36 annualized rate of relapse, & ↓ brain lesion volume on MRI. But 23% vs. 3% thyroid autoimmunity (NEJM 2008;359:1786).

IV methylprednisolone: Dose: 1 g IV daily ×5 days q4mo × 3 yr, then q6mo × 2 yr. Trials: @ 5 yr. 32% ↓ disability progression; better EDSS scores (Neurology 2001;57:1239).

Rituximab (Rituxan): Dose: 1 g IV on days 1 & 15. MOA: Monoclonal ab against CD20 on B lymphocytes, causing B cell depletion. S/E: PML. Trials: Preliminary trial: 1 g IV on days 1 & 15: ↓ no. of pts w/ relapse & in new MRI lesions @ 24 wk (NEJM 2008;358:676).

Azathioprine (Imuran): Dose: 3 mg/kg PO daily. MOA: Inhibits purine synthesis. S/E: Myelosuppression, cardiac disease. Trials: Meta-analysis: Significant ↓ risk in relapses @ 1 yr (20%), 2 yr (23%), & 3 yr (18%) (Cochrane Database Syst Rev 2007;4:CD003982). Combination w/ Rebif or Betaseron may ↓ relapse rate & MRI activity.

Cyclophosphamide (Cytoxan): Dose: 50 mg/kg IV daily. Generic, no RCTs. Use controversial, limit to clinical trials. Use in aggressive PPMS, SPMS, sometimes RRMS.

IV immune globulin (IVIg): Dose: q4-6wk. S/E: Aseptic meningitis, HA, venous thrombosis, pulmonary edema, allergic Rxns, dermatitis. Trials: PPMS, SPMS, Little efficacy; CIS, RRMS: May prevents relapses (more data needed).

Methotrexate (Rheumatrex): Dose: 7.5-20 mg PO wkly. MOA: Inhibits DHFR. S/E: Myelosuppression, hepatitis, pulmonary fibrosis, mucositis.

Trials: May delay progression, relapse rate, & MRI activity.

MANAGEMENT OF MS PROGRESSION

Relapses: Measured in terms of: Rate, % relapse free, time to relapse.

Monitoring: Disability scales:

EDSS (Expanded Disability Status Scale) (0-9): 0 = nl neuro exam, 2 = min. disability, 4 = ↓ walking, 6 = needs assistance, cane, 7 = wheelchair, 9 = helpless, bed-bound, 10 = death. 50% MS pts go from 0 to 6 in 10 years; Weighted for ambulation (vs. cognition, fatigue, & pain).

MSFC: Multiple sclerosis functional composite: Paced-auditory serial addition, 25-ft timed walk, 9-hole peg; Does not encompass vision, fatigue, pain, some cognitive domains.

MRI: Area/activity: Despite stable lesions, may see new fxnal disability; esp advanced MS.

Rx: 4-Aminopyridine (Fampridine-SR): May improve mobility. Dose: 10 mg PO bid.

MOA: Potassium channel blocker. S/E: Seizures. Trials: Phase III DBRCT—@14 wk, 35% pts improved in 25-ft timed walk test vs. 8% in placebo (Lancet 2009;373: 732-738).

MS VARIANTS

Marburg variant (aka Acute MS): Younger pts, usu preceded by fever, rapidly advancing, aggressive, a/w axonal loss, can progress to disability & death.

Balós concentric sclerosis (BCS; aka encephalitis periaxialis concentrica): More common in Chinese/Filipino pts; lesions form concentric rings of alternating demyelinated & undemyelinated tissue; often produces cognitive sx (HA, aphasia, cognitive & behavioral dysfn, sz), rapidly progressive & often unremitting.

Tumefactive MS >2 cm cystic lesions; MRI:“fried egg” appearance, mass effect, edema or ring enhancement, T2 hypointense border (ddx: glioma, metastasis, abscess).

Schilder’s disease (diffuse myelinoclastic sclerosis): Begins in childhood (5-14 yr), progressive; plaques from pseudotumoral lesions often symmetric & >2 cm diameter; cause aphasia, sz, cognitive & behavioral Δs, incontinence, wkness, HA, visual & speech deficits.

Pediatric MS

Epidemiology: 8,000-10,000 children in the US; 2%-5% of MS pts present

before age 18; 1:1 male:female ratio before age 10, then increasing frequency in girls.

Clinical presentation: Similar to adults; also see: szs, lethargy. Commonly, polysymptomatic presentation w/ motor findings.

MRI: Five or more lesions; two or more periventricular lesions; one brainstem lesion.

Course: Usually RRMS; relapse rate more common but remit quicker; course may be slower, but significant dz burden accumulates earlier.

Ddx: Infectious (viral, Lyme, West Nile virus), genetic/metabolic d/os, ADEM, endocrinopathies, vasculopathies, inflammatory d/os, leukodystrophies, mitochondrial d/os, nutritional deficiencies, neoplasms (Neurology 2007;68:S13).

Management: Attend to cognitive, developmental, psychosocial consequences, & familial coping. Rx: (1) Attacks: Methylprednisolone 20-30 mg/kg/day for 3-5 days, then ± prednisone 1 mg/kg/day & taper 5 mg q2-3d. (2) DMTs—no RCTs; consider interferon or copaxone.

OPTIC NEURITIS

Definition: Inflammatory demyelination of the optic nerve, causing acute usually monocular visual loss. Can occur along any segment; termed retrobulbar if posterior. Common manifestation/herald of MS.

Epidemiology: 6.4 per 100,000 in US. F > M (2:1); Ages 20-50; Like MS: Higher latitudes, Western Europe & Northern US, far from equator. HLA-DR15; HLADQA-1B & HLA DQB-1B.

Clinical presentation: Acute: (1) Usually monocular sx (10% b/l, more common in children & non-Caucasian pts). (2) Visual loss (90%): Hours-days, peaks 12 wk. (3) Loss of color vision. (4) Visual field defect: Usually central scotoma. (5) Eye pain (92%): Orbital or retro-orbital; usu w/ eye movement; often precedes visual loss. (6) Photopsias (flashing, flickering of light) precipitated by eye mvt in 30% pts. Chronic: Uhthoff phenomenon: Heat (showers, exercise) temporarily ↑ visual problems. Associations: MS, NMO.

Diagnostic testing: Clinical diagnosis.

Visual acuity testing: Median VA 20/60, 3% w/ no light perception. Persistent visual loss (color vision, contrast sens, light brightness, stereo acuity) detectable in most @ 2 yr.

Color testing: W/ Ishihara plates, Fransworth-Munsell 100 hue test. Color vision loss in about 90% pts, out of proportion to decrease in VA. Chronically:“Red” desaturation: appears “washed out” in affected eye.

Flashlight test: Relative afferent pupillary defect (RAPD) in u/l ON (in dark room, flashlight swung from healthy to affected eye causes dilation). RAPD can persist.

Visual fields: Scotoma, usually central; if extends to the periphery, consider compressive lesion; if altitudinal, consider AION. 56% normalize @ 1 yr, 73% @ 2 yr.

Fundoscopic examination: 1/3 have papillitis w/ hyperemia & disk swelling, blurred disk margins, distended veins. 2/3 have retrobulbar neuritis w/ nl fundoscopic exam. Over time: Optic atrophy, even if VA nl; disc shrunken w/ pallor, particularly temporal, extending beyond its margin into peripapillary RNFL. Other findings: Perivenous sheathing or periphlebitis retinae (12%); uveitis, pars planitis.

MRI brain & orbits w/ & w/out gado: 95% have optic nerve inflammation (T2 signal change best seen on coronal STIR); longitudinal involvement correlates w/VA & visual prognosis; + in 60% MS pts w/o clinical h/o ON. Enhancement persists for 30 days.

LP: Routine (protein, gluc, cell ct/diff, gs, & cx); IgG index (↑ in 20%-36%), oligoclonal bands (+ in 56%-69%). R/o other causes if b/l, <15 yo, e/o infxn. 80% pts w/ acute ON have nonspecific findings (10-100 lymphocytes, elevated protein, 20% have MBP.

Flourescein angiography: Usually nl; 25% w/ dye leakage or perivenous sheathing.

VEP: If exam does not clearly show ON or demonstrate prior asymptomatic ON; will show ↓ amplitude of N95 & delay in the P100 of the visual evoked response due to axonal demyelination. Persists @ 1 yr in 80%-90%; 35% nl @ 2 yr.

Optical coherence tomography (OCT): Detects thinning of RNFL (retinal nerve fiber layer), once early swelling is gone. More thinning → worse visual outcome & worse brain atrophy. OCT in NMO shows more widespread injury than in MS (Neurology 2009;72:1077).

Labs: ESR, ANA, ACE, Lyme (serology & CSF), syphilis; CSF studies (see above).

Ddx of ON: (1) Young children—Infectious & post-infectious. (2) Adults >50 yo Anterior ischemic optic neuropathy (AION; 2/2 DM, HTN or GCA); can

be arteritic or nonarteritic (2a) Arteritic (= Giant cell arteritis = Temporal arteritis) (>50 yo, F > M 3.5:1. Sudden onset visual loss, altitudinal or generalized scotoma, may be b/l. Typical fundus exam: pale swollen disc w/ hemorrhages. MRI= ± enhancement of retina, but not optic nerve. Associated sx: HA, jaw claudication, scalp tenderness. Prognosis: rapid blindness if untreated (in symptomatic or fellow eye). (2b) Nonarteritic: Usually pts > 50 yo, sudden u/l visual loss, not tender, w/ altitudinal (usually inferior) scotoma. Fundus exam: Disc edema. MRI nl. Course: 40% improve, over months, by >3 lines. (3) Infxns: Neuroretin'itis (viruses, toxoplasmosis, Bartonella): Usually in children, over hours-days, often b/l, ± scotoma, ± pain. Exam: Papillitis, macular edema, exudates.

± systemic si/sx. Meningitis, syphilis, Lyme. (4) Genetic: (4a) LHON (Leber hereditary optic neuropathy): Men, ages 25-40. Onset over wks/months of u/l or b/l central or cecocentral scotoma. Not painful. Fundus: Disc hyperemia; peripapillary telangiectasia. MRI nl. Prognosis: 1/3 improve. (4b) Kier type autosomal dominant optic atrophy. (5) Inflammatory: Parainfectious, autoimmune (SLE, Sjögren's), sarcoidosis, paraneo-plastic. (6) Neoplasms: (6a) Optic nerve glioma—initial sx often identical to ON; MRI = expansile, enhancing mass of optic nerve); ± proptosis & other orbital signs. (6b) Meningioma, metastasis, lymphoma. (7) Compression: Abscess, carotid-ophthalmic artery aneurysm, thyroid ophthalmopathy, orbital pseudotumor, pseudotumor cerebri. (8) Toxic-Metabolic: Drugs, toxins, nutritional deficiency (vitamin B_1, B_{12}, folate), radiation. (9) Traumatic optic neuropathy.

Prognosis: (1) Visual recovery: 90% w/ 20/40 or better vision @ 1 yr. Recovery onset w/in wks. Often w/ residual contrast sensitivity. VA worse if: (1) poor VA @ presentation; in ONTT, 65% pts w/ VA LP or worse initially achieved 20/40; (2) longer lesions of ON on MRI, esp extending into optic canal; (3) race: African Americans have worse VA @ presentation (worse than 20/200 in 93% vs. 39% Caucasians); @ 1 year, 61% have VA better than 20/40, vs. 92% Caucasians; (4) Concurrent MS. (2) Children: 20% w/ persistent fxnal visual impairment. (3) Recurrence: 35% recurrence @ 10 yr, a/w greater risk of MS. If rapidly recurrent ON & brain MRI nl, check NMO IgG. (4) ON & MS (ONTT: Optic Neuritis Rx Trial) (Arch Ophthalmol 1991;109:1673-1678): Based on ONTT, risk of clinically definite MS (CDMS) ˜30% @ 5 yr, 40% 12 yr, 50% 15 yr. Median time to dx is 3 yr. 15%-20% MS cases p/w ON. 50% of pts w/ MS develop ON @ some point during illness. (4a) Risk ↑ if: female (74% in women, 34% in men), Caucasian; fundoscopic exam shows retinal perivenous sheathing; MRI w/ demyelinating lesions (56% @ 5 yr if 2+ WM lesions); + OCBs in CSF;

HLA-DR2 allele. (4b) Risk ↓ if: first attack occurs in childhood, or after 40; Asian; b/l ON; no pain; VA better than LP @ presentation; severe papillitis on fundoscopic exam, no severe disk swelling, no peripapillary hemorrhage, no retinal exudates; no WM lesions on MRI.

Treatment: Acute: IV methylprednisolone (250 mg qid ×3 days, then 1 mg/kg prednisone po × 11d w/ 4 day taper) w/in 8 days of onset. Accelerates recovery of visual fxn. @ 1 yr, outcomes similar (Am J Ophthalmol 2004;136:77-83). Risk of conversion to MS @ 2 yr is 7.5 w/ IV steroids (vs. 14.7 w/ 1 mg/kg PO prednisone ×14days w/ 4 days taper & vs. 16.7 in placebo) (Invest Ophthalmol Vis Sci 2000;41:1017). Treat if high MRI lesion burden in order to delay onset of MS; if severe or b/l visual loss to hasten speed of visual recovery. PO prednisone alone NOT recommended. IVIg & plasmapheresis not effective.

Disease modifying therapies: Treat if >15 yo, have 2+ WM lesions on MRI @ presentation. Goals: ↑ attack-free interval, fewer attacks, & longer delay to MS-associated disability. Options: (1) Avonex (IFN B 1a) 30 µg IM TIW (CHAMPS: vs. placebo, 35% vs. 50% cumulative risk of MS @ 3 yr; fewer T2H & CEL on brain MRI @ 18 mo; & 36% vs. 49% risk of MS @ 5 yr). (2) Rebif (IFN B 1a) 22 µg SC q wk (ETOMS: vs. placebo, 34% vs. 45% risk of MS @ 2 yr; increased time until next demyelinating event (569 vs. 252 days), fewer T2H @ 2 yr). (3) Betaseron (IFN B 1b) 250 µg SC qod (Benefit: Fewer developed MS @ 2 yr (28% vs. 45%), delay of 1 yr until 25% pts developed MS; lower cumulative T2H). Children: No trials available. In general, ↓ risk of developing MS. Acute: IV solumedrol for severe debilitating b/l visual loss; 4-8 wk PO prednisone taper; hastens recovery but possibly not final visual outcome. Long term: If over 15, may treat as adults w/ DMTs.

TRANSVERSE MYELITIS

Definition: Transverse myelopathy 2/2 inflammation: Demyelination, infxn or other inflammatory etiologies, ± compression. Other (noninflammatory) causes of myelopathy: Vascular, neoplastic, paraneoplastic processes.

Clinical manifestations: (1) Onset over days; occasionally hrs in necrotizing demyelination (e.g., NMO). (2) Trigger: Often preceded by nonspecific viral illnesses. (3) Complete vs. incomplete: Complete lesions usu longer (>3 vert segments) & central → symm. ↓ motor/sensory/sphincter fxn; vs. incomplete w/ shorter, peripheral lesions involving limited tracts, usu. → incomplete loss of fxn. (4) Sensory level (5) Motor fxn: Depends on level, lesion extent: C spine: quadriplegia, resp. paralysis (C3-5 → diaphragm); C2-T1: UMN/LMN in upper extremities, UMN in lower extremities; T1-T12: spastic paraplegia; L1-S5: UMN/LMN in lower extremities; bowel/bladder dysfn (urinary retention). (6) Spinal shock: Sometimes in hyperacute stage (legs flaccid &

areflexic); then spasticity develops. (7) Pain: Radicular back pain common.

General approach (Seminars in Neurology 2008;28:105; Spinal Cord 2009;47:312; See chapters “Spine and Spinal Cord Disease” and “Neurorheumatology” for more info). MRI spine: Sagittal T1 & T2, axial T2 spin echo sequences, sagittal & axial T1 post gado (shows myelopathy; r/o compression by extramedullary tumors; r/o trauma; r/o h/o XRT to spine in prior 15 yr; r/o longitudinally extensive T2 intramedullary lesion; r/o vascular etiologies, e.g.: anterior spinal artery infarct: elongated “pencil-like” ant cord lesion; posterior spinal artery infarct: Triangular post cord lesion; Dural AVF: Long lesion extending into conus on T2 (tortuous vessels seen on surface of cord; may require spinal angiogram); Hemorrhage (hematomyelia from AVM, cavernoma, HHT, bleeding diathesis). CSF: Cell count, protein/glucose (send blood glucose concurrently), GS & Cx, OCBs, IgG index (send serum SPEP), cytology. Usual findings: CSF inflammatory: Mild pleocytosis, elevated protein or OCBs; r/o intramedullary neoplasias. (NB lymphoma may present like myelitis, w/ OCBs & response to steroids; but persistent enhancement on serial f/u imaging.) Ancillary tests (see table below) to support dx of demyelination or inflammatory d/o: ESR, CRP, Rheumatoid factor, ANA, ANCA, ACL Ab, anti-Ro, antila; B_{12}, MMA, folate, copper; CXR, cultures.

If no specific dx: Empiric steroids &/or plasmapheresis: If steroid responsive: consider lymphoma vs. steroid responsive inflammatory d/o; if high risk recurrence, consider immune suppressive (NMO) & modulatory (MS) Rx. If not steroid responsive, & lesion enlarging: consider bx.

Prognosis: (1) Recurrence risk: Complete TM: Risk ↑ if +NMO IgG or + anti-SSA (Sjögren syndrome). Incomplete TM: May represent CIS. Check brain MRI: if ≥2 lesions: 88% chance MS in next 20 yr; if nl, risk is 19%. (2) Recovery: Begins 2-12 wk after onset of sx, may continue for 2 yr.

Rx: IV solumedrol 1 g daily or IV dexamethasone 100 mg daily × 3 days, (+PPI, Ca/vit D, RISS). Consider IVIg.

DDX & ANCILLARY TESTING FOR TRANSVERSE MYELITIS

Ddx for Demyelinating TM

Clinical	**MRI spine/brain w/gado**	**CSF**
Multiple sclerosis: Sx asymmetric. Common	Spine: Lesions short (<2 vertebral segments),	OCBs+ in 90% ↑ IgG index

syndromes: Sensory useless hand syndrome (↓ JPS in UE); Brown-Séquard.	usually peripheral. Brain: WM lesions, enhance if acute.	in 60%.
NMO: Associated ON. Deficits usually severe. LABS: Serum NMO IgG: if +, risk relapse >50%.	Spine: Lesions central, enhancing, necrotic, w/ cord swelling, & span >3 segs (LETM). Brain: ± periventricular WM abnl.	Pleocytic (eos or PMNs) No OCBs in >80% IgG index nl or transiently ↑.
ADEM: Monophasic. Can evolve over 3M. Often preceding infxn. Encephalopathy. Affects children.	Spine: Lesions generally same age, may not all enhance, variable length. Brain: Large often confluent WM lesions, of similar age.	Pleocytosis; OCB & IgG index may be transiently abnl.
POST VACCINE: Monophasic. Vaccination in prior 3 wk.	Spine: Lesions variable. Brain: ± Lesions.	Pleocytosis; OCB & ± abnl IgG index (transiently).
IDIOPATHIC: Monophasic. No other cause identified.	Spine: Lesions variable. Brain: No lesions.	Inflammatory. ± ↑ IgG index & OCBs.

(*Seminars in Neurology* 2008;28:105.)

Autoimmune: Look for classical systemic features of individual dzs. MRI shows enhancing lesions, CSF inflammatory. “Screening” serologies: ANA, ANCA, ESR, Rh factor IgM. Specific testing: Sjögren’s: ANA, Anti Ro/La; Scleroderma: Anti-U1RNP; Neurosarcoidosis: ACE, CXR, CSF w/ OCBs. SLE: ANA, ENAs, anti-dsDNA, anti-sm Ab; Behcet’s: Serum IgG, IgA, IgM, CRP, ESR, α_2-globulin; MCTD: anti-U1-RNP.

Paraneoplastic: See “Neuro-Oncology” chapter for more details. May see longitudinally extensive tract-specific lesions, ± enhance. Include: SCLC: amphiphysin IgG; CRMP-5 IgG: TM & ON, NMO mimic; GAD; Cation channel Ab; Breast ca—PCA 2; Ovarian ca—ANNA 2; NSCLC—Neuronal & muscle AchR Ab.

Infectious: H&P: Fever, confusion, meningismus; rash (e.g., vesicular, dermatomal, or erythema migrans characteristics); systemic infxn; immune

compromised; lymphadenopathy; residence in endemic area; recurrent genital infxns. Imaging: CXR/ chest CT.

Infectious Causes of TM

	Pathogen	CSF	Serum
Viral	HSV, VZV, CMV, HHV6, EBV, HTLV, HIV; dengue; JEV, SLEV, WNV, WNV, tick-borne enceph. virus, influenza A virus, measles, mumps, rubella, coxsackievirus, echovirus, enterovirus, HAV, HCV, poliovirus	**PCR:** HSV1, HSV2, HHV6, VZV, CMV, EBV, HTLV1, enterovirus, Lyme. ?Viral cx	HSV, VZV, HIV, HTLV1, CMV, EBV, HAV, HBV, HCV, enterovirus, coxsackie A, adenovirus
Bacterial	Abscess, mycoplasma, Lyme, syphilis, TB	Gram stain, cx, AFB smear, TB culture	Blood Cx, Lyme, syphilis, Mycoplasma
Fungal	*Actinomyces, Blastomyces, Coccidioides, Aspergillus*	India ink Fungal Cx	
Parasitic	Neurocysticercosis, *Schistosoma, Gnathostoma*, angiostrongylosis		Parasite serology

NEUROMYELITIS OPTICA (AKA DEVIC DZ, OPTICOSPINAL DZ)

Epidemiology: Unknown prevalence. F:M 2:1; among relapsing pts, 80% female; pregnancy might trigger dz exacerbation. More common in Asian populations (esp “Asian optic-spinal MS” variant). Thought to be nonfamilial.

Clinical manifestations: (1) Course: Relapsing (85%), or fulminant monophasic. (2) TM: LETM: longitudinal extensive transverse myelitis (spans >3 vert segments). Demyelination + necrotic cord lesion. Myelopathy more severe & less likely to recover than in MS. (3) ON: Onset more often acute & b/l. Poorer prognosis re: recovery of vision than MS. OCT in NMO shows more widespread injury than in MS: thinner average RNFL, severely involving superior & inferior quadrants. (4) Other: Brain lesions more

common than initially described; encephalopathy; ophthalmoparesis, ataxia, szs, intractable vomiting, hiccups, endocrinopathies, PRES. (5) Associated d/os: Adults: 1/3 with associated collagen vascular dz; SLE, Sjögren's, thyroid & other autoimmune dzs, VZV, EBV, HIV, drug exposures (clioquinol, antituberculosis drugs). Children: 42% w/ concurrent autoimmune d/os (SLE, Sjögren's, juvenile RA, Graves, autoimmune hepatitis).

Variants: (1) Standard NMO: LETM & ON occur concurrently or follow one another. (2) Limited NMO: Recurrent or monophasic LETM; b/l monophasic or recurrent isolated ON. (3) Asian optic-spinal multiple sclerosis—can have CNS involvement similar to MS. (4) LETM or ON a/w systemic autoimmune dz. (5) LETM or ON a/w brain lesions (in hypothalamus, periventricular nucleus, brainstem).

Diagnostic testing: Serum: + serum NMO IgG (anti-aquaporin-4 ab) (73% Se, 91% Sp for NMO (Lancet 2004;364:2106); If serum (-) but strong suspicion, check CSF NMO IgG. Some seropositive pts have systemic autoimmune dz (SLE or Sjögren's). In children: Se 47%; ↑'s if NMO is relapsing. 98% of seropositive children 4-18 yo have ON, TM, or both w/in 12 mos; 93% attacks recurrent, 90% w/ residual disability. CSF: Usu pleocytosis (eos, PMNs). No OCBs bands in >80%. IgG index nl or transiently ↑. MRI ± gado: Spine: LETM, spans >3 vert segments; Brain: If clinical suspicion (often periventricular—Brainstem, supra- & infra-tentorial white matter, cerebellum, thalamus, hypothalamus).

Diagnostic Criteria for NMO

Adults—Mayo Clinic Criteria	Pediatrics
Require both TM and ON, AND:	
Supportive Criteria: Need 2/3 of:	**Require 1/2 of:**
1. MRI spine w/ contiguous T2-signal abnlity over >3 vertebral segments.	1. MRI spine w/ contiguous T2-signal abnlity over 3+ vertebral segments
2. Serum NMO IgG + Brain MRI not c/w criteria for MS @ dz onset	2. Serum NMO IgG +

(*Neurology* 2006;66:1485.)

Treatment: Attacks: IV methylprednisolone × 5-7 days. If sx progress despite steroids, plasmapheresis (seven exchanges over 2 wk) may minimize EDSS (Mult Scler 2009;15:487).

Recurrent or progressive sx: No RCTs & no FDA approved Rxs. Aim for humoral suppression w/ immune-suppressive Rx to prevent disability. Immune modulatory therapies used in MS likely not effective. Commonly tried: (1) Trial of: PO: azathioprine (Imuran) 2-3 mg/kg PO qd or mycophenolate mofetil (Cellcept) 1,000 mg PO bid. Combine w/ prednisone during first 4-6M until reach immune suppressive effects, then taper steroids. (2) IV: Mitoxantrone (Novantrone) IV (S/E: CHF). (3) Others: Cyclophosphamide; Rituximab (may prevent attacks for up to 18 mo (Neurology 2005;64:1270)); IVIg.

Prognosis: Generally expect some improvement w/in wks of onset. Monophasic: ON & TM occur simultaneously or w/in days of each other; 20% have permanent visual loss & 30% have permanent paralysis in @ least one leg. Relapsing (85%): Better motor recovery after initial TM event; 55% relapse in first year & 90% in first 5 yr. 50% have paralysis or blindness w/in 5 yr. Secondary progressive: Rare.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Definition: Acute monophasic multifocal demyelination. Neurologic sx multifocal & include encephalopathy. Usually postinfectious.

Epidemiology: Usually in children & adolescents (average age 5-8 yr). 0.8/100,000; ˜3-6 cases/yr @ regional medical centers in US/UK/Australia.

Pathophysiology: Immunologic dysregulation in genetically susceptible individuals triggered by environmental stimulus, probably through molecular mimicry (e.g., pentapeptide sequence of EBV antigen homologous to myelin basic protein epitope).

Etiology: Post-infectious: ˜75%; etiologies: Viral: Enterovirus, EBV, CMV, HIV, HSV, VZV, HAV, influenza, coronavirus, coxsackie virus, mumps, measles; Bacterial (Borrelia, Chlamydia, Mycoplasma, beta-hemolytic Strep, Rickettsia, Leptospira); Parasitic). Vaccination: ˜5%; typically w/in 4-14 days; must be <3 mo. Usu after MMR, but risk is greater & dz more severe w/ measles (1/1,000) & rubella (1/5,000) than MMR vaccine (1-2/million)). Others: Rabies, HBV, influenza, DPT, Japanese B encephalitis, pneumococcus, polio). Spontaneous: Rare; usually organ transplant pts.

Diagnostic criteria for ADEM (Neurology 2007;68:S7-S12).

Clinical features: (1) First clinical attack of inflammatory or demyelinating dz in CNS. (2) Acute or subacute onset (febrile illness 4 wk prior in 50%-75% children; Sx appear 1-3 wk after infxn or vaccination, max severity over 4-7days). (3) Multifocal: Affects multiple areas of CNS. (4) Polysymptomatic (e.g., n/v, meningismus, cranial neuropathies incl ON; pyramidal (long tract) signs, acute hemiparesis, cerebellar ataxia, transverse myelitis, szs (in ˜1/3); Less common: Aphasia, mvt d/os, sensory deficits). (5) Must include encephalopathy: Acute behavioral Δ (e.g., confusion or irritability) &/or alteration in consciousness (range: somnolence-coma). (6) Subsequent improvement by clinical/imaging measures (but may have residual deficits). (7) No better explanation (other etiologies ruled out). (8) “Relapses” (new or fluctuating sx, si, or MRI findings) w/in 3 mo of inciting ADEM episode are considered part of same acute event; during steroid taper or w/in 4 wk of completing taper part of the initial event.

Lesion characteristics on MRI FLAIR & T2: (1) Large (>1-2 cm) multifocal, hyperintense, b/l, asymm. lesions in supratentorial or infratentorial WM. Rarely: Single large lesion (may see hemorrhagic demyelinating lesions in hyperacute ADEM variants). (3) Gray matter, esp basal ganglia & thalamus, may be involved. (4) Spinal cord MRI may show confluent intramedullary lesion(s) w/ variable enhancement. (5) No radiologic evidence of prior destructive WM changes (most ADEM lesions resolve @ least partially, vs. MS lesions).

Diagnostic testing: LP: R/o viral & bacterial meningitis or encephalitis. Send CSF for: GS & bacterial Cx, EBV, HSV, CMV, VZV, mycoplasma, rubella, oligoclonal bands. [CSF can be nl. May see pleocytosis (if WBC >50, NOT MS) &/or increased protein; ± OCBs (nonspecific—also seen in MS, CNS infxns, viral syndromes, neuropathies).] Serum: CBC (leukocytosis in 2/3; often lymphocytic); ± ↑ ESR & CRP. Micro: Studies usually negative. Blood Cx, CSF for bacterial & viral Cx; nasopharynx & stool viral cultures. Check HSV, VZV, CMV, EBV, Mycoplasma, rubella. EEG: Background slow wave activity c/w encephalopathy. VEPs: ↑‘d if ON present. MRI w/T2, FLAIR, gado. See above for characteristics. Sequential imaging to detect multiphasic ADEM or MS; most ADEM lesions resolve @ least partially.

Differential diagnosis: (1) Infectious: Viral/bacterial meningitis or encephalitis. (2) Inflammatory demyelinating d/os: MS (Encephalopathy required for ADEM

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dx, not typical for MS. CSF > 50 WBC/mm, sometimes seen in ADEM,

atypical for MS. MRI shows old lesions for MS.); ON, TM, NMO; Others. (3) CNS angiitis (PACNS; see chapter on “Central Nervous System Vasculitis”; MRI: multifocal T2 hyperintensities; DWI = acute infarcts; Clinical: multifocal neurologic impairments, HAs, focal szs, & behavior Δs; Cerebral angiography: vascular beading & intraluminal narrowing. Dx usu. requires brain bx.) (4) Malignancy—CNS lymphoma or glioma w/ tumefactive demyelination; CSF cytology = atypical cells; dx requires brain bx. (5) Mitochondrial dz—w/ intercurrent infxn. MRI w/ typical symmetric T2 signal in basal ganglia or parietooccipital regions; ↑ serum & CSF lactate. (6) Leukodystrophies—WM involvement usu symmetric.

Treatment: No controlled trials to date. (1) Antibiotics: Consider empiric acyclovir & antibiotics until infectious etiology excluded. (2) Steroids: IV methylprednisolone (superior to decadron), then 3-6 wk oral prednisolone taper. (3) Steroid alternatives: If steroids fail or contraindicated: plasmapheresis, IVIg (70% show complete recovery); mitoxantrone, cyclophosphamide. (4) In children: In children not responding to steroids or IVIg: consider combination. Steroids felt to be better for impaired cognition, consciousness, & rigor while IVIg better w/ sensory & motor disturbances.

Course: Monophasic: Evolves over up to 3 mo, even during glucocorticoid taper or up to 1 mo post taper. Recurrent & multiphasic ADEM (MDEM)—@ least 3 mo after initial event & 1 mo after completion of glucocorticoid taper. Recurrent: Similar sx as initial event, original lesions may be enlarged. Multiphasic: sx are different, w/ new anatomic areas on MRI & complete or partial resolution of lesions from initial event.

Prognosis: Overall good: 50%-75% recover completely, 70%-90% w/ min residual disability. 5% mortality. MRI can show complete recovery. Avg recovery time 1-6 mo. Motor deficits: 8%-30% residual; range from clumsiness to ataxia & hemiparesis. Neurocognitive deficits (attention, ST memory, affect, behavior, verbal processing speed): Less severe than in MS, usually w/in 1 std deviation from norm. Poor prognostic factors: Adults (children more favorable), unresponsive to steroids, unusually severe neurological sx, sudden onset, lack of fever (either protective, or pushes toward earlier dx & Rx).

ADEM variants: Acute hemorrhagic leukoencephalitis—hyperacute variant, more rapidly progressive & more severe. Most cases occur after URI. Includes AHL— acute hemorrhagic leukoencephalitis; AHEM—acute hemorrhagic encephalomyelitis;

ANHLE—acute necrotizing hemorrhagic leukoencephalitis (Weston Hurst syndrome or Hurst dz).

Epidemiology: Very rare; 2% of ADEM cases.

Pathophysiology: Necrotizing vasculitis of venules w/ hemorrhage & edema.

Sx: HA, fever, szs, multifocal neurological deficits, obtundation/coma.

MRI: Diffuse WM lesions w/in 72 h onset, cerebral edema, ICH.

CSF: ↑ WBC & RBCs, ↑ protein.

Prognosis: Worse for AHL than ADEM; some recover w/ Rx; 70% mortality usually w/in first week; 70% survivors w/ residual deficits. May be improved w/ aggressive corticosteroids, IVIg, cyclophosphamide, plasmapheresis.

CEREBELLITIS (AKA ACUTE CEREBELLAR ATAXIA)

Definition: Inflammatory process of cerebellar white matter. Acute or subacute onset of cerebellar ataxia following an infxn, most often viral (GI or respiratory: VZV, EBV). Usually occurring in children (1-6) & young adults, sometimes in the elderly.

Etiology: (1) Viral: Children: VZV (occurs in 0.05%-0.1% children w/VZV), measles, mumps, EBV, hepatitis A, parvovirus B_{19}, rubella; Adults: EBV, influenza, parainfluenza, enterovirus (polio, coxsackie, echo), HSV, VZV, CMV, adenovirus, HIV. (2) Bacterial: Pertussis, Q fever (C. burnetti), Lyme, Mycoplasma, Legionella, Salmonella typhi. (3) Parasitic: Rickettsia, Malaria (P. falciparum). (4) Post vaccination: DTP, MMR, VZV, Influenza, HBV.

Clinical manifestations: Cerebellar sx: Acute or intermittent ataxia: (55% limb, 42% truncal or gait); onset 1-4 wk post infx, progresses over hours-days. Dysarthria (45%). Oculomotor disturbances (75%): Impaired smooth pursuit, saccades, suppression of VOR; nystagmus, etc. Extracerebellar sx: Cranial neuropathies, uni-/b/l sensory disturbance, hyperreflexia, upgoing plantar responses, increased tone, nausea/vertigo, szs, drowsiness.

Differential diagnosis: (1) Infectious: Listeria, TB. (2) Demyelinating: MS, ADEM. (3) Inflammatory: Sarcoid; AIDP (or Miller Fisher variant). (3) Neoplastic: Cerebellar/posterior fossa tumor (primary or secondary); neuroblastoma; paraneoplastic cerebellar degeneration; lymphoma. (4) Drugs: Thallium, lead, barbiturates, dilantin,

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piperazine, alcohol, solvents, antineoplastic drugs. (5) Structural: Hydrocephalus, foramen magnum compression.

Diagnostic testing: (1) CSF: Routine studies [pleocytosis (WBC up to 250/µL), 60%-99% lymphs; Protein ↑; Glucose ↔ or ↓; IgG/albumin ratio: nl in 40%; OCBs usually absent]; Viral Cx/PCR: VZV, EBV, HSV, CMV, HIV;

Serology, acute & convalescent; Blood films (malaria). (2) EEG/VEPs depending on clinical manifestations. (3) CT/MRI: Inflammation (T2 bright, enhancing), edema/swelling (10%-15%), obstructive hydrocephalus.

Treatment: (1) Corticosteroids: Controversial as dz self-limited. If sx severe: IV methylprednisolone 1 g/day × 5 days followed by oral taper. (2) Treat underlying infxn: (VZV/HSV: Acyclovir 10 mg/kg IV q8h × 10-14 days—↓ duration & severity if given early; Lyme's dz: Ceftriaxone 2g IV bid × 2 wk; Q fever (C. burnetti): Minocycline 4 mg/kg daily).

Prognosis: Complete recovery in majority in 1-30 wk. Mild to moderate cerebellar deficits in 10%-40% pts. Bad prognostic si/sx during acute phase: yawning, hiccups, age >40. Pts w/ long, term sequelae usually demonstrate moderate to severe cerebellar atrophy.

CENTRAL PONTINE MYELINOLYSIS

Definition: Syndrome of hyperosmotically induced pontine demyelination resulting in rapidly progressive encephalopathy, spastic quadriplegia, & brainstem dysfn. Osmotic demyelination syndrome describes pontine & extrapontine myelinolysis (EPM).

Pathophysiology: Following rapid correction of chronic hyponatremia, rapid shifts of water from intra-/extracellular to intravascular compartments → relative glial dehydration & myelin degradation &/or oligodendroglial apoptosis, in areas of the brain that are slowest @ reaccumulating osmolytes.

Risk factors: Chronic alcoholism (40%)—chronic hyponatremia, cirrhosis, malnutrition, renal failure; Rapid correction of hyponatremia (21%); Liver transplantation (17%) & HSCT; Immune suppressive therapy (cyclosporine); In children, has been described following severe burn injuries. Concurrent hypoxia → brain ischemia → worse prognosis.

Clinical features: (1) Sx usually delayed 2-6 days after correction of hyponatremia. Encephalopathy may progress from szs → coma, persistent vegetative state. (2) Sudden onset of spastic para- or quadriplegia, dysarthria, diplopia, dysphagia, dysarthria. (3) Locked-in syndrome (ddx: brainstem infarction from basilar artery occlusion).

Diagnostic testing: MRI: Lags behind clinical picture. Symmetric "bat-wing" T2 hyperintensity from myelin disruption centrally in the basis pontis. Called EPM if outside pons, e.g., cerebellar, gray/white junctional areas of neocortex, thalamus, & striatum.

Treatment: Mainly supportive. Early recognition of at-risk pts → more rapid dx.

Prevention: Asymptomatic hyponatremia: Correct Na by 10-12 mEq/L during first 24 h, & by 18 mEq/L over first 48 h, max rate during any 1 h 0.5-1 mEq/L/h. Symptomatic hyponatremia: Correct 1.5-2 mEq/L/h initially, but same total rate as above for first day.

Prognosis: Mortality common. Recovery over months; deficits: spastic quadriparesis to locked-in syndrome to spastic quadriparesis. In EPM may have tremor & ataxia.

MARCHIAFAVA-BIGNAMI DISEASE

Definition: Progressive dz characterized by demyelination & necrosis of the corpus callosum w/ subsequent atrophy → stupor, coma, szs, & apraxia.

Epidemiology: ˜250 case reports, usu men >45 yo, h/o alcoholism & malnutrition.

Clinical features: (1) Subtypes: 2 subtypes depending on CC involvement (J Neurol 2004;251:1050). Type A: Entire corpus callosum; stupor, coma, pyramidal-tract sx predominant. Type B: Partial or focal corpus callosum; mental status nl or mildly impaired. (3) Si/sx: Encephalopathy: lethargy, stupor, coma; Szs (common); Apraxia of nondominant hand suggestive of interhemispheric disconnection; Ideomotor apraxia; Dementia (acute, subacute, or chronic onset; aphasia may be present); Spasticity & gait dysfn. (4) Associations: Look for e/o chronic EtOH: Wernicke-Korsakoff (disconjugate eye movements, confusion), DTs, alcoholic neuropathy, truncal ataxia.

Management: No proven Rx. Manage szs & coma. Possibly helpful: Thiamine, folate, vitamin B_{12} supplementation (see chapter on “Poisons and Vitamin Deficiencies”). Trial of IV corticosteroids (methylprednisolone 250 mg q6h) or amantadine (100 mg po bid) theoretically warranted (e.g., some case reports of overlap with inflammatory CAA).

Prognosis: Generally: High mortality & morbidity (at least 200/250 reported cases died & 30 were demented or bed-bound) (Eur J Neurol 2001;8:269). Variability by subtype (J Neurol 2004;251:1050): Type A: Long-term disability 86%, mortality 21%. Type B: Long-term disability 19%, mortality 0%. MRI & CT show resolution of a pt who recovered.

DELAYED HYPOXIC CEREBRAL DEMYELINATION

Definition: Onset of cerebral demyelination following a hypoxic-ischemic event.

Pathophysiology: White matter selectively vulnerable to hypoxic injury,

resulting from widely spaced arterioles & lack of anastomoses.

Triggers: (1) Cardiac arrest; (2) “Leukotoxins”: CO, asphyxial gas poisoning, surgical anesthesia, solvents, chemoRx, & drugs of abuse (alcohol, cocaine, BZDs, & heroin).

Clinical features: Sx onset 2-40 days (usually 1-2 wk) after event. Cognitive deterioration; speech disturbance. Basal ganglia (indirect pathway) dysfn prominent: Hypo/akinetic motor syndrome w/ parkinsonism, akinetic mutism, motor neglect, increased tone. Urinary or fecal incontinence. Reflexes: Glabellar, grasp. Gait disturbance: Short step gait, retropulsion.

Diagnostic testing: MRI: b/l diffuse T2 WM hyperintensity, spares subcortical U-fibers & posterior fossa, w/out vacuolization. MR spectroscopy: Increased choline to creatine ratio, decreased N-acetyl aspartate levels, no lactate peak. LP: Myelin basic protein > 40 ng/mL (CSF marker of acute widespread CNS demyelination).

Prognosis: 75% recovery at 1 yr w/ residual cognitive deficits, follows late remyelination.

CARBON MONOXIDE POISONING

Epidemiology: Most common cause of injury & death due to poisoning worldwide. Risk factors: Suicide attempts, faulty car exhaust or furnaces; faulty scuba diving equipment; burn victims; exposure to methylene chloride. 40,000/yr in the US present to medical attention; 500 die from unintentional exposure & 2,000 from suicide.

Pathophysiology: CO binds Hb w/ >200 × more affinity than O_2; Leads to prolonged cerebral hypoxia & acidosis → cardiac toxicity, hypotension → cerebral hypoperfusion.

Clinical features: Early: At 20%-30% carboxyhemoglobin concentration: HA (dull, frontal, continuous), N/V, SOB, confusion, dizziness, ataxia, vertigo—may be confused w/ gastroenteritis or flu-like sx; Cyanosis more common than cherry-red cheeks. At higher levels: Blindness, visual field defects, papilledema. At 50%-60% carboxyhemoglobin concentration: Coma, posturing, szs, & generalized slowing on EEG. Delayed: 2-40 days; see above: Delayed hypoxic cerebral demyelination: Extrapyramidal sx: Parkinsonian gait, bradykinesia; Depression, cortical blindness, amnesia, psychosis, dementia. Chronic: Persistent HA, LH, depression, confusion, dementia, N/V—may resolve after exposure.

Diagnostic testing: (1) Carboxyhemoglobin concentration in blood (stable complex of hemoglobin & CO in RBCs): nl 5%, up to 15% in chronic smokers. May use a pulse co-oximeter. (2) Imaging: Initially: CT: nl or mild

cerebral edema. Delayed: CT or MRI: b/l globus pallidus & medial putaminal demyelinating lesions; ± watershed infarcts if HoTN.

Management: (1) Initially: O_2 via nonrebreather; (2) Hyperbaric O_2 (try two to three sessions @ 2-3 atm in first 24 h after exposure—may ↓ incidence of cognitive sequelae [Toxicol Rev 2005;24:75] when (1) carboxyhemoglobin concentration >40%; (2) coma or szs present); (3) Supportive Rx: Szs & motor activity (BZD, dantrolene), HoTN (IVF, pressors), cardiac arrhythmias (ACLS, tele), pulmonary edema, metabolic acidosis (bicarb, O_2 therapy).

PROGRESSIVE SUBCORTICAL ISCHEMIC DEMYELINATION

(Aka Leukoaraiosis, Binswanger disease—Review in Pract Neurol 2008;8:26)

Pathophysiology: (1) Chronic ischemia from arteriosclerosis & lipohyaline deposits in arterioles penetrating WM → demyelination. (2) ↑ perivascular interstitial fluid, thickened tortuous sclerotic vessels, then brain atrophy. (3) Necrosis if severe ischemia & infarction. (4) Pathology: Myelin pallor, enlargement of perivascular spaces, gliosis, axonal loss.

Risk factors: Age, HTN, DM. May be precipitated by hypotension or hypoxia 2/2 cardiac or carotid disease. Men & women equally affected.

Clinical features (Stroke 1987;18:2): (1) Onset in the 4th decade, worsens w/ age, more prominent in 6th/7th decades. (2) Sx often insidious, may occur in a stepwise

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fashion. (3) Cognitive impairment (30% patients): Dementia w/ prominent disruption of executive fxn; deficits in short-term memory, organization, attention, decision-making, inappropriate behavior, psychomotor slowing, forgetfulness, speech disturbance; Mood d/o w/ apathy, irritability, depression. In about 1/3 patients, cognitive dysfn dx'ed after TIA or stroke. (4) Gait d/o (60% patients): clumsy, frequent falls. (5) Other: Hyperreflexia, b/l Babinski, grasp & sucking reflexes, cerebellar ataxia. (6) Advanced cases: Urinary incontinence.

Complications: Risk of strokes, particularly lacunar (NASCET, Stroke 2002;33:1651); Vascular death; Coumadin-associated hemorrhage (SPIRIT, Neurology 2002;59:193); Hemorrhage following tPA after stroke (CASES, Neurology 2007;68:1020); Falls; PNA.

Diagnostic testing—CT: Diffuse periventricular hypodensity. MRI: T2/FLAIR hyperintensities w/ well defined but irregular margins, mostly subcortical & periventricular. May include optic radiations, basal ganglia, & brainstem, but spare the subcortical U-fibers & corpus callosum. May be

mildly hypointense on T1. Nonenhancing. Ventricles appear enlarged due to white matter loss. Over time, multifocal pattern becomes confluent.

Differential diagnosis: (1) Other forms of vascular dementia (e.g., CADASIL, CAA); (2) Alzheimer disease; (3) NPH; (4) Radiologic ddx: other WM abnlities (MS, lymphoma, leukodystrophy, disseminated WM mets), which are distinct epidemiologically & clinically.

Management: Largely symptomatic. (1) Depression, anxiety: SSRIs; (2) Agitation, behavioral dysregulation: antipsychotics (risperidone, olanzapine); (3) Stabilization of cognitive fxn: memantine; (4) General: sleep hygiene, exercise, EtOH/tob cessation; (5) Carotid imaging to assess for stenosis requiring intervention; (6) Risk factor modification: diet modification, aggressive Rx of DM, HTN (goal SBP 135 to avoid hypotension), smoking cessation; (7) Use coumadin only w/ clear indication (atrial fibrillation) due to ↑ risk of ICH.

TOXIC LEUKOENCEPHALOPATHY

Description: Demyelination of cerebral white matter as a result of toxic insult. (Also known as: toxic spongiform leukoencephalopathy, drug-induced leukoencephalopathy.)

Major Etiologies of Toxic Leukoencephalopathy

Antineoplastic agents	Methotrexate, carmustine, cisplatin, cytarabine, fluorouracil, levamisole, fludarabine, thiotepa, interleukin-2, interferon-α
Immunosuppressives	Cyclosporine (posterior lobes), tacrolimus (parieto-occipital)
Antimicrobials	Amphotericin B, hexachlorophene
Drugs of abuse	Toluene (inhale vapor from spray paints & glues); Ethanol, cocaine, MDMA/ecstasy, IV/inhaled heroin, psilocybin
Environmental	Carbon monoxide, arsenic, carbon tetrachloride

Methotrexate leukoencephalopathy: Dose & route dependent (40% intrathecal vs. 10% IV); worse if a/w cranial XRT (potentiates effects vs. disrupts BBB); gradual cognitive ↓ month-year after exposure (mild learning disability to

severe dementia); w/ somnolence, szs, ataxia, sphincter dysfn, myoclonus, hemiparesis. May stabilize or improve after d/c MTX. CSF: ↑ protein, lymph. pleocytosis. MRI: Periventricular FLAIR changes in WM & swelling.

"Chasing the Dragon" (Heroin leukoencephalopathy): Heat heroin on tin foil & inhale vapors → WM changes & degeneration of multivacuolar oligodendrocytes. Clinical features: Behavior changes, ataxia, quadriparesis, chorea, myoclonus, death. MRI: Typically involvement of posterior limb of internal capsule & cerebellum.

Clinical features (NEJM 2001;345:426)

Neurobehavioral: Mild: Confusion, inattention, forgetfulness, personality ▲; Moderate: Somnolence, apathy, dementia; Severe: Abulia, akinetic mutism, stupor, coma, death.

Neuropsych: Mild: Sustained attention & memory retrieval deficits, depression, & anxiety; Moderate: Deficits in attention, memory, visuospatial skills, & executive fxn; language relatively nl; Severe: Severe global impairment.

Imaging: CT: Mild: Usually nl. Moderate: Mild WM hypodensity, nonenhancing. Severe: Diffuse WM hypodensity, nonenhancing; necrosis. MRI: Mild: Periventricular WM hyperintensity. Moderate: Diffuse WM hyperintensity. Severe: Severe WM hyperintensity, necrosis.

Neuropathology: Mild: Patchy intramyelinic edema w/ preservation of myelin. Moderate: Widespread edema, demyelination w/ axonal preservation. Severe: Destruction of oligodendrocytes, axonal loss, necrosis.

Workup: History: Toxic exposures, e.g., medications, EtOH, illicits, OTC formulation, environmental & occupational (dry cleaners, pain strippers, degreasing industry, paint manufacturers, lacquer, varnish, rubber, & dyes) toxins. Examination: Signs of hepatic, cardiac, & hematologic dysfn. Neuro encephalopathy. Lab data: Tox screen (urine, serum drugs of abuse, 24 h for toluene). Spectrophotometric blood analysis (carboxyhemoglobin, i.e., CO). Urine heavy metals (arsenic, lead, mercury) if suggested by HPI. Imaging: CT & MRI (see above): MRI: Diffuse WM hyperintensity, w/ sparing of the subcortical U fibers.

Management: Prevention; Supportive therapy (may include corticosteroids, anticoagulation). Prognosis: Depends on degree of WM dz & degree of reversibility.

RADIATION-INDUCED NECROSIS

Epidemiology: Occurs in 20%-25% pts s/p XRT for brain tumors (can also occur s/p focal stereotactic radiation); usually >5,500 cGy total or >200 cGy fractionated daily dose.

Pathophysiology: Vascular injury & occlusion, perivascular inflammation, BBB disruption, demyelination, oligodendroglial damage, reactive gliosis. ± WM vasogenic edema, necrosis, vacuolation, petechial hemorrhage; ↓ cerebral blood flow 2/2 endothelial hyperplasia.

Clinical features: Onset usually 6-24 M after XRT, may take decades.

Acute Rxn: @ time of XRT, usually 2/2 vasogenic edema: Transient confusion, temporary worsening of preexisting deficits. Self-limiting.

Early delayed Rxn: Weeks-months after XRT; Pathology = demyelination: Confusion, somnolence. Near complete recovery.

Late delayed Rxn: Usually 6 mo-2 yr after XRT (up to 20 yr); Pathology = severe demyelination & necrosis: Progressive dementia; focal deficits; learning disability in children; szs; mass effects, ↑ ICP, obstructive hydrocephalus, herniations. ICH occasionally.

Diagnostic testing: (1) MRI: Tumor + edema, mass effect, radiation necrosis. T2: confluent, initially symmetric signal changes in periventricular WM, sparing CC & arcuate fibers; eventually margins become scalloped as they extend toward peripheral arcuate fibers. May see: contrast enhancement; hemosiderin in basal ganglia; atrophy. (2) To distinguish residual/recurrent tumor vs radiation changes: may need Bx, FDG-PET or SPECT.

Treatment: No good data. Can try as indicated: (1) Steroids (decadron 10 mg IV then 4 mg q6h until sx subside, then taper) for vasogenic edema; (2) Hyperbaric oxygen to improve perfusion & angiogenesis; (3) Anticoagulation: Heparin (adults: 80 U/kg initially then 18 U/kg/h; Children: 50 U/kg initially then 100 U/kg IV q4h or 20,000 U/m^2/24 h maintenance) or coumadin (PT/PTT 1.5× nl) to prevent further vascular thrombosis & occlusion; (4) Surgical management of ICP & debulking; (5) Ventriculoperitoneal shunting (hydrocephalus).

Spine and Spinal Cord Diseases

APPROACH TO BACK PAIN

Common problem w/ broad differential. Majority of pts have musculoskeletal or mech causes that require only conservative management & most recover naturally. Goal: Identify causes that require further diagnostic workup & intervention.

Warning Signs in History

- Age >50 yr, history of cancer, unexplained weight loss
- Recent fever, immunosuppression, IV drug use, skin infxn, UTI
- Osteoporosis, prolonged corticosteroid use
- Pain > 1 mo, night time pain, pain not relieved by lying down
- Pain increased w/ coughing, sneezing, or Valsalva maneuver
- Unresponsiveness to previous therapies
- Significant wkns or paralysis
- Pain w/ wkns/sens loss & bowel/bladder dysfxn

Exam

General exam: Fever, rash, track marks, cachexia, new cardiac murmur (endocarditis), abdominal bruit (AAA), costovertebral tenderness (pyelonephritis), Grey-Turner or Cullen sign (retroperitoneal hemorrhage; pancreatitis), palpable abd mass, peripheral pulses (vasc claudication). Rectal exam for sphincter tone, palpable mass, prostate enlargement.

Spine examination: Inspect/assess deformities, ROM of spine. Palpate for vertebral tenderness, step-offs, paraspinal musc spasm, paraspinal masses (tumor, TB cold abscess). Hip or SI joint pain: Reproduced w/ int & ext rotation of hip w/ knee flexed (Patrick sign). Straight leg raise: Reprod

radicular pain, buttock thru posterior thigh; indicates nerve root compression. Crossed straight leg raise: in supine position, raising unaffected leg reproduces radicular pain in affected leg; indicates severe root compression from prolapsed disc. Neuro exam: eval for wkns, sens loss, saddle or perianal anesthesia, hyper- or hyporeflexia.

Labs: CBC, ESR, CRP (helpful when infxn or malig considered). Other labs if indicated: UA, SPEP/UPEP, amylase/lipase, LFTs, Ca, blood cultures.

Neuroimaging: Unnecessary in many cases as pain is most likely 2/2 musc etiologies & mild disc herniations & are usually self-limited. Indications: Strong suspicion for underlying systemic process, e.g., cancer or infxn; persistent or progressive neuro deterioration; unresponsive to conservative management for >4 wk; pre-operative planning

MRI: Sens & spec for mult causes of back pain: disc herniation, spinal stenosis, osteomyelitis, discitis, epidural abscess, metastases, arachnoiditis, & myelopathies. MRI w/gado necessary if suspected infxn/inflam/neoplast process.

CT: Rapid, useful for bony structures & fractures. CT myelogram: Contrast is injected intrathecally into subarachnoid space; eval lesions compressing cord & nerve roots; consider if MRI contraindicated.

Plain films: Rarely definitive; may be useful to assess for fracture & vertebral bony metastases such as from prostate ca; lateral of the LS spine are routine; flexion-extension views in surgical fusion procedures or in spondylolisthesis; hip & pelvis when osteoarthritis is presenting as LBP.

EMG/NCS: Help r/o radic mimics such as plexopathy & entrapment neuropathy. Help localize radic in potential surg candidates w/ multilevel dz or poor corr between sx, exam, & imaging. Useful in cases w/ give-way wkns or when pain limits exam. Usually unnec in pts where exam corr clearly w/ lesion on MRI. Pain or sens sx w/o wkns often have nl EMG/NCS.

Differential Dx of Back Pain

Congenital

- Spondylolysis & spondylolisthesis
- Spina bifida occulta
- Tethered cord

Neoplastic

- metastatic, hematologic, primary bone, neurofibromas

Infectious/inflammatory

Mechanical/mildly traumatic

- Back strain/sprain
- Whiplash

Fractures

- Traumatic—falls, MVA
- Nontraumatic—osteoporosis, prolonged glucocorticoid use, tumor

Disc herniation

Degenerative spine

- spondylosis, spinal stenosis

Arthritic

- spondylosis, facet or sacroiliac arthropathy, autoimmune (ankylosing spondylitis, Reiter's syndrome)
- Vertebral osteomyelitis, discitis
- Spinal epidural abscess
- Arachnoiditis

Vascular

- aortic aneurysm, vascular malformation, infarct, & hemorrhage

Visceral dz/referred pain

- Pelvic dz—endometriosis, PID, prostatitis, uterosacral ligament traction
- Renal dz—pyelonephritis, nephrolithiasis, werinephric abscess
- GI—peptic ulcer dz, pancreatitis, cholecystitis
- Retroperitoneal bleed—anticoagulation or various systemic processes

Conservative Rx: Indicated for most nonspec causes of LBP. General measures: Early ambulation, resumption of nl phys act w/o heavy lifting; discourage bed rest >2 days; avoid activities that promote back pain. Acute nonpharm Rx: Heat pads, spinal manipulation. Chronic Rx: PT, cog behavtx, spinal manipulation, interdisciplinary rehab (Ann Intern Med 2007; 147:505);

possible role for massage, yoga, acupuncture. Medications: First line: NSAIDs, acetaminophen, muscle relaxants. Second line: Short-term opioid analgesics, tramadol, benzos. Gabapentin (for radic); systemic corticosteroids controversial but may be helpful in select cases; consider TCAs in chronic LBP (>4 wk). Epidural steroid & anesthetic injections may give short-term benefit for radic.

Spinal Cord Syndromes

Syndrome	Causes	Clinical findings
Complete cord	Trauma Compression Demyelination Post-infectious	Bilat wkns (initially flaccid, then UMN) below lesion Bilat loss of all sens modalities below level Sens level: transverse over torso Loss of bowel, bladder, sexual fxn Hyporeflexia then hyperreflexia Radiating pain; relieved w/ sitting/standing w/ malignancy
Hemicord (Brown-Séquard)	Trauma Demyelination Compression Tumors	Ipsilateral UMN wkns (corticospinal), vibration & proprioception (dorsal column) below level of lesion Contralateral pain & temperature (spinothalamic tract) 1-2 segmental levels below lesion
Central cord	Hyperextension Syringomyelia Tumors Anterior spinal artery (ASA) ischemia Demyelination Hematomyelia	Wkns: Arm > leg; distal > proximal Loss of pain & temperature in cape-like distribution (shoulders, neck, upper trunk) or suspended sens level Relative preservation of light tough, position, vibration Sacral sens sparing
ASA	Decreased ASA flow Vascular or thoracoabdominal surgery Cardiac arrest Hypotension	Loss of motor, sens (pinprick, temperature), autonomic fxn below level Preservation of vibration & proprioception (dissociated transverse sens loss) Abrupt onset w/in min to hours; back & neck pain Initial flaccid

		paraplegia, then spasticity & hyperreflexia Vulnerable area is watershed zone at approx T6 & region around artery of Adamkiewicz
Conus medullaris	Tumors Lipomas Metastases Disc herniation Fractures	Onset sudden & bilat Early bowel/bladder incontinence Impotence & loss of anal reflexes Saddle anesthesia; may have sens dissociation Symmetric wkns, may be mild Loss of Achilles but not patellar reflexes
Cauda equina	Central disc herniation Tumors Infxns Arachnoiditis	Severe lumbosacral radicular pain Saddle anesthesia, may be asym Flaccid paraparesis Late bowel/bladder incontinence; impotence Loss of ankle jerks; possibly knee jerks

COMPRESSIVE MYELOPATHIES

NEOPLASTIC SPINAL CORD COMPRESSION

Suspect in pt w/ known or suspected cancer & back pain w/ or w/o neurodeficits. W/ neuro dysfxn, urgent w/u & Rx nec. Cancers commonly met to spinal column: Adults: Prostate, breast, lung, renal cell, myeloma, lymphoreticular. Children: Sarcoma, neuroblastoma, germ cell, & lymphoma. Location: Thoracic > lumbar > cervical, but thoracic most sx. Pain: Often initial complaint; no relief w/ lying down, worse w/ Valsalva; often nocturnal; local pain from stretching of periosteum; axial pain from fracture; radicular pain from root compression.

Dx: MRI entire spine w/ gado. CT for spinal stability, operative planning. Plain radiograph: To eval for fracture/collapse; rarely useful alone. Metastatic w/u if primary unknown.

Rx: Steroids: Widely used in acute setting until more definitive Rx, but optimal dose not clearly defined (Curr Oncol Rep 2008;10:78). If significant neurologic impairment: Dexamethasone 100 mg load, then 24 mg q6h. If minor neuro impairment: dex 10 mg load, then 4 mg q6h., questionable additional benefit of using high vs low dose steroids (Neurology 1989;39:1255). Debulking surgery w/ decompress followed by RT may be

sup to RT alone (Lancet 2005;366:643). Radiotherapy (RT): If expected

survival <3 mo at dx, presence of a very radiosens tumor (lymphoma, small cell lung ca, breast, prostate, mult myeloma, seminoma, neuroblastoma, Ewing sarcoma), mult areas of spinal cord compression, or total paraplegia for longer than 48 h, consider RT alone. Systemic chemotherapy in sens tumors.

CERVICAL SPONDYLOTIC MYELOPATHY

Most common cause of myelopathy in older adults. Prog degen changes of discs & subseq degen changes in verteb bodies, hypertrophic changes in facet joints & hypertrophy of ligamentum flavum causes narrowing of spine, compression of roots, & compromise of vascular supply leading to a radiculomyelopathy.

Exam: Pain in the neck, subscapular region, shoulder, & radicular arm pain; Lhermitte sign. Sens loss or paresthesias in dermatomal distrib; loss of proprioception & vibration from dorsal column dysfxn, loss of pain sensation. UE wkns in LMN pattern; LE wkns in UMN pattern. Hoffman & Babinski signs. Spastic gait or scissoring of limbs (may be dom sign w/ little wkns). Bladder dysfxn (urgency, frequency, retention).

Dx: MRI: Eval for canal narrowing, cord compression or signal abnlities w/in cord implying compressive or ischemic changes. EMG/NCS: Not routinely needed; may find evidence of motor neuron or nerve root involvement; helpful to exclude other causes (ALS).

Rx: Conservative: Immobilization w/ soft collar or brace; restrict high risk activ, pain control. Indications for decompression: Acute deterioration in neuro fx; consider w/ progressive deterioration; disabling neuro deficits; consider in mild cases w/ risk of deterioration.

LUMBAR SPINAL STENOSIS

Narrowing of lumbar spinal canal. Sx result from nerve root compress & ischemia or indirectly from ↑ intrathecal pressure from ↓ canal size. Standing erect narrows the lumbar canal, flexion opens up canal.

Etiology & classification: Congenital: Short pedicles, symptomatic onset 20-40s; idiopathic; achondroplastic. Acquired: Central canal—disc degen, facet hypertrophy, ligamentum flavum hypertrophy; lateral recess stenosis; spondylolisthesis. Iatrogenic: Post-laminectomy/fusion; at adjacent level or at previously operated site. Spondylotic: Presents in 20s, assoc w/ spondylolisthesis. Post-traumatic. Misc: Corticosteroid excess, Paget dz, acromegaly, ankylosing spondylitis, achondroplasia.

Clinical manifestations: Neurogenic pseudoclaudication: buttock, hip, thigh or leg pain, sens loss, & wkns; often bilat & asym; worse w/ prolonged standing

& walking, relieved w/ sitting, lying, or positions that flex at waist (squatting, pushing shopping cart). Can also have lumbosacral radic, conus medullaris, or cauda equina syndrome. Distinguish from hip osteoarthritis (pain into groin provoked w/ internal rotation of hip), trochanteric bursitis (tenderness of greater trochanter), & vascular claudication).

Exam: May be nl when sx result from intermittent ischemia; may progress to fixed neurol findings consistent w/ radic, conus lesion, or cauda equina synd; palpate peripheral pulses; listen for aortic & femoral bruits.

Workup: MRI lumbar spine: Helps assess degree of stenosis (caveat of poor correlation of degree of stenosis w/ severity of sx & prognosis; can be incidental finding); loss of CSF signal in areas of severe stenosis; CT or CT myelogram when MRI contraindicated. If concern for vascular claudication, measure ankle to brachial BPs & Doppler studies. EMG/NCS: Not routinely necessary; may help eval for radic or neuropathy.

Rx: Conservative measures: for those w/o fixed or progressive neuro impairment; NSAIDS, epidural steroid injections, PT (abdominal strengthening, min activities w/ lumbar extension), bicycling (lumbar flexion) better tolerated than walking, lumbar corset promote lumbar flexion (limit to several hours/day to avoid atrophy). Surgical referral (Nat Rev Neurol 2009;5:392): if fail conservative Rx for 3-6 mo, +functional disability, persistent neuro deficits; laminectomy ± fusion; interspinous distraction; new minimally invasive techniques. Progressive neuro dysfxn, bladder dysfxn, rapidly progressive cauda equina or conus medullaris syndrome warrant urgent surgical eval.

ACUTE TRAUMATIC SPINAL CORD INJURY (SCI)

Etiology: MVA, falls, gunshot wounds, sporting accidents. Predisposing conditions: Cervical spondylosis, osteoporosis, atlanto-axial instab. Diverse mechanisms but typically vertebral injury leads to spinal cord compression.

Eval: History: Mechanism, LOC, sx (pain/numbness/wkns). Physical exam: Motor, sens, reflexes, autonomics, spinal palpation. Imaging: Helical CT, MRI if stable.

ASIA Scale

A No motor or sens fxn below level through the sacral segments S4-5

B Sens but not motor fxn preserved below level & includes S4-5

C Motor fxn preserved below level & majority of key muscles less than antigravity

D Motor fxn preserved below level & majority of key muscles at least antigravity

E Motor & sens fxn nl

Initial management

ABCD: Chin lift w/o neck extension; no jaw thrust. Nasotracheal intubation if breathing spont. Avoid tracheostomy/cricothyroidotomy (may compromise later surgery). Goal MAP ≥90; dopamine as pressor of choice; avoid phenylephrine (possible bradycardia). Fluids w/ caution for pulm edema. MAST. Immobilization (CPR takes precedence). Foley.

SCI steroid protocol (if w/in 8 h of injury): Controversial; considered a tx option & not standard of care. Exclusion: Gunshot wound or other penetrating trauma to spine, cauda equina syndrome, other life threatening morbidity, pregnancy, narcotics addiction, < 13 yo, on maintenance steroids. Methlyprednisolone 30 mg/kg bolus over 15 min, 45 min pause, then maint 5.4 mg/kg/h for 23 h (consider 47 h if initiated 3-8 h after injury) (JAMA 1997;277:1597).

COMPLICATIONS OF CHRONIC SPINAL CORD INJURY

Pressure sores: Turn q2h; wheelchair lifts 5-10 s q15-30 min; daily skin exams; proper nutrition; wound care.

DVTs: Prophylaxis up to 3 mo post injury or d/c from rehab; LMWH: Start 48-72 h after injury unless contraindications; compression stockings & pneumatic pressure devices × 2 wk following injury. IVC filters—when anticoagulation contraindicated, failing anticoagulation, complete C2 or C3 injury.

Autonomic dysreflexia: Paroxysmal severe HTN, sweating, flushing, piloerection, HA, CP, tachy/bradycardia in response to rel benign stimuli below level of injury. Serious consequences: ICH/stroke, sz, pulm edema, MI, death. Mechanism: 2/2 injury above the major splanchnic outflow tracts (T5-6); Sens nerves transmit signals up spinothalamic & dorsal columns → symp neurons, intermediolateral gray matter → large symp surge because of loss of inhibitory input from cerebral vasomotor centers → vasoconstriction & HTN; Brainstem vasomotor reflexes → increased parasymp tone → bradycardia, sweating, skin flushing above level of lesion. Common precipitating factors:

Painful or irritating stimulus below lesion; bowel & bladder distention; instrumentation; irritation. Management: Initial: Elevate HOB, loosen clothing & constrictive devices; identify precipitant—check foley for blockage, check for fecal impaction—KUB, careful rectal exam w/ lidocaine jelly, look for sores or ulcers, r/o abdominal process; HTN management: elevate HOB & pharmacotherapy; Nifedipine 10 mg PO, bite & swallow; Nitroglycerin 2% ointment, 1 in, above level of injury; Captopril 25 mg SL; IV meds for hypertensive crisis (e.g., hydralazine, diazoxide, nitroprusside); profuse sweating: Propantheline 15 mg po or oxybutynin 5 mg po. Prophylaxis: Nifedipine 10 mg po, 30 min prior to procedure; phenoxybenzamine 10-20 mg tid; scopolamine for sweating.

VASCULAR MYELOPATHIES

SPINAL CORD ISCHEMIA

Presentation: Radicular pain, wkns in minutes to hours (max at 12 h), urinary retention, usually lower thoracic/ lumbar, ASA territory.

Physical exam: Bilat lower extremity flaccid paresis, ↓'d reflexes below lesion, bladder distension, ↓'d rectal tone, loss of temp/light touch below lesion. Predictors of poor outcome: Proprioception loss, urinary dysfxn, gait disturb at onset; lack of sig motor recovery in 24 h.

Dx: MRI (T2 hyperintensity w/in 2 h).

Etiology: Exercise, esp w/ preexisting spine dz; local vascular intervention such as >30 min clamping of aorta above renal arteries; rare complication of transforaminal steroid injection; hypotension: Lumbosacral regions most susceptible, not thoracic watershed; local atherosclerosis; thromboembolism, incl meningovascular syphilis; fibrocartilaginous embolism; XRT causes a progressive delayed microvascular occlusive dz.

Rx: Supportive: Keep MAP > 90; spinal cord perfusion pressure = MAP - intrathecal pressure; lumbar drain [although limited evidence for this (Eur J Vasc Endovasc Surg 2008;35:46; J Neurosurg Spine 2009;10:181)]; consider endovascular intervention, antiplatelet therapy; no definitive role for steroids.

SPINAL CORD HEMORRHAGE AND VASCULAR MALFORMATIONS

SAH: Sudden onset of severe back pain, usually starts focal then becomes diffuse. LP: Gross blood, elevated OP. Very rare, unclear etiology.

Spinal epidural/subdural hemorrhage (SEH/SDH): Severe pain at level of bleed. Sensorimotor sx over hours-days, slower in SDH. Usually iatrogenic—

therapeutic anticoagulation, LP in setting of plt < 20 K. MRI diagnostic. SEH more common in males; child: cervical, adults: thoracolumbar. SDH more common in females, thoracolumbar. Surgical emergency.

Hematomyelia: Sudden onset of radicular pain, then spinal shock. Usually 2/2 trauma. MRI is study of choice. Consider surgical drainage. Selective spinal angio for dx, precise localization of feeder, & to locate artery of Adamkiewicz. Rx: Angiographic embolization, surgical ligation/resection, or combination of both.

Spinal Vascular Malformations

Classification	Features
Extradural AVF: Abnl connection b/w extradural arterial branch & epidural venous plexus	Venous engorgement causes mass effect on nerve root & spinal cord, venous HTN, & vascular steal leading to myelopathy
Intradural dorsal AVF: Radicular a. feeder to venous connection at the dural sleeve of root	Venous outflow obstruction causes arterialization of venous plexus leading to venous hypertension & myelopathy
Intradural ventral AVF: ASA to an enlarged venous network at ventral midline	High flow into venous system causes vascular steal from intrinsic spinal cord leading to ischemia
Extradural/intradural AVM	Multiple tissues (bone/skin/etc.); severe = Cobb syndrome
Intramedullary AVM	Similar to intracranial AVM
Conus medullaris AVM	Multiple feeders

Presentation: Varying tempo & sx 2/2 mass effect & venous congestion. If root compression, may have radic & myelop. Lower thoracic/lumbar predom. Spinal AVM may have bruit. Coexisting vasc malform of skin, Cobb syndr.

Spinal dural AVF: Most common spinal vasc malf.

Presentation: Male:female 9:1; middle-aged. Usually progressive. May p/w acute deterioration after exercise, standing, singing, bending over, eating.

Improves w/ rest.

Dx: MRI: Central cord T2 hyperintensity along five to seven segments, usually mild & diffuse enhance w/ cord expansion, evidence of ischemia & hemorrhage; reflects venous HTN; subarachnoid flow voids (tortuous dilated veins) on T2/FLAIR. MRA spine to localize region of involvement (AJNR 2007:28:1249). Selective spinal angio for dx, localize feeder, & locate Adamkiewicz.

Rx: Angiographic embolization, surgical ligation/resection, or combination of both.

DEMYELINATING AND INFLAMMATORY MYELOPATHIES

(Comprehensively covered in Chapters “Demyelinating Diseases of the Central Nervous System” and “Neurorheumatology”)

P.209

	MS	**NMO**	**ADEM**
History	F:M = 2:1 Age: 20s-50s	F:M = 9:1 Variable age of onset	F:M= 1:1 Children > adults Antecedent infxn or vaccination
Clinical	Dissemination of lesions in time & space	Severe myelopathy Progress hours to days ± H/o optic neuritis NMO Ab positive Relapsing course	Fever Encephalopathy Monophasic Rarely relapsing
MRI spine	Gado enhancement of active lesions <2 segments May see old T1 dark lesions Cord expansion rarely	Longitudinally extensive (>3 segments) Gado enhancement of active lesions Cord expansion	Variable length May be >3 segments Often thoracic cord Can see cord expansion

			Variable enhancement
MRI brain	WM lesions, Dawson fingers, periventricular, juxtacortical, infratentorial lesions Variable enhancement May see old T1 dark lesions	Nl or nonspec periventricular lesions May see atypical lesions in thalamus, hypothalamus, brainstem, cerebellum ± Optic nerve enhancement	Large subcortical or deep confluent white matter lesions C-shaped lesions, open ring sign Gray matter lesions in the basal ganglia & thalami Uniform enhancement
Spinal fluid	Acellular or mild pleocytosis (<50 cells) Lymph predominance Increased IgG index +OCB	Pleocytosis (50-1,000 WBC) Neutrophil predominance ± Increased IgG index Usually OCB neg	Pleocytosis (>50 WBC) Lymph predominance Variable IgG & OCB
Rx	IV steroids for acute exacerbation Dz modifying tx	IV steroids ± plasma exchange Immunosuppression to prevent relapse	IV steroids IVIg or plasma exchange for steroid refractory cases

MYELOPATHY 2/2 NUTRITIONAL DEFICIENCIES

Vitamin B_{12} deficiency: Etiology: Autoimmune pernicious anemia, excessive antacid use, atrophic gastritis, HIV, gastric surgery, nitrous oxide abuse,

nitrous oxide exposure during anesthesia, fish tapeworm infestation of the gut, strict vegetarianism. Clinical manifestations: Subacute combined degen (SCD); loss of vibration & proprioception below lesion w/ nl pinprick & temp; corticospinal wkns; painful paresthesias in hands in some, w/ accom evidence of myelop; + Romberg, + Lhermitte's. Dx: ↓ serum B_{12}, ↑ methylmalonic & homocysteine, CBC w/ macrocytic anemia & hypersegmented neutrophils; Myelopathy can occur in absence of anemia. MRI spine: Longitudinal T2 signal in post & lat columns of cervicothoracic cord; not necessary for the dx of early myelopathy when it is most treatable. Rx: B_{12} 1,000 µg IM daily × 5 days, then B_{12} 1,000 µg po daily indefinitely; early dx & prompt rx essential for optimal recovery.

Folate deficiency: Etiology: Drug-induced impairment of folate metabolism (TMP, MTX), alcoholism, inborn error of folate metabolism. Clinical manifestations: Resembles SCD; rare cause of myelop. Dx: ↓ serum folate & ↑ homocysteine, screen for B_{12} def. Rx: Folate 1 mg po tid × 5 days, then 1 mg po daily, monitor homocysteine levels.

Copper deficiency: Etiology: Gastric surgery, zinc toxicity (denture cream), TPN, copper chelators (clioquinol & ethambutol). Clinical manifestations: Resembles SCD w/ sens ataxia & spasticity, rarely optic neuropathy. Dx: ↓ serum & urine copper levels, ↓ ceruloplasmin; MRI w/ ↑ T2 signal in dorsal columns of cervical cord. Rx: Stop zinc. Copper 6 mg po daily × 1 wk, then 4 mg po daily for 1 wk, then 2 mg po daily. If IV therapy needed, copper 2 mg IV daily × 5 days.

Vit E deficiency: Etiology: Pancreatic insuff, chronic cholecystitis, hypobetalipoproteinemia (Bassen-Kornzweig dz), chylomicron retention dz, ataxia w/ vit E deficiency, inherited forms of vitamin E malabsorption. Clinical manifestations: Ataxia, dysarthria, hyporeflexia, peripheral neuropathy, loss of vibration & proprioception, gaze palsies, retinitis pigmentosa. Dx: Calculate effective serum vitamin E level by div serum vitamin E by sum of serum chol & triglycerides. Genetic studies when approp. MRI: ↑ T2 signal in dorsal column. Rx: Vitamin E 200 mg po daily; genetic disorders may require higher doses (200 mg/kg/day); avoid excess fat in diet.

TOXIC MYELOPATHIES

Fluorosis: Etiology: Overconsumption of fluoride in water → fluoride deposits in vertebra; endemic in many parts of India; myelopathy caused by compression of cord by extensive & hypertrophic changes in bony spine. Sx: Back pain, stiffness, cord compression, spastic paraparesis, ↓ hearing 2/2 nerve compression. Dx: ↑ alk phosp & PTH, nl Ca & PO_4. Plain films:

Osteosclerosis, calc of ligaments, & interosseous membrane.

Cassava toxicity (Africa): Etiology: Insuff processing of cassava root → cyanide poisoning. Sx: Abrupt onset of spastic paraparesis or slowly prog ataxia, periph neurop. Dx: Serum thiocyanate level.

Lathyrism (India, Ethiopia, Bangladesh): Etiology: Consumption of grass pea w/o other cereals or improper processing. 2/2 toxin β-N-oxalylamino-L-alanine. Sx: Subacute paraparesis & autonomic dysfxn.

Organophosphate toxicity: Etiology: Phosphorylation of neurotoxic esterase. Sx: Onset >1 wk after acute exposure; distal paresthesias & cramping muscle pain; prog limb wkns & wasting in lower > upper extremities. Dx: RBC cholinesterase activity.

Intrathecal chemotherapy: Etiology: Methotrexate, vincristine, doxorubicin, cytarabine, cisplatin, vinorelbine, carmustine. Sx: Transient, flaccid, areflexic paraparesis w/pain & anesthesia after injection. Progressive spastic-ataxic paraparesis w/ sphincter dysfxn (less common). Dx: MRI spine w/ enhancement of lateral columns.

Hepatic myelopathy: Etiology: Cirrhosis & portosystemic shunting → toxicity of ammonia & metabolites; venous shunting may interfere w/ spinal vascular supply. Sx: Progressive spastic paraparesis. Dx: ↑ serum manganese; MRI brain & spine w/ manganese deposition in basal ganglia, lateral corticospinal tract demyelination.

Heroin myelopathy: Etiology: Unclear mechanism. Sx: IV or intranasal heroin leads to acute myelopathy; inhalation leads to progressive myelopathy. Dx: Toxicology screen. MRI brain & spine: Acute: Transverse myelitis & cord expansion; Chronic: ↑ T2 signal of ventral pons, dorsal & lat columns.

INHERITED AND NEURODEGENERATIVE MYELOPATHIES

Spinocerebellar ataxias: Sx: Limb & trunk ataxia, periph neurop, loss of vibration, proprioception, & variable corticospinal sx in limbs. SCA 1-28: Dx by genetic testing, MRI w/ cerebellar atrophy. Friedreich ataxia: Most common form of hereditary SCA; autosomal recessive, FRDA gene w/ GAA trinucleotide expansion. TTE to eval for hypertrophic obstructive cardiomyopathy; milder & adult-onset phenotypes increasingly recognized & may have intact DTRs unlike classic form w/ areflexia. Machado-Joseph dz (SCA 3): SCA3 gene mutation; MRI w/ cerebellar atrophy. Abetalipoproteinemia (Bassen-Kornzweig): Lipoprotein electrophoresis. Familial vit E def: low serum vit E.

Leukodystrophies causing myelopathy: Sx: Cog impairment, UMN signs, optic neurop, periph neurop, behav dist, szs. Adrenomyeloneuropathy: Chronic, prog spinal cord form of ALD seen in young/middle-aged men & rarely middle/older aged women, X-linked, ABCD1 gene mut, ↑ serum VLCFA. Metachromatic leukodystrophy: Demyelinating peripheral neuropathy, deficiency of arylsulfatase a.

INFECTIOUS MYELOPATHIES

Viral: HIV, HTLV I & II, HSV-1, HSV-2, VZV, CMV, enterovirus, polio, West Nile virus.

Bacterial: Syphilis, Tb, Lyme, epidural abscess.

Fungal: Aspergillus, blastomycosis, coccidiodes, cryptococcus.

Parasitic: Toxoplasma, schistosomiasis, echinococcus, cysticercosis.

Motor Neuron Disease

APPROACH TO MOTOR NEURON DISEASE

History and physical exam: Points to consider

- Sx, distribution of sx, time course.
- Presence of upper motor neuron (UMN) or lower motor neuron (LMN) sx.

  UMN: Weakness, spasticity, increased tone, hyperreflexia, + Babinski.
  LMN: Weakness, fasciculations, decreased tone, hyporeflexia, - Babinski.
- Presence of hyperreflexia: Babinski, palmomental, Hoffmann's, brisk jaw jerk, clonus, brisk abdominal reflexes.
- Presence of pseudobulbar palsy. Due to involvement of corticobulbar tracts which exhibit supranuclear control over motor nuclei controlling speech, chewing, swallowing. Sx: Dysarthria, dysphagia, emotional lability, or emotional incontinence with spontaneous laughter or crying.
- ROS: Night sweats, fevers, weight loss, gynecomastia, impotence, rash, neck pain, sx suggestive of systemic disease.
- Exposure to toxins/travel history/military history/family history; HIV risk factors; h/o malignancy, systemic disease.

DDx: See charts below for diseases affecting UMN, LMN, & both. Chronic, motor peripheral neuropathies, Charcot-Marie-Tooth disease, cervical spondylosis or disc

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disease/cervical spine pathology, muscular dystrophies, myasthenia gravis, myopathies such as polymyositis, inclusion body myositis, pseudobulbar palsy secondary to vascular disease, chronic Lyme disease, spinal muscular atrophies.

Workup: Labs (chem 10, CBC, coags, CK, Lyme, ESR, CRP, HIV, SPEP, UPEP, IFE, B_{12}, TSH); EMG/NCS; MRI brain or spine depending on clinical history & distribution of sx; consider CT chest, abdomen, or pelvis, or PET scan to evaluate for malignancy; genetic testing, depending on clinical history.

Rx: For many of these illnesses, no Rx to slow progression of disease. For amyotrophic lateral sclerosis (ALS), Riluzole shown to prolong survival (see below in “Amyotrophic lateral sclerosis” section for details). Supportive care: PT, OT, speech therapy, walking assist devices, walking aids (cane, walker, or wheelchair), braces, trach/PEG if pt wishes, genetic counseling in appropriate cases, supportive groups. Agents for spasticity, medications to reduce drooling. Important to diagnose or excluded diseases w/available Rx.

Summary Table of Motor Neuron Diseases

UMN	**LMN**	**UMN & LMN**
Primary lateral sclerosis (PLS)	Multifocal motor neuropathy (MMN)	ALS
Hereditary spastic paraparesis (HSP)	Monomelic amyotrophy	ALS-FTD
HTLV	Spinal muscular atrophy (SMA)	ALS parkinsonian complex of Guam
Adrenomyeloneuropathy	Kennedy disease	Machado-Joseph disease
Lathyrism	Progressive muscular atrophy	Adult hexosaminidase deficiency
Konzo	Paraneoplastic or neoplastic LMN disorder	Adult polyglucosan body disease
	Post-radiation LMN syndrome	Paraneoplastic syndrome
	Polio	
	Post-polio syndrome	

DISEASES AFFECTING PRIMARILY UPPER MOTOR NEURONS

Primary lateral sclerosis

Clinical features: 2%-4% cases of ALS;onset typically in 50s. Gradual spastic paraparesis spreading to UE, weakness, & unstable gait; may cause pseudobulbar palsy, fasciculations, urinary urgency, atrophy, subtle cognitive deficits.

Dx: Dx of exclusion; pure PLS defined by isolated UMN si/sx >4 yr (Neurology 2006;66:647). Exclude other causes of UMN sx: Chiari malformation, spinal cord lesions, myelopathies such as MS, HTLV, HIV, Lyme, syphilis, or adrenomyeloneuropathy. Family history to r/o HSP, spinocerebellar ataxia (SCA), familial ALS (FALS), hexosaminidase A, adrenomyeloneuropathy.

Hereditary spastic paraparesis

Clinical features: Most commonly AD, but can be recessive or x-linked. Progressive spasticity of LE. Complicated form may also exhibit optic neuropathy, deafness, ataxia, ichthyosis, amyotrophy, peripheral neuropathy, dementia, autoimmune hemolytic anemia, thrombocytopenia (Evan syndrome), extrapyramidal dysfunction, mental retardation, bladder dysfunction.

Dx: Family history; if no family history, then differential dx is the same as PLS. 40% cases w/ mutation in spastin on 2p22-21; other AD mutations on 2, 3, 8, 11, 12, 14, 15, 19 (Arch Neurol 2009;66:509).

Adrenomyeloneuropathy

Clinical features: X-linked recessive mutation in ABCD gene on Xq28 → very long chain fatty acid (VLCFA) accumulation; most common phenotype affects young boys 4-8 years of age. Adrenal insufficiency, progressive cognitive decline, seizures, blindness, deafness, & spastic quadriparesis. Milder cases: Slowly progressive spastic paraparesis & mild polyneuropathy in adult men w/ or w/o sensory disturbances.

Dx: Family history. Sural nerve biopsy: Loss of both myelinated & unmyelinated axons w/ onion bulb formation. EMG/ NCS: Primarily axonal sensorimotor polyneuropathy w/ lesser component of demyelination. Increased VLCFA levels in plasma, RBCs, or cultured skin fibroblasts. EM: Empty lipid clefts in Schwann cells (J Neuropathol Exp Neurol 1995;54:740).

Human T-Cell Lymphotrophic Virus (HTLV)

Clinical features: HTLV-1 causes tropical spastic paraparesis in Caribbean or HTLV-1 associated myelopathy in Japan. HTLV-2: Similar to HTLV-1 but may exhibit periventricular white matter changes on MRI. Chronic, slowly progressive myelopathy beginning after age 30. Spastic paraparesis, paresthesias, painful sensory neuropathy, bladder dysfunction

Dx: HTLV-1 & HTLV-2 serology in blood & CSF. Combination of PCR, HTLV-1 antibody, & oligoclonal bands (Lancet 2006;5:1068).

Lathyrism

Clinical features: Caused by chronic ingestion of flour made from chickpea, Lathyrus sativus. Neurotoxin: BOAA or beta-N-oxalylamino-L-alanine, a glutamate receptor agonist. Found in Bangladesh, China, Ethiopia, India, Romania, Spain. Acute or chronic onset; UMN degeneration; muscle spasms, cramps, leg weakness. May have sensory sx, bladder dysfunction, & coarse tremor.

Dx: Based on clinical history & exam.

Konzo

Clinical features: Caused by chronic ingestion of cassava root; endemic in Tanzania, Zaire, Eastern Africa. Spastic paraparesis; appears to target corticospinal tracts & motor cortex affecting LE.

Dx: Based on clinical history & exam (Drug Metab Rev 1999;31:561).

DISEASES AFFECTING PRIMARILY LOWER MOTOR NEURONS

Multifocal motor neuropathy

Clinical features: Pure motor sx in association w/ motor nerve demyelination. Cause unclear but believed to be autoimmune due to presence of anti-GMI ganglioside ab. Ddx: ALS, Progressive muscular atrophy (PMA), adult onset SMA, benign focal amyotrophy, CIDP. Age of onset 20-75 & more common in men, disease progresses over many years. Asymmetric, slowly progressive weakness more common in distal UE involving two or more individual peripheral nerves; fasciculations may be present. Paresthesias or subjective reduced sensation but objective sensory is absent.

Dx: EMG/NCS: Focal conduction block along two or more motor nerves. Prolonged distal latencies, prolonged F wave latencies, temporal dispersion of CMAPs. Sensory NCS wnl. High titers of serum IgM anti-GMI ab. CSF protein is usually normal but may be modestly elevated to < 100 mg/dL.

Rx: IVIg 2 gm/kg IV in divided doses over 2-5 days, followed by a maintenance dose of 400-600 mg/kg once every 3-8 wk. Check IgA level prior to administering IVIg (Neurology 2000;55:1256; J Neurol Neurosurg

Psychiatry 1995:248; Brain 2001;124:145).

Polio

Clinical features: Caused by poliovirus, an enterovirus; spread via fecal-oral route. Risk of paralytic disease increases w/ age & level of virulence of virus. 3-6 day incubation period followed by viremia where 90% are asymptomatic. 10% develop acute, flu-like illness w/ cough, malaise, diarrhea, myalgia, headache, & fever lasting 2-3 days; 2%-3% develop aseptic meningitis w/ severe headache & meningeal irritation; < 1% develop acute paralytic syndrome w/ fasciculations, severe myalgias, hyperesthesias, & focal & asymmetrical paralysis. Improvement may begin w/in first week after the onset of paralysis. 80% recover by 6 months & may continue over 18-24 months. 2/3 left w/ significant impairment.

Ddx: Acute paralytic disease caused by West Nile virus or other enteroviruses, GBS, AMAN, myasthenia gravis, neuralgic amyotrophy, acute intermittent porphyria, periodic paralysis, tic paralysis, & acute rhabdomyolysis.

Dx: EMG/NCS: Performed 21 or more days after onset. Low amplitude CMAPs, no demyelination or conduction block. SNAPs normal. EMG in acute phase may show positive sharp waves, fibrillation potentials, & fasciculations. CSF: Pleocytosis with polymorphonuclear cells predominating in acute phase & lymphocytes later. CSF protein is mildly to moderately elevated. CSF poliovirus IgM. Stool cx: Positive for poliovirus in 90% patients by the 10th day of illness. >4-fold increase in serum poliovirus Ab titer.

Post-polio syndrome

Clinical features: Also called progressive post-poliomyelitis muscular atrophy; cause unclear. Occurs in pts w/ h/o polio at least 10 years after their recovery. Stable course for many years after initial polio infection, followed by progressive, often asymmetric muscle weakness & atrophy, cramps & fasciculations. Pain, generalized fatigue, cramps, fasciculations, sleep disturbances, cold intolerance, dysphagia, & dysarthria.

Dx: Dx of exclusion. Dx based on clinical history & excluding other diseases w/ similar sx. EMG/NCS: Provides evidence of remote poliomyelitis & may help exclude other diseases. NCS may show low CMAP, EMG may show reduced number of motor units & chronic neurogenic motor unit potentials. Sensory NCS wnl (Muscle Nerve 2005;31:6).

Benign focal amyotrophy/monomelic amyotrophy/juvenile segmental

muscular atrophy

Clinical features: Segmental atrophy involving several myotomes; C5-T1 myotomes most commonly involved. Ddx: ALS, MMN, cervical or lumbosacral radiculopathy, plexopathy, syrinx. Usually begin in later teens but can present up to the fourth decade. Idiopathic, slowly progressive, painless weakness, & atrophy in one hand or forearm. Affects only a few myotomes in the affected limb; reflexes hypoactive or absent; may have hypesthesias to pinprick & touch.

Dx: No pathognomonic labs or electrodiagnostic tests; goal is to exclude other dx. EMG/NCS: Motor NCS normal or slight reduction of CMAPs. SNAPs are modestly reduced in 1/3 pts. EMG may reveal fibrillation & fasciculation potentials & chronic neurogenic motor unit changes. CK may be modestly elevated. MRI may reveal segmental cord atrophy, increased T2 signal, or cervical cord enlargement.

Infantile & juvenile SMA

Clinical features: One of the most common genetic causes of death & disability in childhood. Almost 98% cases AR w/ mutation on 5q 11.2-5q 13.3. Molecular genetic analysis to identify mutations in SMN gene on chromosome 5q. CK may be elevated up to 10 × normal in SMA-3. EMG/NCS: CMAPs may be reduced in amplitude; conduction velocities & sensory conduction studies normal. EMG may reveal acute denervation in the form of fibrillation potentials & positive sharp waves, fasciculation potentials, & motor unit remodeling. There may be reduced recruitment of polyphasic motor units. Complex repetitive discharges may be seen in SMA-3. Muscle biopsy may be helpful.

Three types of SMA

SMA-1 (infantile SMA or Werdnig-Hoffman): Onset at birth or w/in first few months of life. Unable to sit w/o support; floppy baby; frog leg posture at rest. Severe generalized proximal limb & bulbar weakness, diminished reflexes. Pts die from respiratory failure/ pneumonia usually before age 2.

SMA-2 (intermediate): Onset usually before age 18 mo. Milder & slower progression compared to type 1. Able to roll over & sit unsupported but rarely able to walk. Kyphosis, contractures of the hips/knees, & scoliosis, & dislocations of hips. Small involuntary movements of fingers called minipolymyoclonus.

SMA-3 (juvenile SMA or Kugelberg-Welander): Onset usually between 5 and 15 yr & present w/ difficulty walking; waddling (Trendelenburg gait); lordosis, difficulty climbing stairs, fasciculations, slowly progressive limb

girdle weakness. If onset before age 2, then often unable to walk by age 15. Most pts require wheelchair by mid-30s.

Adult onset SMA

Clinical features: 10% cases of SMA; mean onset mid-30s; clinically similar to SMA-3; AR in 70% cases. Slowly progressive limb-girdle weakness w/ difficulty walking, ascending stairs, rising from chair. Fasciculations, quadriceps weakness, muscle cramps. Bulbar sx, scoliosis rare.

Ddx: Limb girdle muscular dystrophy, Duchenne & Becker muscular dystrophy, polymyositis, adult-onset acid maltase deficiency, CIDP, Charcot-Marie-Tooth Type II, HMN-5, hexosaminidase A deficiency, PMA variant of ALS.

Dx: Labs (CK & aldolase are typically elevated to < 10-fold normal values). Muscle biopsy: Chronic denervating disease similar to SMA-3 but w/ changes of myopathy. EMG/ NCS: Normal velocities & reduced CMAPs, normal SNAPs. EMG: Marked chronic neurogenic motor unit changes & modest evidence of acute denervation. Fasciculation potentials may be seen (Lancet 2008;371:2120).

Kennedy disease

Clinical features: Also called X-linked recessive bulbospinal neuronopathy; occurs in men after age 30. Due to CAG repeat on androgen receptor gene located on the X chromosome. Gynecomastia, testicular atrophy, infertility, DM. Muscle cramps, twitching, fasciculations, atrophy, difficulty walking, limb-girdle muscle weakness, dysarthria, dysphagia. Muscle weakness typically LMN w/ decreased reflexes.

Dx: Labs (molecular genetic testing to identify abnormal expansion of the CAG repeat in exon 1 of the androgen receptor gene on × chromosome; CK levels may be elevated 10 times normal; androgen levels are normal or decreased). Muscle biopsy: Modest denervation, prominent reinnervation, fiber type grouping. Sural nerve biopsy: Loss of myelinated fibers & replacement of nerve w/ connective tissue. EMG/NCS: Motor

NCS normal, reduced CMAPs. EMG shows prominent chronic denervation changes in motor units, modest acute denervation changes. Sensory neuropathy, fasciculations in the face & limbs (Eur J Neurol 2009;16:556).

Progressive muscular atrophy

Clinical features: 8% of adult onset motor neuron diseases; believed to be an ALS variant; however, it’s not included in clinical trials or El Escorial criteria.

Exclusive LMN involvement. Commonly presents w/ focal asymmetrical muscle weakness in distal extremities w/ gradual spread to other contiguous muscles. May present w/ proximal weakness; bulbar & respiratory weakness eventually develop.

Ddx: MMN, CIDP, inflammatory myopathy, myasthenia gravis.

Dx: CK can reach 10 × normal. EMG/NCS: Widespread disorder of anterior horn cells. Muscle biopsy: Denervation atrophy but is usually unnecessary. Should exclude other possible causes.

Subacute motor neuronopathy in lymphoproliferative disorders: Subacute progressive, painless motor neuron syndrome in Hodgkin lymphoma, non-Hodgkin lymphoma w/ or w/o paraproteinemia, such as myeloma or macroglobulinemia. Typically LMN presentation w/ patchy, asymmetrical lower extremity weakness & muscle wasting. Rarely there may be UMN involvement as well. Neuropathology: Loss of anterior horn cells & ventral motor root fibers, inflammation of anterior horn cells. In some, the disease may have a benign course. Rarely, the disease may respond to Rx of underling lymphoproliferative d/o.

Postradiation LMN syndrome: LMN syndrome which may occur as a result of radiation directed to the lumbar paravertebral area for Rx of testicular cancer. EMG/ NCS c/w disorder of cauda equina with sparing of SNAPs. Disease usually progresses over the first few years after symptom onset but sx subsequently plateau.

DISEASES AFFECTING BOTH UMN AND LMN

Amyotrophic lateral sclerosis

General: Neurodegenerative disease of unclear cause; incidence 1-3 per 100,000. Most common onset in mid-50s; mean duration ˜3 yr from symptom onset & ˜19 mo from dx (Neuroepidemiology 2005;25:114; Neurology 2003;60:813).

FALS: 5%-10% ALS; most common inheritance for FALS is AD. 15%-20% FALS associated w/ several genetic abnormalities including mutations involving SODI on chromosome 21q21, FUS/TLS on chromosome 16, VAPB, & TDP-43 (Nature 1993;362:59; Science 2009;323:1205; Science 2008;319:1668; J Biol Chem 2006;281:30223).

Si/sx: Weakness typically begins focally & spreads to surrounding muscles. Rarely, weakness may begin the respiratory muscles. Some pts may present w/ unilateral weakness (Mill’s hemiplegic variant). 10% have bilateral UE wasting (flail arm variant). Fasciculations, cramps, exertional fatigue, atrophy. Sleep disturbances may occur as a result of multiple factors, such as hypoxia

while lying supine, discomfort, immobility, or anxiety. Depression is common.

Dx: Features atypical of ALS which should prompt a search for an alternative dx: Sensory loss, dementia, extrapyramidal dysfunction, eye movement abnormalities, autonomic disturbances, abnormal sphincter control. No blood test to diagnose sporadic ALS, but several lab tests are usually ordered to evaluate for other causes: CXR or Chest CT in smokers or pts older than 50, anti-Hu if cancer found, Hex-A assay in young pts w/ atypical features, VLCFA if adrenal insufficiency. CK, CBC, chem 10, VDRL, anti-GMI Abs, ESR, SPEP, or IFE, thyroid function studies, B_{12}. Acetylcholine receptor or VGCC antibodies if features suggestive of disorder of neuromuscular junction.

Rx: Riluzole 50 mg qhs, increase to 50 mg bid after 2 wk (N Engl J Med 1994;330:585). Aggressive supportive care/ symptomatic Rx (fatigue, spasticity, cramps, depression, sialorrhea, constipation, respiratory failure). PT/OT/speech; nutritional care for dysphagia & aspiration risk. Consider PEG. Respiratory support. Consider BiPAP or tracheostomy. Home/hospice care if pt wishes.

ALS-FTD: Earlier studies reported lower incidence (<5%) of cognitive impairment in ALS. Recent studies w/ higher rates of cognitive impairment in ALS: Present in 31%-55% of ALS pts; ˜20% w/ severe cognitive impairment c/w dementia; 15% meet criteria for FTD-ALS (Acta Neurol Scand 1977;56:185; J Clin Exp Neuropsychol 1996;18:291; J Neurol Neurosurg Psychiatry 1996;61:450; Neurology 2005; 65:586).

ALS parkinsonian complex of Guam: Disorder w/ combination of ALS & parkinsonism. Most common cause of death for adults in the native Chamorro population of Guam. Believed to due to toxin caused by the native cycad seed, which contains BMAA (β-methylamino-L-alanine), an amino acid that is toxic to cortical & spinal motor neurons.

Machado-Joseph (SCA type III): AD syndrome w/ onset ranging from 4th to 7th decade. Sx: Cerebellar ataxia. Patients w/ earlier onset may present w/ spasticity & fasciculations of the tongue & face. Other sx include extrapyramidal si/sx, dystonia, rigidity, protruberant eyes, & progressive external ophthalmoplegia. Due to CAG repeat on chromosome 14q32.1 which encodes for the ataxin-3 gene.

Adult onset hexosaminidase-A deficiency: AR, late onset GM2 gangliosidosis. Encoded by gene on chromosome 15q23-q24. Sx: Slowly

progressive weakness of proximal muscles of UE & LE, cramps. Sensory, cerebellar, cognitive, psychiatric, & extrapyramidal features may develop. May be mistaken for ALS in early stages of the disease. EMG/NCS: Complex repetitive discharges & abnormal SNAPs.

Adult polyglucosan body disease: Rare, slowly progressive disorder characterized by UMN & LMN signs, cognitive decline, distal sensory loss, & loss of bowel & bladder function. MRI brain: Diffuse white matter signal increase on T2 weighted images. Dx: Skin or peripheral nerve biopsy w/ periodic acid-Schiff-positive polyglucosan bodies.

Paraneoplastic motor neuron disease: Described in cases of Hodgkin & non-Hodgkin lymphoma, ovarian & breast cancers. May occur as a part of a larger paraneoplastic syndrome (anti-Hu). Rx: Treat underlying tumor.

Peripheral Neuropathy

EVALUATION OF NEUROPATHY

Definition: Impairment of function of one or more peripheral nerves.

Initial evaluation

Obtain a careful history: Ask about motor, sensory, or autonomic disturbances, obtain time course & distribution of sx, h/o toxic or infectious exposures, family history, meds, vitamins, sx of systemic diseases. Detailed physical exam: Determine anatomic pattern & localization: Mononeuropathy, mononeuropathy multiplex, polyneuropathy, predominant motor or sensory & to which modalities, autonomic sx. Evaluate for lymphadenopathy, organomegaly, musculoskeletal/ joint abnormalities, rash. Examine hair, skin, & nails; evaluate oropharynx (tonsils, palate movement); palpate peripheral nerves; evaluate for pes cavus & hammertoes. EMG/NCS: Helpful to confirm neuropathy; provide localization of lesions; distinguish between axonal vs. demyelinating neuropathy. Nerve biopsy: Most useful for suspected vasculitis & amyloid neuropathy. Also may be helpful to evaluate for infection (e.g., leprosy) & occasionally inflammatory disorders (e.g., sarcoid); typically sural nerve since sensory deficit is restricted to a small area over the heel & dorsolateral foot. Superficial peroneal is useful when vasculitis is suspected since the underlying peroneus brevis muscle can be biopsied at the same time; 15% complication rate such as minor wound infections, wound dehiscence, stump neuromas. 1/3 report unpleasant sensory sx. Labs for w/u of peripheral polyneuropathy: Chem 10, CBC, ESR, TSH, B12, SPEP & UPEP w/ IFE, ANA, anti-Ro & La. Fasting glucose & HbA1c; if normal, do 2 h glucose tolerance test. Screen for monoclonal proteins in pts w/ chronic neuropathy, especially if age > 60.

MONONEUROPATHIES

ENTRAPMENT MONONEUROPATHIES: UPPER EXTREMITY

Musculocutaneous nerve (C5-6): Risk factors: Shoulder dislocation, general anesthesia, weight lifting. Si/sx: Weakness & atrophy of biceps brachii & brachialis, sensory loss over lateral forearm. Dx: History, exam, EMG/NCS. Rx: Generally recovers spontaneously; consider steroid injection for sxs.

Suprascapular nerve (C5-6): Compression site at suprascapular notch. Risk factors: Trauma, repetitive forward traction. Si/sx: Atrophy of supraspinatus & infraspinatus muscles, aching posterior shoulder pain. Dx: History, exam,

EMG/NCS. Rx: Most spontaneously improve over time. Steroid injection/surgery for refractory cases.

Dorsal scapular nerve (C5): Compression site at scalene muscle. Risk factors include trauma. Si/sx: Winging of scapula on arm abduction.

Radial nerve (C5-8): Compression sites: (1) Axilla. (2) Spiral groove. (3) Posterior interosseous. (4) Superficial sensory branch (Cheiralgia Paresthetica). Risk

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factors: (1) Axilla: Crutches. (2) Spiral groove: Compression/ drunken sleep (Sat. night palsy). (3) Posterior interosseous nerve: RA, trauma, fracture, soft tissue mass, strenuous use of arm. (4) Superficial sensory branch: Wristbands, handcuffs. Si/sx: (1) Axilla: Weak triceps, brachoradialis, supinator, wrist/ finger extension; sensory loss over entire extensor surface of arm, forearm, & hand. (2) Spiral groove: Weak brachoradialis, wrist/ finger extension; triceps spared; minimal sensory loss in dorsum of hand, thumb, index finger, middle finger. (3) Posterior interosseous nerve: Weak wrist/ finger extension, extensor carpi ulnaris. (4) Superficial sensory branch: Numb dorsoradial hand. Dx: EMG/ NCS; MRI at compression site. Rx: For compression at axilla, spiral groove, & posterior interosseous nerve, conservative Rx w/ rest, modification of activities, & wrist splint; usually improves after 6-8 wk. For superficial sensory branch, sx usually self-limited.

Medial nerve (C6-T1): Compression sites: Wrist (carpal tunnel), anterior interosseus, pronator teres syndrome. Risk factors: Wrist tenosynovitis, arthritis, trauma, repetitive use, vibrating tools, DM, pregnancy, thyroid disease, gout, hemodialysis shunt, amyloid. For anterior interosseous syndrome: Forearm fracture; may occur w/ brachial plexitis & spontaneously improve. Si/sx: (1) Wrist/ carpal tunnel syndrome: Paresthesias & pain in lateral, palmar 3.5 fingers, thenar atrophy, Phalen & Tinel sign. Sx worse at night. (2) Anterior interosseous syndrome: Weakness of flexion of thumb & index finger & forming circle w/ thumb & index finger, normal sensation. (3) Pronator teres syndrome: Forearm aching, weak grip, median distribution numbness. Rx: carpal tunnel syndrome: Wrist splints, anti-inflammatory medications, steroid injections, PT, surgery for refractory cases or if thenar atrophy. Anterior interosseous syndrome: Conservative Rx, surgery if fracture/trauma or refractory sx. Most occur w/ brachial plexitis & spontaneously improve over time.

Ulnar nerve (C7-T1): Compression site: Elbow (cubital tunnel); wrist (Guyon canal). Risk factors: At elbow (cubital tunnel): Elbow leaning, trauma. For wrist (Guyon canal): Mechanics, cyclists, RA or degenerative disease of wrist

joints, wrist fractures.

Clinical features: (1) Elbow (cubital tunnel): Numbness of medial 1.5 fingers (dorsal & palmar aspect.) Atrophy of intrinsic hand muscles, weakness of flexion of wrist & fourth, fifth digits, claw hand. Tinel sign at elbow, Froment sign. (2) Wrist (Guyon canal): Numbness of palmar medial 1.5 hand and fingers, hypothenar or interossei atrophy.

Rx: Conservative management w/ rest, modification of activities, immobilization w/ splint, or corticosteroid injections. In more severe cases, surgical decompression.

ENTRAPMENT MONONEUROPATHIES: LOWER EXTREMITY

Ilioinguinal (L1): Compression site: Abdominal wall. Risk factors: Trauma, scar, surgical incision. Si/sx: Groin pain, direct hernia, sensory loss in the iliac crest & crural areas. Rx: Rest, NSAIDs, neurolysis in refractory cases when mechanical lesion suspected.

Lateral femoral cutaneous/meralgia paresthetica (L2-3): Compression site: Inguinal ligament. Risk factors: Tight clothing, obesity, DM, pregnancy, pelvic/ abdominal mass. Si/sx: Sensory loss, burning, tingling in the anterior & lateral thigh. Dx: EMG/ NCS. Rx: Conservative Rx. Weight loss or rest. Injection or local anesthetics or steroids. AEDs, tricyclics, topical anesthetics. Rx underlying tumor.

Obturator (L2-4): Compression site: Obturator canal. Risk factors: Tumor, surgery, pelvic fracture, DM. Si/sx: Radiating pain & numbness of groin & inner thigh; weak hip adduction. Dx: EMG/ NCS; CT or MRI pelvis to look for tumor. Rx: Conservative Rx; treat underlying tumor.

Femoral (L2-4): Compression site: Inguinal ligament. Risk factors: Lithotomy, aortic or iliac aneurysms, retroperitoneal hematoma, trauma, pelvic/ abdominal surgery. May be affected as forme fruste of L5 radicular plexus neuropathy, which may be idiopathic or related to diabetes. Si/sx: Weak hip flexion & knee extension, absent knee jerk. Dx: EMG/ NCS. If suspect hematoma or unclear cause, CT abdomen/pelvis. Rx: Depends on etiology. Conservative Rx if due to lithotomy, trauma, position/stretch. If retroperitoneal hematoma, surgical evacuation & discontinue anticoagulation/antiplatelet agents. If due to malignancy, treat underlying tumor.

Sciatic (L4-S3): Divides into common fibular (peroneal) & tibial nerves. Compression site: Sciatic notch, distally in piriformis muscle or popliteal fossa. Risk factors: Endometriosis, IM injections, trauma, fracture dislocations, hip replacement surgery, compression during coma, anesthesia,

prolonged sitting. Si/sx: Pain down thigh, foot drop, absent ankle jerk. Weakness of all knee flexors & muscles below knee & sensory loss of entire foot except over medial malleolus. Dx: EMG/ NCS. Rx: See below for Rx of peroneal & tibial nerves.

Common fibular (peroneal) nerve (L4-S1): Divides into superficial (L5-S1) & deep peroneal (L4-S1) nerves. Compression site: Fibular neck. Risk factors: Leg crossing, squatting/trauma. Si/sx: (1) Common peroneal: Weakness of foot dorsiflexion & eversion, sensory loss in dorsum of foot. Tinel's at fibular head. (2) Superficial peroneal: Sensory loss of lateral part of the leg and dorsum of foot except for web space between first & second toes. Weak ankle eversion. (3) Deep peroneal: Sensory loss of web space between first & second toes. Weak ankle dorsiflexion. Dx: EMG/ NCS. Rx: Conservative Rx. Relieve underlying compression. Ankle foot orthosis, splints.

Tibial nerve (L4-S2): Compression sites: (1) Popliteal space, (2) Tarsal tunnel, or (3) Foot. Risk factors: (1) Popliteal space: Baker cysts, trauma, nerve tumors, entrapment. (2) Tarsal tunnel: Ankle fracture, tenosynovitis/RA, ill-fitting shoes, tumors. (3) Foot: Trauma, tumors. Si/sx: (1) Popliteal space: Weakness w/ inversion & plantar flexion of foot & toes, sensory loss in sole & lateral foot. (2) Tarsal tunnel: Sensory loss, burning pain of plantar foot; atrophy of intrinsic foot muscles. Pain w/ percussion below medial malleolus (Tinel sign). (3) Foot: Pain, paresthesias, & numbness in sole of foot. Dx: EMG/ NCS. Rx: Conservative therapy; steroid injections for sx relief, surgical decompression.

MONONEUROPATHY MULTIPLEX

Definition: Involvement of multiple separate peripheral nerves.

Causes: Primary or systemic, including Leprosy, DM, SLE, vasculitis, sarcoidosis, RA, PAN, amyloidosis, Sjogren syndrome, Wegener granulomatosis, HIV, CMV, Hepatitis B & C.

Dx: Labs: Chem 10, CBC, ESR, rheumatological markers (ANA, ESR, RF, c- & p-ANCA, anti-Ro & La, ACE), hepatitis panel, cryoglobulins, SPEP/ UPEP, fasting blood sugar, Lyme titer, HIV. EMG/NCS: Biopsy: Sural nerve or superficial peroneal nerve/peroneus brevis muscle biopsy depending on clinical exam & EMG/NCS results.

POLYNEUROPATHIES

AUTOIMMUNE/INFLAMMATORY CAUSES OF POLYNEUROPATHY

Guillain-Barré syndrome

Si/Sx: Ascending, predominantly motor paralysis; may progress to respiratory failure; evolves over days-weeks; pain in hips, thigh, & back; reduced vibratory & position sensation; reduced tendon reflexes; facial diplegia may occur; autonomic instability; may be preceded by Campylobacter, EBV, CMV, Mycoplasma; paresthesias in toes & fingers. Variants: (1) Acute inflammatory demyelinating polyneuropathy (AIDP; classical demyelinating form). (2) Descending form (facial/brachial onset). (3) Miller Fisher syndrome: Ophthalmoplegia w/ ataxia & areflexia. (4) Acute motor & sensory axonal neuropathy or "Axonal GBS": Worse prognosis & slower recovery. (5) Acute motor axonal neuropathy. Ddx: Spinal cord disease/myelopathy, necrotizing myelopathy, carcinomatous meningitis, poliomyelitis, brainstem disease, neuromuscular disorders such as myasthenia gravis, myopathy, polyneuropathy of critical illness, porphyria, acute hypophosphatemia.

Dx: LP: High protein, few cells (<50), albuminocytological dissociation. If increased cell count, consider GBS in setting of alternative dx such as Lyme disease, HIV, neurosarcoidosis, CNS lymphoma or leukemia w/ nerve infiltration. EMG/ NCS: Demyelination except in axonal variant. MRI: Gadolinium enhancement of cauda equina roots. Labs: May be abnormalities in LFTs, EKG, hyponatremia secondary to SIADH. Antibodies: Anti-GM1 (AIDP), anti-GQ1b (Miller— Fisher variant).

Rx: Close VS monitoring, NIFs, FVCs. If NIF <-20, FVC < 1.5 L or downward trend, consider intubation; monitor electrolytes. Consider plasmapheresis or IVIg → Plasmapheresis: Exchange 200-250 mL/kg of plasma in four to six treatments qod; IVIg: 0.4 g/kg/day × 5 days. Adverse effects: Rarely ARF, proteinuria, aseptic meningitis, anaphylaxis if IgA deficient, headache, rash, thromboembolic events (Ann Neurol 2001;49:694).

Chronic inflammatory demyelinating polyneuropathy: Slowly progressive, motor > sensory sx in both proximal & distal muscles. CSF albuminocytological dissociation (see GBS for same ddx if cell count is high). Multifocal inflammatory demyelination. Weakness must be present >2 mo. Generalized hyporeflexia or areflexia, can have nerve root enlargement. May be associated w/ HIV, SLE, MGUS, plasma cell dyscrasias, hepatitis, inflammatory bowel disease, Hodgkin lymphoma.

Dx: Labslx-ray: Chem 10, CBC, LFTs, ESR, HIV, SPEP, UPEP, immunofixation, skeletal bone survey for evaluation of underlying systemic disorder. EMG/NCS: Multifocal demyelination & partial conduction block. CSF: High protein w/ normal cells. Nerve biopsy: May reveal demyelinating or axonal changes. Usually not necessary. MRI: lumbosacral roots may reveal gadolinium enhancement.

Rx: IVIg 2 g/kg over 2-5 days monthly for 3 mo. If sx improve, may continue IVIg 1 g/kg at intervals depending on disease response, generally every 1-2 mo. Prednisone started at 60-80 mg for 2-3 mo followed by a slow taper as tolerated (5-10 mg/mo or the lowest possible dose that controls the neuropathy). May add a second line steroid-sparing immunosuppressive agent (e.g., azathioprine, mycophenolate mofetil, methotrexate). Plasma exchange biweekly initially & then individualized (Ann Neurol 1994;36:838; Ann Neurol 2001;50:195).

Multifocal motor neuropathy: Partial conduction block; demyelinating features in motor axons w/ muscle weakness. Progressive, asymmetric, predominantly distal limb weakness (90% are in the distal upper extremity), muscle cramps, fasciculations, & atrophy over months-years. May be confused w/ ALS but absent UMN sx. Depressed tendon reflexes.

Dx: EMG/NCS: Persistent focal motor conduction block or other features of demyelination. Multifocal motor demyelination. CSF: Protein usually normal but may be slightly increased. Antibodies: IgM anti-GM1 antibodies in 80% of patients.

Rx: IVIg per rx of CIDP (Neurology 2000;55:1256). Rituximab 750 mg/m^2 (up to 1 g) IV w/ repeat dose in 2 wk. Repeat rituximab on an individualized basis (every 6-12 mo in most cases). Cyclophosphamide 1 g/m^2 IV qmo × 6-8 mo for nonresponders to IVIg.

Acute sensory neuronopathy: Sensory ataxia, areflexia, numbness, pain. No weakness. May be GBS variant. Also seen in HIV, Sjogren syndrome, or idiopathic in nature. CSF protein may be elevated. EMG/NCS: Absent or reduced sensory amplitudes w/ normal motor studies. May treat w/ IVIg as per GBS.

Critical illness polyneuropathy (CIP): Acute or subacute neuropathy in the setting of multi-organ failure or sepsis/SIRS. Most cases are actually critical illness myopathy as opposed to CIP. Often diagnosed w/ failure to wean from ventilator. Predominantly motor weakness & mild sensory sx. Dx: EMG/NCS revealing primary axonal process w/ early denervation. Normal CSF.

POLYNEUROPATHIES SECONDARY TO GENETIC DISEASE

Charcot-Marie-Tooth disease: Most common inherited neuropathy. Also called hereditary motor & sensory neuropathy.

Clinical presentation: (1) Type I, II: Usually begin in 1st or 2nd decade of life but can have later onset (particularly CMT II). Autosomal dominant. Si/sx include foot deformity & difficulties in running or walking, symmetric

weakness, wasting in intrinsic foot, peroneal, & anterior tibial muscles, pes cavus, hammer toes, mild kyphosis, & enlarged hypertrophic peripheral nerves. Absent ankle reflexes. Mildly diminished sensation to vibration & light touch in feet & hands. (2) Type III: Onset in infancy or early childhood. Autosomal dominant but usually due to new mutations so no family history. Proximal weakness, global areflexia, enlarged peripheral nerves, & severe disability. (3) Type IV: Childhood onset of progressive weakness, inability to walk, AR inheritance. (4) CMT X: X-linked. Onset in childhood or adult life. Onset earlier & more severe in men.

Dx: EMG/NCS: Demyelinating in I, III, IV. Axonal in II. Mixed axonal-demyelinating in X-linked CMT. Biopsies: Sural nerve biopsies are no longer used to diagnose CMT but showed hypertrophic neuropathy w/ onion bulb formation in the demyelinating forms. Genetic testing.

Rx: Genetic counseling. Supportive care w/ ankle foot braces, orthopedic procedures for foot drop. Avoid neurotoxic agents.

Metachromatic leukodystrophy: AR disorder of sulfatide metabolism caused by deficiency of arylsulfatase A. Sulfatide accumulation in brain, nerves, & other tissue. Infantile, juvenile, & adult forms. Leads to progressive demyelination. Causes gait disorder, hypotonia, lower limb areflexia, behavioral abnormalities, progressive dementia (more prominent in adult onset form). Dx: EMG/ NCS w/ demyelination. Nerve biopsy w/ demyelination. MRI brain. Increased urinary sulfatide excretion & abnormal arylsulfatase A assays in leukocytes or fibroblasts. Rx: Bone marrow transplantation may increase brain levels of arylsulfatase A.

Fabry disease: X-linked lysosomal storage disorder but women can be affected as well. Deficiency of a-galactosidase A leads to accumulation of ceramide trihexoside in tissue. Causes progressive vascular disease leading to renal failure, cardiac disease, strokes. Angiokeratomas of trunk, buttocks. Distal paresthesias, lancinating pain worse w/ heat, exertion, fever. Autonomic dysfunction. Dx: EMG/NCV w/ mildly reduced amplitudes. Sural nerve biopsy: Neuronal degeneration, selective loss of small myelinated & unmyelinated fibers. α-galactosidase A assay. Rx: Analgesics, phenytoin, carbamazepine, & avoiding precipitating factors. Recombinant α-galactosidase therapy.

Krabbe disease or globoid cell leukodystrophy: AR inheritance; mutation on 14q31; deficient galactocerebroside β-galactosidase. Extensive CNS & PNS demyelination; multinucleated macrophages (globoid cells) in cerebral white matter. Infantile form: Rapidly progressive motor & intellectual deterioration,

hypertonicity, opisthotonic posture, optic atrophy, & seizures. Adult form: Peripheral neuropathy, spasticity. Dx: EMG/ NCS w/ demyelination. Sural nerve biopsy: Segmental demyelination, tubular or crystalloid inclusions w/i Schwann cells & macrophages. Rx: Hematopoietic stem cell transplantation (N Engl J Med 1998;338:1119).

Adrenomyeloneuropathy: Leukodystrophy; X-linked but women can be affected. Causes adrenal insufficiency, progressive myelopathy, & peripheral neuropathy. Often misdiagnosed as MS. Defective β-oxidation of very long chain fatty acids (VLFCA) in peroxisomes. Accumulation of tetracosanoic & hexacosanoic acid in tissue. Presents in 2nd to 3rd decades w/ progressive spastic paraparesis, distal muscle weakness, sensory loss, sphincter disturbances, spinocerebellar ataxia. Dx: Elevated serum VLCFA. EMG/ NCS w/ distal axonopathy, 10% w/ demyelination. Sural nerve biopsy: Loss of myelinated fibers; onion bulbs; lipid inclusions in Schwann cells. MRI Brain w/ white matter changes. May have lab abnormalities suggestive of adrenal insufficiency. Genetic testing (Neurology 1996;46:112). Rx: Dietary restriction of VLCFA w/ administration of oleic & erucic acids (Lorenzo oil). Does not work well & has side effects. Corticosteroids for adrenal insufficiency.

Refsum disease (phytanic acid storage disease): AR; defect in phytanoyl-CoA-hydroxylase leading to phytanic acid accumulation in tissues. Onset in childhood to 3rd decade of life w/ night blindness or visual field constriction, chronic neuropathy, ataxia/cerebellar signs, weakness, areflexia, distal leg atrophy, large fiber sensory impairment, enlarged nerves, pes cavus, overriding toes, short fourth metatarsals, sensorineural hearing loss, anosmia, cardiomyopathy, & ichthyosis. Dx: EMG/NCS: Low motor conduction velocities. Reduced or absent SNAPs. CSF protein increased from 100-700 mg/dL. Sural nerve biopsy: Hypertrophic neuropathy w/ onion bulb formation. Elevated serum phytanic acid levels. Rx: Dietary restriction of phytanic acid & its precursor phytol. Plasma exchange to lower serum phytanic acid levels in critically ill patients.

Porphyric polyneuropathy: Caused by acute intermittent porphyria, an autosomal dominant disease. CNS & PNS affected in variegate porphyria. Severe, symmetric, rapidly ascending, motor > sensory neuropathy. May p/w tachycardia, fever, leukocytosis, abdominal pain, psychosis, convulsions. Attacks precipitated by sulfonamides, griseofulvin, estrogens, barbiturates, phenytoin, & succinimide. Dx: Increased porphobilinogen, & delta-aminolevulinic acid in urine. Rx: IV glucose to suppress heme synthesis. Hematin 4 mg/kg daily for 3-14 days. Respiratory, cardiac support. Use of β-blockers for severe tachycardia. Vitamin B_6/pyridoxine 100 mg bid. Avoid

precipitants.

Tangier disease: AR; deficiency of HDL; leads to cholesterol ester deposits in many tissues. Si/sx: Symmetric neuropathy, loss of pain & temp in face, arms, trunk. Faciobrachial muscle wasting & weakness. Relapsing multifocal mononeuropathies. Orange tonsils. Dx: Low HDL & cholesterol; triglycerides elevated. EMG/NCS w/ axonal degeneration & demyelination. Sural nerve biopsy w/ segmental remyelination & loss of small axons. Rx: No known Rx.

Abetalipoproteinemia (Bassen-Kornzweig syndrome): AR disorder of lipoprotein metabolism. Causes fat malabsorption; hypocholesterolemia; severe deficiency of Vitamins A, E, & K; abnormal spiky red cells (acanthocytes), retinitis pigmentosa, spinocerebellar degeneration. Progressive, large fiber sensory neuropathy, gait ataxia, areflexia, impaired proprioception, & modest distal weakness. Rx: Dietary fat restriction & large oral doses of Vitamin E (100 mg/kg/day).

Familial vitamin E deficiency: Caused by mutation in the α-tocopherol transfer protein. Failure to incorporate α-tocopherol in LDL in the liver & leads to low vitamin E levels. Rx: Dietary fat restriction; Vitamin E po (100 mg/kg/day).

Familial amyloid polyneuropathy: Amyloid deposition in peripheral nerves & other organs. Familial amyloid due to deposition of transthyretin, apolipoprotein A1, gelsolin. Insidious onset in 3rd & 4th decade w/ sensory impairment to temp, lancinating pains in LE, paresthesias, autonomic dysfunction. Dx: EMG/NCS w/ distal axonal neuropathy affecting sensory > motor fibers. Sural nerve biopsy revealing amyloid deposition. Genetic testing.

Hereditary neuropathy w/ liability to pressure palsies: Recurrent episodes of isolated mononeuropathies typically affecting the common peroneal, ulnar, brachial plexus, radial, & median nerves. Initial attack in 2nd or 3rd decade of life. Sudden onset,

painless mononeuropathy, w/ complete recovery w/in days or weeks. Dx: EMG/ NCS w/ evidence of focal slowing distally & across sites of compression. Sural nerve biopsy reveals tomacula, segmental demyelination, axonal loss. Biopsy often not necessary. Genetic testing: Most pts have a deletion of chromosome 17p11.2 leading to only one copy of a PMP22 gene. (Neuromus Disord 2002;7-8:651).

Neuropathy associated w/ mitochondrial diseases: Myopathy associated w/ Kearns-Sayre, MELAS, & MERRF. May also have a mild, sensory

polyneuropathy detected by electrophysiological & pathological studies. Peripheral neuropathy may be a presenting feature in following syndromes: (1) Neurogenic weakness, ataxia, & retinitis pigmentosa, a mild form of ATPase mutation. A severe phenotype results in Leigh syndrome. (2) Mitochondrial neurogastrointestinal encephalopathy. (3) Sensory ataxia neuropathy associated w/ dysarthria & CPEO.

Hereditary sensory & autonomic neuropathy: Prominent sensory loss, shooting pain, numbness in the extremities w/ autonomic features but w/o significant weakness. Types I-V. Rx: Prevention of stress fractures, ulcers, good foot care.

TOXIC NEUROPATHIES

Introduction: Most often affect the long axons & p/w paresthesias & distal sensorimotor, stocking glove distribution neuropathy. May often p/w signs of systemic toxicity w/ skin, cardiovascular, renal, GI, & hepatic injury. Dx: Clinical h/o exposures, exam for systemic signs, serum or urine testing for specific agents, EMG/NCS. Most toxic neuropathies are axonopathies, although perhexiline, amiodarone, suramin, & hexacarbons may cause a demyelinating neuropathy. Rx: Remove offending agent. Chelation w/ some agents, such as arsenic, mercury, lead.

Alcoholic neuropathy: Insidious onset, slow progression from distal to proximal. Gait difficulty, weakness, muscle cramps, distal muscle wasting, loss of tendon reflexes, & sensory loss of all modalities in a stocking glove distribution, burning paresthesias. Dx: Clinical history & EMG/NCS w/ predominantly axonal sensorimotor neuropathy. Rx: Alcohol abstinence, balanced diet. Supplementation w/ thiamine & B vitamins. Symptomatic rx of neuropathic pain.

Other causes of toxic neuropathies: Medications: Amiodarone, amitriptyline, chloroquine, cimetidine, cisplatin, colchicine, dapsone, didanosine, disulfiram, doxorubicin, ethambutol, fialuridine, gold, hydralazine, isoniazid, lamivudine, lithium, nitrofurantoin, nitrous oxide, metronidazole, paclitaxel & other taxanes, perhexiline, phenytoin, pyridoxine, statins, stavudine, suramin, thalidomide, vincristine & other vinca alkaloids, zalcitabine, zidovudine. Recreational drugs: Alcohol, nitrous oxide, n-hexane. Amphetamines, heroin, & cocaine may cause a vasculitis, which may affect peripheral nerves. Industrial toxins: N-hexane, organophosphates, toluene. Heavy metals: Arsenic, lead, mercury, thallium.

Systemic Si/Sx associated w/ specific toxic neuropathies: Arsenic: Mees lines, abdominal pain, n/v, liver failure, anemia, dermatitis, cardiomyopathy. Colchicine: Myopathy. Lead: GI sx, muscle pain, Mees lines, anemia,

basophilic stippling of RBCs. Lithium: Tremor. Phenytoin: Gingival hyperplasia, coarsening of facial features, ataxia, osteoporosis. Thallium: Alopecia, GI sx, encephalopathy, Mees lines, cardiac, renal, & respiratory failure. Organophosphates: Bradycardia, salivation, nausea, bronchospasm, miosis, diarrhea, sweating, CNS dysfunction, weakness, & fasciculations (Neurol Clin 2007;25:257-276).

POLYNEUROPATHY ASSOCIATED WITH SYSTEM DISEASE

Diabetic neuropathy: Leading cause of peripheral polyneuropathy in developed countries. Types of neuropathy caused by DM: Distal symmetric polyneuropathy (most common), small fiber polyneuropathy, autonomic neuropathy, proximal neuropathy or lumbosacral radiculoplexopathy or diabetic amyotrophy, truncal neuropathy, limb mononeuropathy, multiple mononeuropathies, cranial mononeuropathies. Also increased risk for entrapment neuropathies, such as carpal tunnel syndrome. Dx: Clinical history & exam; known or new dx of DM; EMG/ NCS. Rx: Optimal glucose control; proper skin care. For orthostatic hypotension: Sleep w/ head of bed elevated, increase salt & fluid intake, elastic body stockings. Consider fludrocortisone 0.1-0.6 mg daily. For gastric emptying difficulties: metoclopramide. Diabetic diarrhea may be treated w/ anti-diarrhea agents for sx relief or short courses of tetracycline or erythromycin. GU complications: Urology evaluation. Frequent voiding schedule during the day (N Engl J Med 1993;328:1676; N Engl J Med 1995;333:89; Muscle Nerve 2001;24:1225).

Uremic neuropathy: Occurs in 60% of chronic hemodialysis patients. Often chronic progressive, primarily sensory neuropathy, although may cause a motor neuropathy. Rx: Avoid neurotoxic medications. Improvement in neuropathy w/ renal transplantation.

Neuropathy in liver disease: May occur due to chronic liver disease or as a result of underlying condition (i.e., cryoglobulinemia, viral infections leading to AIDP & CIDP, malabsorption syndromes in cholestatic liver disease).

Hypothyroid neuropathy: Carpal tunnel syndrome or sensory > motor peripheral neuropathy may occur. Dx w/ thyroid function studies & Rx w/ thyroid replacement.

Neuropathy associated w/ malignancy: Neuropathy may occur w/ malignancy secondary to compression or infiltration of nerves, toxic neuropathies as a side effect of chemotherapy, or paraneoplastic neuropathies (see below).

Polyneuropathies Associated w/ Paraneoplastic Syndromes

Antibody	Malignancy	Symptoms
ANNA-1/anti-Hu	Small cell lung cancer	Malignant inflammatory sensory peripheral neuropathy, gastrointestinal dysmotility, autonomic neuropathy, limbic encephalitis
ANNA-2/anti-Ri	Breast, small cell lung cancer	Opsoclonus/myoclonus, jaw dystonia, ataxia, sensorimotor neuropathy
ANNA-3	Small cell or lung adenocarcinoma	Sensory neuropathy, sensorimotor neuropathy, ataxia, encephalomyelitis
CRMP-5	Thymoma, small cell lung cancer	Dementia, sensorimotor neuropathy, vision loss, chorea
Anti-Yo/PCA-1	Ovarian, breast	Cerebellar ataxia, sensorimotor neuropathy
Amphiphysin ab	Small cell lung, breast cancer	Stiff person syndrome, sensory neuropathy
P/Q type Ca channel ab	Small cell lung cancer	Lambert-Eaton myasthenic syndrome
Voltage-gated K channel ab	Thymoma, lung cancer	Peripheral nerve hyperexcitability (Isaac syndrome)

POLYNEUROPATHY ASSOCIATED WITH PARAPROTEINEMIA

Monoclonal gammopathy of undetermined significance (MGUS): Onset typically in 6th decade, subacute-chronic course. Male predominance. Most commonly a distal symmetrical sensorimotor polyneuropathy. May mimic CIDP. Sensory loss w/ variable involvement of light touch, pinprick, vibration & proprioception. 20% patients have a predominantly sensory neuropathy w/ gait ataxia & upper limb postural tremor (usually IgM cases w/ demyelination). Lower limbs involved earlier than the upper. Diminished

reflexes. Dx: (1) Labs: Immunoelectrophoresis or immunofixation, urine studies to evaluate for light chains/Bence Jones proteins, CBC, quantitative immunoglobulins, skeletal bone survey. (2) If monoclonal spike > 1.5 g/dL, should obtain bone marrow aspirate or biopsy. (3) EMG/NCS: Demyelinating or axonal features. (4) CSF protein may be elevated in demyelinating forms or w/ amyloidosis. (5) Sural nerve biopsy: Nerve fiber loss, segmental demyelination, & axonal degeneration. Congo red stain to look for amyloid deposition. (6) May have + antibodies to MAG, disialosylganglioside IgM. Rx: Optimal Rx not established. If minor sx then no Rx. If similar features to CIDP, may respond to immunomodulatory therapies. For MAG + neuropathy, consider rituximab but most patients do not respond well.

Multiple myeloma: Most common neurological sx: Cord & root compression from lytic lesions. Also causes mild distal sensorimotor polyneuropathy. Less commonly a pure sensory neuropathy. AL (amyloid light chain) amyloidosis may complicate neuropathy in 30%-40% cases. Painful dysesthesias, small fiber sensory sx, autonomic dysfunction, carpal tunnel syndrome. Dx: Sural nerve, rectal, or abdominal fat biopsy to dx amyloidosis. NCS/EMG: Axonal process w/ loss of myelinated fibers.

Osteosclerotic myeloma or POEMS: POEMS: Polyneuropathy, organomegaly, endocrinopathy, M protein, & skin changes. Motor > sensory neuropathy w/ symmetric weakness & variable sensory loss. Hepatosplenomegaly, gynecomastia & impotence in men, secondary amenorrhea in women, DM, hypothyroidism, hyperpigmentation, hypertrichosis, diffuse skin thickening, hemangiomas, white nail beds, pitting edema, ascites, pleural effusions, & clubbing. Dx: EMG/NCS w/ demyelinating features & axonal loss. CSF w/ elevated protein (> 100 mg/dL). M protein in 90% cases. Biopsy of plasmacytoma. Rx: Irradiation &/or surgical excision for solitary lesions. Prednisone ± melphalan or high dose chemo & stem cell transplant for multifocal lesions.

Waldenstrom macroglobulinemia: Proliferation of malignant lymphocytoid cells in bone marrow, lymph nodes that secrete an IgM monoclonal spike of more than 3 g/dL. Fatigue, anemia, bleeding, hyperviscosity. Typically chronic symmetric, predominantly sensory polyneuropathy associated w/ IgM M protein. May also p/w pure sensory or pure motor neuropathies, multiple mononeuropathies associated w/ cryoglobulins & typical amyloid neuropathy.

Dx: (1) Immunoelectrophoresis or immunofixation, urine studies for evaluation of light chains/Bence Jones proteins, CBC. If positive M protein, should obtain quantitative immunoglobulins, skeletal bone survey. If monoclonal spike > 1.5 g/dL, should obtain bone marrow aspirate or biopsy.

Anti-MAG + in 50% patients. (2) EMG/NCS: Usually axonal but may have demyelinating features. Rx: Chemotherapy (N Engl J Med 1998;338:1601).

POLYNEUROPATHIES IN CONNECTIVE TISSUE DISORDERS

Vasculitis: May manifest as mononeuritis multiplex or subacute distal sensorimotor polyneuropathy. Systemic sx: Fever, malaise, weight loss, HTN. Dx: ESR, CBC w/ diff, chem7, UA, LFTs, RF, ANA, C3, C4, ANCA, cryoglobulins, anti-Ro & La, Hepatitis B, C Ag & Ab. EMG/NCS revealing axonal damage. Sural nerve biopsy. Rx: Prednisone + cytoxan followed by methotrexate.

RA: May cause compression neuropathy, distal sensory polyneuropathy, mononeuritis multiplex, or sensorimotor polyneuropathy. Dx: Labs as above. Sural nerve or muscle biopsy may show necrotizing vasculitis. Rx: As above if vasculitic.

SLE: May cause symmetric, subacute, or chronic axonal polyneuropathy w/ predominantly sensory sx, mononeuritis multiplex, brachial plexopathy, GBS or CIDP presentation. Dx: Labs as above. Sural nerve biopsy w/ perivascular inflammatory infiltrate around epineurial vessels, occasionally vasculitis. Rx: As above if vasculitic.

Systemic sclerosis: May cause myopathy, peripheral sensorimotor neuropathy, mononeuritis multiplex. Dx: Labs as above. In CREST pts, nerve biopsy w/ vasculitis, perivascular inflammation. Rx: As above if vasculitic.

Sjogren syndrome: May cause distal symmetrical sensory neuropathy w/ mixed large & small fiber deficits. Less commonly causes a sensorimotor neuropathy, polyradiculoneuropathy, multiple mononeuropathies, painful dorsal root ganglionopathy, & trigeminal sensory neuropathy. Dx: Labs as above. Schirmer test, salivary gland biopsy. EMG/NCS w/ axonal features. MRI C-spine: T2 bright in the posterior columns. Sural nerve biopsy: Usually shows axonal loss; may see perivascular infiltrates or vasculitis. Rx: Most pts do not respond to Rx but can try immunosuppression w/ corticosteroids alone or in combination w/ other immunosuppressive agents, IVIg.

Sarcoid: May cause cranial neuropathies, multiple mononeuropathies, bilateral phrenic nerve palsies, truncal sensory mononeuropathies, acute polyradiculoneuropathy resembling GBS, cauda equina syndrome, chronic symmetrical sensorimotor neuropathy. Dx: EMG/NCS w/ axonal degeneration. CSF w/ pleocytosis, high protein, & IgG index. May have elevated serum ACE. May require biopsy of lymph nodes, muscles, conjunctiva, or BAL for dx. On sural nerve biopsy, may see sarcoid granulomas, evidence of angiitis. Rx: Corticosteroids w/ or w/o other immunomodulating or immunosuppressive agents.

NEUROPATHIES SECONDARY TO NUTRITIONAL DEFICIENCIES

B_{12} deficiency: Subacute combined degeneration: Caused by pernicious anemia w/ intrinsic factor deficiency, gastric or ileal resection w/ malabsorption, strict vegetarian diet, tapeworms, nitrous oxide use. Causes macrocytic anemia, atrophic glossitis. Peripheral neuropathy: Paresthesias & loss of vibration & proprioception. Spinal cord: Posterior & lateral column damage w/ sensory level, UMN deficits. Cerebral involvement: Behavioral changes, forgetfulness, dementia, stupor. Dx: EMG/NCS w/ axonopathy. Sural nerve biopsy reveals axonal degeneration. Serum B_{12} < 170 pg/mL; folate normal. Elevated homocysteine & methylmalonic acid. May have Ab to intrinsic factor. Rx: Cyanocobalamin 1,000 µg IM daily × 5-7 days, followed by q wk injections × 12 doses & then maintenance injections of 1,000 µg q1-3mo.

Copper deficiency: Causes a myelopathy & clinical presentation similar to subacute combined degeneration. Dysfunction of dorsal columns resulting in loss of vibratory sensation & proprioception, sensory ataxia, + Romberg. May have spasticity of LE, increased patellar reflexes & upgoing toes, sensory level, UMN deficits. Dx: Low serum copper level, ceruloplasmin, urinary copper. Serum & urinary zinc may be elevated or normal. Check B_{12} & methylmalonic acid to evaluate for B_{12} deficiency. Rx: Oral supplementation: Copper sulfate 1.5-3 mg daily. IV copper. Supplementation improves serum levels however clinical response is variable (Neurology 2004;63:33).

Niacin (B_3) deficiency: Pellagra: Dermatitis, diarrhea, dementia. Distal sensorimotor polyneuropathy in 40%-65% patients. May be indistinguishable from thiamine deficiency clinically. Dx: Niacin levels. Rx: Oral nicotinic acid.

Pyridoxine (B_6) deficiency: May occur w/ use of isoniazid, hydralazine, penicillamine. Si/sx Distal sensory & motor deficits w/ insidious onset. Pyridoxine toxicity may cause sensory polyneuropathy. Dx: Pyridoxine levels. Rx: Pyridoxine 100 mg daily.

Folate deficiency: Axonal sensory polyneuropathy w/ diminished joint position, vibratory sensation, & diminished reflexes. May affect spinal cord & cause encephalopathy. Exclude B_{12} deficiency because folate therapy w/o cobalamin may exacerbate neurological sx. Dx: Folic acid levels. Rx: Folic acid supplementation.

Vitamin E deficiency: Occurs w/ chronic malabsorption. Si/sx:

Spinocerebellar syndrome w/ loss of vibratory sensation & proprioception, ataxia, areflexia, ophthalmoplegia, pigmentary retinopathy. Dx: EMG/NCS w/ low amplitude or absent SNAPs, 72 h fecal fat study, Vitamin A & D levels, amylase, LFTs, blood smear to look for acanthocytes. Rx: Vitamin E supplementation.

NEUROPATHIES ASSOCIATED WITH INFECTIOUS DISEASE

(See chapter “Neurologic Infectious Diseases”)

Peripheral neuropathies associated w/ HIV: Multiple neuropathies associated w/ HIV. Distal symmetric polyneuropathy: EMG/NCS w/ borderline to low amplitude sensory & motor responses. Sural nerve biopsy w/ loss of myelinated & unmyelinated fibers.

Lumbosacral polyradiculoneuropathy: (1) CMV polyradiculoneuropathy: Uncommon but devastating. Presents w/ rapidly progressive, flaccid paraparesis, sphincter dysfunction, perineal sensory loss, & lower limb areflexia. EMG/NCS: Low amplitude CMAPs, prolonged or absent F wave latencies, reduced or absent SNAPs. EMG w/ active denervation after several weeks. LP: Pleocytosis (> 50/μL) w/ > 40% polys, elevated protein, decreased glucose. Rx: Empiric IV ganciclovir in HIV pts w/ CSF pleocytosis & rapidly progressive sx. (2) Other causes of lumbosacral polyradiculoneuropathy in HIV: Syphilis, mycobacterial infections, toxoplasmosis, leptomeningeal carcinomatosis secondary to lymphoma, herpes zoster radiculitis.

Mononeuritis multiplex: More common late in the course of HIV or w/ CD4 count < 200/μL. May be secondary to HSV, CMV, hepatitis C, syphilis, lymphoma, necrotizing vasculitis. Workup: Test for CMV & if negative, nerve biopsy to evaluate for vasculitis.

AIDP: Presents during seroconversion & early stages of disease. Clinically indistinguishable from GBS. CSF protein elevated (> 100 mg/dL). Demyelination & inflammation of nerve roots. Rx: Plasmapheresis or IVIg. CIDP: Clinically similar to CIDP not associated w/ HIV. CSF pleocytosis. Rx: Plasmapheresis or IVIg. Cranial neuropathies: May occur early in HIV, particularly facial nerve. Sensory neuropathy.

CMV: AIDP, meningoencephalitis, lumbosacral polyradiculoneuropathy in HIV.

EBV: Rhombencephalitis, mononeuritis multiplex, myelitis, brachial & lumbosacral plexopathy.

HSV: HSV-1: Infection of gasserian ganglion most common. HSV-2: Infection of sacral dorsal root ganglion cells more common. May present as segmental recurrence or disseminated disease. Rx: Acyclovir 200 mg 5 × /day

× 10 days or famciclovir 125 mg bid ×5 days to reduce duration of eruption.

VZV/Herpes zoster: Most common symptomatic peripheral nerve viral infection. Cranial zoster: Commonly affects trigeminal or geniculate ganglion. Radicular zoster: Also called segmental zoster, zoster radiculopathy or shingles. Polyradiculoneuropathy; 5% w/ motor involvement. Rx: Famciclovir 500 mg po tid × 7 days or acyclovir 800 mg 5× daily × 10 days.

Hepatitis: Hepatitis B: Associated w/ GBS, mononeuritis multiplex, necrotizing vasculitis. Hepatitis C: Associated w/ cryoglobulinemia, vasculitic neuropathy, mononeuritis multiplex.

HTLV-1: Typically affects spinal cord but may have peripheral nerve involvement as well.

West Nile virus: May p/w clinical picture similar to poliomyelitis (asymmetric flaccid limb & facial weakness w/ few sensory deficits) ± encephalitis.

Mycobacterium leprae (Hansen disease): Mycobacterium leprae transmitted through respiratory tract. EMG/NCS: Reduced amplitudes of CMAPs & SNAPs w/ focal conduction slowing. Skin or nerve biopsy: Intense granulomatous inflammation in tuberculoid disease; multiple acid-fast organisms, demyelination, & nerve fiber loss in lepromatous disease. Classified into tuberculoid & lepromatous forms based on host

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reaction to infection. Tuberculoid: Active cell-mediated immunity w/ local destruction of infected nerves & rare organisms detected. Causes well-demarcated, hypopigmented lesions w/ sensory loss. Palpable nerves secondary to intense inflammation. Rx: Dapsone 100 mg daily + rifampin 600 mg daily for >6 mo, followed by dapsone monotherapy for 3-5 yr. Lepromatous: Minimal inflammatory response, disseminated skin, & nerve lesions. Predilection for cool areas: Ears, nose, dorsal hands, forearms, feet. Skin w/ multiple nodules, papules, ulcerations, waxy appearance. Preserved tendon reflexes. Rx: Dapsone 100 mg daily + rifampin 600 mg daily + clofazimine 50 mg qd for minimum of 2 yr or until skin smear neg.

Diphtheria: Rare illness caused by Corynebacterium diphtheriae. Neurological complications in 15% & pts present w/ paralysis of palate, numbness of pharynx, impaired pupillary accommodation, diaphragmatic weakness, limb neuropathy. May progress after 3-15 wk to generalized mixed sensorimotor polyneuropathy or sensory polyneuropathy w/ ataxia. Dx: LP w/ normal or elevated protein (> 100 mg/dL). EMG/NCS w/ segmental demyelination w/ sparing of axons. Rx: Antitoxin w/in 48 h, respiratory support if necessary. Recovery over several weeks & usually complete if

antitoxin given w/in 48 h.

Lyme: Caused by Borrelia burgdorferi. Primary infection p/w erythema migrans. Secondary infection: Neurological sx in 15% & consist of cranial neuropathy, radiculoneuropathy, lymphocytic meningitis. Months-years after infection, late neurological syndrome w/ sensory polyradiculoneuropathy. Dx: LP w/ lymphocytic pleocytosis & mildly elevated protein. In polyradiculoneuropathy, EMG/NCS reveals widespread axonal process, sensory > motor involvement. Lyme serologies (ELISA & Western blot). Lyme PCR of CSF. Rx: If CSF normal: Oral doxycycline or ampicillin. If CSF abnormal: Ceftriaxone 2 g IV daily for 2-4 wk w/ improvement over 3-6 mo.

American trypanosomiasis (Chagas disease): Caused by protozoan Trypanosoma cruzi. Three phases: (1) Acute: Asymptomatic or general malaise, lymphadenopathy, GI sx. (2) Second phase: At 3 months-years. Asymptomatic & serologies for trypanosoma become +. (3) Third phase: Begins 10-20 yr after infection. GI, cardiac, & neurological sx. 10% develop predominantly sensory neuropathy. Dx: Trypanosomiasis serologies. EMG/NCS reveals low amplitude sensory & motor responses, reduced NCVs, distal neurogenic motor unit potential changes. Rx: Itraconazole & allopurinol for underlying disease; little data to support improvement in neuropathy.

Radiculopathy and Plexopathy

RADICULOPATHY

CERVICAL RADICULOPATHY

Definition: Caused by cervical spinal nerve compression or irritation, often secondary to arthritis, herniated disc, osteophyte formation, cervical spondylosis, space-occupying lesions such as tumors, abscesses, cysts.

Si/sx: Numbness & paresthesias in the fingers in a dermatomal distribution, lancinating pain radiating down the arm, weakness depending on the cervical roots involved.

Exam: Weakness and/or sensory loss in upper extremities depending on which nerves are affected (see chart below). Spurling maneuver (passive cervical extension w/ lateral flexion toward the affected side which reproduces symptoms), vertical traction. Be careful in performing maneuvers w/ spinal instability, traumatic cause, RA. Most common cervical radiculopathy C6-7. Pain in dorsal forearm, paresthesias/ numbness in third & fourth digits. Weakness w/ arm extension, finger & wrist flexors & extensors. Diminished triceps reflex.

Dx: MRI C-spine; EMG/ NCS: Most useful <3 wk after initial injury, since EMG/NCS may be normal in the first few days after injury.

- NCS: Sensory & motor NCS are typically normal, except in case of a severe radicular lesion causing Wallerian degeneration distal to the lesion where CMAP may be reduced. NCS are useful in radiculopathy primarily to exclude other dx, such as a peripheral neuropathy.
- EMG: In acute setting: Characterized by fibrillation potentials & positive sharp waves. In chronic setting: Characterized by abnormal motor units, such as long duration or polyphasic motor units. Should test two muscles supplied by the same root but different peripheral nerves, & one paraspinal muscle.

Rx: Urgent surgical evaluation for patients w/ evidence of cervical spine instability or myelopathy. Otherwise, conservative Rx initially for 3-6 wk. Ice or heating pad, muscle relaxants, NSAIDs, gentle massage, stretching, PT. May consider cervical epidural steroid injections. Surgery if conservative Rx

fails.

LUMBOSACRAL RADICULOPATHY

Definition: Caused by nerve root compression, most often of L4, L5, & S1. May be secondary to disc herniation, space-occupying lesions such as tumors, abscesses, cysts, foraminal or spinal stenosis, ligamentous hypertrophy.

Si/sx: Brief, lancinating pain, often worse w/ standing, weakness, numbness.

Exam

- L3-L4: Back pain. Numbness & pain in the medial thigh/ calf in the L3-4 dermatomal distributions. Weakness of knee extension & hip flexion. Decreased patellar reflex.
- L5: Pain radiating to the posterior thigh, calf, foot, hallux. Numbness in L5 dermatomal distribution. Foot drop, hallux extension weakness. Typically reflexes intact.
- S1: Pain in the buttock, posterior thigh, calf, heel. S1 dermatome numbness.

Dx: Straight leg raise: Good sensitivity for herniated disc but poor specificity; rectal exam to evaluate sphincter tone, particularly if concerned for cauda equina syndrome. EMG/NCS. MRI L-spine w/ gadolinium.

EMG/NCS

- Useful if dx is unclear, since it can help exclude other causes of sensory or motor weakness such as peripheral neuropathy.
- See above under cervical radiculopathy for expected EMG/NCS changes w/ radiculopathy
- H-reflex: Assesses afferent & efferent S1 fibers (similar to the ankle reflex). Useful in distinguishing a S1 from a L5 radiculopathy.

Rx: Urgent surgical evaluation if rapidly progressive motor deficits or if evidence of cauda equina syndrome w/ loss of bowel/bladder function. Otherwise, conservative Rx initially. Ice or heating pad, muscle relaxants, NSAIDs, gentle massage, stretching, PT, TENS (transcutaneous electrical nerve stimulation). May consider epidural steroid injections. Surgery if conservative Rx fails.

Common Radiculopathies

Root	Sensory loss	Weakness	Reflexes	Disc
C5	Shoulder, lateral proximal arm	Shoulder abduction, external rotators of arm, elbow flexion	Biceps, brachoradialis	C4-5
C6	First & second digits, lateral forearm, & arm	Elbow flexion, arm pronation, finger & wrist extension	Biceps, brachoradialis	C5-6
C7	Third & fourth digits	Elbow extension, finger/ wrist flexors & extensors	Triceps	C6-7
C8	Medial forearm & hand, fifth digit	Intrinsic hand muscles	Finger flexor	C7-T1
L4	Knee, medial leg	Hip flexion, knee extension, dorsiflexion, foot inversion	Patellar	L3-4
L5	Lateral leg, dorsum of foot, large toe	Foot dorsiflexion, eversion, & inversion	None	L4-5
S1	Lateral foot, sole of foot, small toe	Foot plantar flexion	Achilles	L5-S1

PLEXOPATHY

BRACHIAL PLEXOPATHY

Definition: Injury/irritation of the brachial plexus most often secondary to trauma, such as stretch injuries, lacerations, birth trauma, fracture-dislocations, orthopedic surgery. May also be caused by radiation, infections, & malignancy.

Dx: MRI C-spine & brachial plexus. Plain films if h/o trauma to r/o bony

fracture or dislocation. EMG/NCS.

Neuralgic amyotrophy or Parsonage-Turner syndrome

Si/sx: Acute, severe shoulder pain radiating to the arm, neck, & back; weakness & atrophy of the shoulder girdle/ scapular muscles. Phrenic nerve weakness may occur. Arm held in flexion at the elbow & adduction at the shoulder.

Cause: Idiopathic but may be secondary to autoimmune process, virus, trauma, strenuous exercise, immunization, & childbirth.

Rx: Conservative management, PT. Can consider trial of steroids or IVIg.

Erb-Duchenne palsy or upper trunk plexopathy

Si/sx: Weakness, atrophy of the deltoid, biceps, brachoradialis, & brachialis muscles. Arm is internally rotated & adducted ("waiter's tip" position). Sensory typically intact but there may be sensory loss over the outer surface of the upper arm. Diminished biceps or brachoradialis muscles.

Cause: Lesions of the fifth & sixth cervical roots or the upper trunk of the plexus. Often caused by trauma separating the head & shoulders or pressure on the shoulders, birth injury.

Rx: Conservative management, PT.

Dejerine-Klumpke palsy or lower trunk plexopathy

Si/sx: Claw hand, weakness wrist & finger flexion, & intrinsic hand muscles. Sensation may be intact or lost on the medial forearm & ulnar aspect of hand, diminished finger flexors. Ipsilateral Horner syndrome may be present.

Cause: Lesions of the eighth cervical & first thoracic roots. Usually secondary to trauma, such as arm traction, & associated w/ lung tumors (Pancoast tumor) or other mass lesions.

Rx: Conservative management, PT.

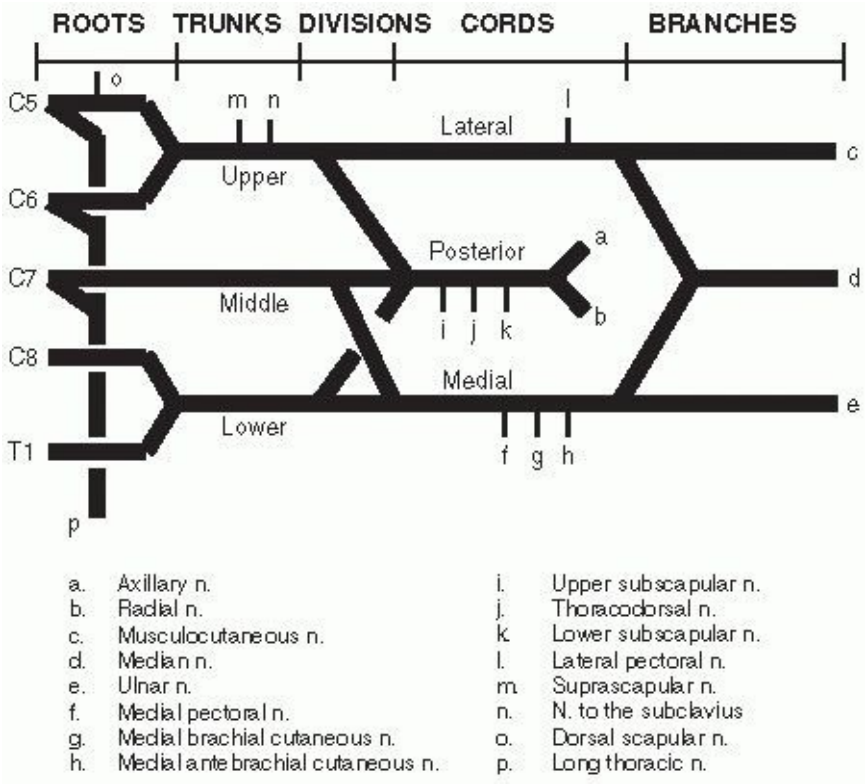
Thoracic outlet syndrome

Si/sx: Recurrent coldness, cyanosis, pallor of hand. Bruit in the supra or infraclavicular areas. Lower trunk or medial cord is involved. Pain in the ulnar border of the hand & medial forearm. Paresthesias/numbness may occur in the same distribution. Motor & reflex exam may be similar to a lower plexus lesion, although T1 may be spared.

Cause: Compression of the brachial plexus of the subclavian vessels in the space between the first rib & clavicle. May be due to cervical rib, enlarged

transverse process, & hypertrophied scalene muscle.

Rx: Conservative management or surgery in refractory cases.



LUMBOSACRAL PLEXOPATHY (BRUNS-GARLAND SYNDROME)

Si/sx: Hip pain, weakness of iliopsoas, quadriceps, & thigh adductor muscles. Occurs in patients w/ diabetes, idiopathic, & in connective tissue diseases.

Exam: Weakness, sensory loss, & loss of knee reflex.

Dx: EMG/ NCS.

Neuromuscular Junction Disorders

Neuromuscular junction (NMJ): Composed of presynaptic, synaptic, & post-synaptic regions. Dzs affect one of these three → failure of transmission across NMJ. Waxingwaning course common in NMJ dz.

DIFFERENTIAL DIAGNOSIS OF NMJ DYSFUNCTION

Presynaptic: Lambert-Eaton myasthenic syndrome, congenital myasthenic syndromes (CMS), botulism, tick paralysis, some drugs, & venoms.

Synaptic: CMS of end-plate AChE deficiency, cholinesterase inhibiting drugs, organophosphates.

Postsynaptic: MG, transient neonatal MG, CMS, drugs/venoms.

MYASTHENIA GRAVIS

Epid: Prevalence ˜1/5,000 to 1/50,000. Annual incidence ˜1/50,000-1/200,000. For age <50 yo, F > M incidence; for age >50 yo, M > F incidence.

Pathophys: Autoimmune (AI) d/o of synaptic transmission. Abs interfere w/ fxn, placement, or survival of nicotinic AChRs. Muscarinic receptors not affected → pupillary/autonomic responses spared. Cases of occurrence after injury/surgery suggests antigenic exposure important.

Presentation: Patient history: Variable or fatiguable weakness, 20% p/w pharyngeal weakness, fatigability or hoarse voice, diplopia (in subtle cases, pts may report blurred vision), orthopnea 2/2 diaphragmatic weakness. Neurologic exam: Ptosis (usu asymmetric & fatigues w/ upgaze), hypercontracted frontalis to maintain eye opening, fatigability, ophthalmoparesis, bulbar weakness, nl pupillary reflexes, prox limb weakness, tachypnea & shallow respirations, intact sensation, variably depressed reflexes.

Subtypes: (I) Anti-MuSK: Young F w/ orofacial weakness & early resp weakness. (2) Ocular: Sx limited to ocular weakness for >2 yr → 90% do not generalize; electrodiagnostic challenge; mono-Rx w/ AChEIs usu sufficient. (3) Antibody negative: Classic presentation, neg ab tests (MuSK Ab discovery ↓‘d no. in this subgroup), 70% poor response to AChEIs.

Ddx: MND, Lambert-Eaton myasthenic syndrome (LEMS), GBS, diphtheria, tic paralysis, thyroid ophthalmopathy, mitochondrial d/os, CMS, botulism, organophosphate & other toxins, inflammatory myopathy, skull-based tumors,

cholinergic crisis.

Dx: (1) Tensilon test (edrophonium, an AchEI) IV test dose 2 mg, then 3-8 mg at a time up to 10 mg; observe 90 s b/n each dose & 3-5 min after last dose. Follow clinically observable deficit & only accept unequivocal improvement as (+). Onset 30 s, lasts 5-10 min. Side effects: Salivation, sweating, nausea, cramping, fasciculations, & bradycardia, ↓ BP, resp distress. AMBU bag at bedside, telemetry. Utility: Se 70%-95%, Sp unknown. (2) Ice test: Put ice pack on closed eye ×3 min-ptosis improves (Se 80%-90%). (3) EMG/NCS: Repetitive Nerve Stimulation: Low rates of rep stim (2-5 Hz) deplete ACh, → decrement > 10% (Se 50%-100% for general MG & 10%-20% for ocular MG). SFEMG: increased jitter or variation in contraction time b/n muscle fibers (Se 80%-99%). (4) Ab testing: (4a) AChR antibodies: Binding Ab: Se 80%-85% in generalized MG; Se 55% in ocular MG; Blocking aAb: + in isolation in ˜1% of MG; Modulating ab: + in 3%-4% MG in isolation, ↑ freq w/ thymoma. (4b) Anti-MuSK (anti-muscle-specific tyrosine kinase abs). Prominent orofacial & resp sx at onset; rarely isolated ocular sx. Classic pt 20-30 yo F w/o thymoma. (4c) Striated muscle ab: Se ˜75% for MG w/ thymoma; can be present in older MG pts; utility limited by poor Sp.

Prognosis: Early in course, exacerbations are often severe, but w/ Rx remissions lasting many months are common. Max dz severity reached in 2 yr in 66% pts. Spontaneous & durable remission in 10%-15%. On avg, active dz lasts 7 yr followed by 10 yr of relative quiescence, then finally “burned out” phase characterized by some degree of fixed deficit.

TREATMENT OF ACUTE EXACERBATIONS/CRISIS

Causes: Dz progression, stressor/illness, withdrawal/↓ in MG Rx, contraindicated medication.

Cholinergic crisis (salivation, lacrimation, diarrhea, bradycardia): If pt in crisis, ↓/ hold AChE meds.

Medications exacerbating MG: (1) Absolutely contraindicated: Curare, penicillamine, botox, IFN-α. (2) Relatively contraindicated: Antibiotics: FQs (ciprofl oxacin, levofl oxacin, etc.), macrolides (erythromycin, azithromycin, etc.), aminoglycosides (gentamicin, tobramycin, etc.), quinine; Class IA antiarrhythmics (procainamide, quinidine, lidocaine, etc.); Magnesium. (3) Use w/ caution: Ca-channel- & β-blockers, Li, statins, steroids.

Supportive care: Aspiration precautions, temporary NPO or NG tube feeding, close resp monitoring w/ NIF & VC, ventilatory support if necessary.

Short-term immunotherapy: IVIG 2 g/kg over 2C5 days. Potential side effects: Aseptic meningitis, ARF, CHF exacerbation, allergic Rxn (test IgA levels prior: r/o IgA defi ciency), headache common with infusion.

Plasma exchange (PE) requires large-bore catheter & performed qod. Potential side effects: Line infection, CHF exacerbation, hypothermia, electrolyte shifts, bleeding. Pyridostigmine: Initial adult dose 15C30 mg qid; goal 30C90 mg qid (max 360 mg daily). Max effect 30C45 min after doseCCpts w/ dysphagia can take 30 min before meal.

Steroids: Mainstay of Rx. Initial dosing can be safely started at 10 mg/day & titrated to goal dose. May worsen exacerbation acutely; ˜8% → intubation; thus should consider hospitalization when initiating steroids during an exacerbation for monitoring. Onset of action ˜2C8 wk after initiation of high doses.

CHRONIC TREATMENT

Nonimmune modulatory: Pyridostigmine. Dosing adjusted PRN.

Immune modulatory: Steroids, steroid sparing agents, & thymectomy.

- Steroids: Max 1C1.5 mg/kg/days × 1C3 mo. Once in remission, ↓ dose and/or dosing. Chronically dose should be minimized. Side effects: Cataracts, osteoporosis, immune suppression, ↑ wt, mood d/o, psychosis, skin sensitivity to sun, glucose intolerance/DM, peptic ulcers, avascular necrosis, steroid myopathy, growth stunting in kids.
- Thymectomy: Indicated if thymoma on CT chest (˜15% cases). Often done in absence of thymoma if generalized, AChR ab+, & onset <50 yo (but no RCTs to support this).
- Steroid sparing immune therapies.

Steroid Sparing Immune Therapies

Medication	Mechanism	Efficacy/use	Dosing	eff
Azathioprine (Imuran)	Purine antimetabolite—inhibits T-& B-cell proliferation	Effective in >70% Onset takes 6C12 moUse w/steroids or to ↓ steroid dose	Initiate 50 mg/day po; ↑ weekly by 50 mg/day to 2C3	rel tox leu Idi rxı

			mg/kg/day	f/n
Cyclosporine	Calcineurin Inhibitor—↓'s T-cell & IL-2 production	Used if intolerant/r unresponsive to AZA Onset of action 1C2 mo after start	4C6 mg/kg/d po divided bid	hir tre hy HT fai
Cyclophosphamide (cytoxan)	Alkylating agent	Useful for severe, generalized, poorly responsive MG	Monthly IV pulses of 500 mg/m^2	CA ma cy
Mycophenolate mofetil (Cellcept)	Purine synthesis inhibitor	Small RCTs failed to show efficacy, but sometimes used	1,000 mg po bid	tol
Tacrolimus (FK-506)	Calcineurin inhibitor	Less evidence; early reports encouraging	3C5 mg/day	hy PR

LAMBERT-EATON MYASTHENIC SYNDROME

Epidemiology: Second most common NMJ d/o. autoimmune (AI), presynaptic d/o; 2/3 are paraneoplastic (small cell carcinoma ˜90% paraneoplastic cases; sx precede tumor by ˜10 mo avg). Nonparaneoplastic: often young F w/ other AI dz. ˜85% LEMS cases >40 yo.

Pathophysiology: Abs to P/Q-type (or less commonly N-type) voltage-gated Ca channel on presynaptic membrane → low Ca entry & fewer vesicles released into synapse.

Si/sx: (1) Fatigable weakness (like MG); fatigue often >> weakness. (2) LE followed by UE weakness (UE wknss + in 80% at some point in dz).(3) Muscle aching/stiffness after exercise; (4) Heat →↑ weakness. (5) Ocular sx, dysarthria, dysphagia (less common than in MG). (6) Autonomic sx: Xerostomia, xerophthalmia, blurred vision, constipation, urinary hesitancy.

Exam: Sluggish pupillary rxn. Ptosis may improve w/ upgaze. Weakness worst on initiation of movement, then potentiates, but may fatigue with prolonged sustained effort. DTRs: ↓ initially but ↑ following brief sustained effort.

Dx: (1) Serum: Abs for P/Q-type voltage-gated Ca channels in 85%-90% overall. Abs for N-type Ca channel + in 74% of paraneoplastic & 40% of nonparaneoplastic patients. AChR ab + in 13%. (2) Electrodiagnostics: H-reflex may be absent on initial test & appear w/ repeated testing. CMAP: Uniformly reduced (key feature distinguishing from postsynaptic); incremental response w/ 10-15 s exercise or fast rep stim; ± decremental response w/ slow rep stim or in end-stage dz. EMG: Low amplitude, short motor units that may increase w/ sustained effort. SFEMG: Jitter ± blocking in all muscles (not patchy like MG).

Rx: (1) Resection of tumor: Can be curative; if no known tumor → close surveillance. (2) Symptomatic Rx: (2a) AChEI (see MG Rx for details). (2b) Guanidine: Prolongs AP in nerve terminal, ↑'s ACh released, but side effects limit use—myelosuppression, renal & hepatotoxicity, GI discomfort. (2c) 4-DAP: Use limited by CNS toxicity → szs. (2d) 3,4 DAP: Not FDA approved, but can be obtained by calling Jacobus Pharmaceuticals. (3) Plasmapheresis: ↓'s sx w/ transient effect peaking at 2 wk. (4) IVIg: Studied only in small studies suggesting transient effect. (5) Immune modulating therapy (see MG).

CONGENITAL MYASTHENIC SYNDROMES

Epidemiology: Rare group of syndromes 2/2 genetic defects in NMJ structure and fxn. Typically in neonates/children, but can occur in adolescents/young adults. Transient neonatal myasthenia gravis is not CMS (is ab-mediated MG from transfer of mother's abs during pregnancy).

Pathophysiology: Genetic defects →↓ ACh release (presynaptic),↓ AChE (synaptic), or ↓ AChR activity (postsynaptic). All →↓ synaptic transmission or ↓ reserve. NOT ab-mediated.

Clinical features: Neonates-children: Reduced fetal movements, hypotonia, underdeveloped muscles, resp crisis, pupillary involvement in congenital AChE deficiency, progressive myopathy & no response to AChEIs in AChE def & slow channel congenital myasthenic syndrome (SCCMS). Neonates may have high arched palate, facial dysmorphism, arthrogryposis, scoliosis. Adolescents-adults: Difficult to clinically distinguish from AI MG. Myopathy sometimes present. SCCMS: Shows AD inheritance.

Ddx: Infants-young adults w/ MG, seroneg MG, myopathy, peripheral neuropathy, MND.

Dx: Ab testing always neg in CMS; genetic testing is not widely available, but may be done in certain academic labs.

Rx: Symptomatic Rx depends on the entity (see table). Some respond to AChEIs. No role for immunotherapy; genetic counseling advisable.

Syndrome	Pathophy	Notes
	Presynaptic	
Choline acetyltransferase deficiency (ChAT def)	Rate limiting enzyme in ACh production from acetyl-CoA & choline Due to *CHAT* gene mutation	• Resembles LEMS clinically; AR inheritance • In severe cases in infants, crises of weakness, ptosis, dysphagia, & hypoventilation • FH of "sudden infant death" • CMAP: marked, prolonged decremental response to rep stim during a crisis • Partial response to AChEIs • Sx lessen in teens, adults have mild sx
Paucity of synaptic vesicles	Unknown	• Infants: hypotonia & poor feeding • Children: Fatigable ptosis, limb/bulbar weakness • CMAP decrement w/ slow rep stim • Intercostal muscle bx w/ 80% ↓ in synaptic vesicles

Congenital Lambert-Eaton-like syndrome	Unknown	• Infants w/ LEMS-like sx but Ca channel abs neg • Infants may require chronic ventilator • Low amplitude CMAP at baseline w/ decrement at slow rep stim & facilitation at fast rep stim
	Synaptic	
Endplate Acetyl Cholinesterase (AChE) Deficiency	Lack of AChE anchoring, increases AChR exposure to ACh endplate myopathy	• Second most common CMS (15% of CMS) • *COLQ* mutation, encoding AChE anchoring protein • Infants/young children w/ weakness, pupillary involvement, & myopathy • Decrement w/ slow repetitive stimulation • Lack of response to AChEIs
	Postsynaptic	
***Reduced AChR expression*: AChR subunit mutations**	AChR subunit mutations lower expression or clustering	• Most common cause of CMS; AR inheritance • Resembles seroneg MG; improves w/ AChEIs • ± hypotonia, arthrogryposis, feeding difficulties • CMAP decrement w/ fast > slow rep stim • β-subunit mutation:

		common, mild form; γ-subunit mutation: Escobar syndrome
Rapsyn mutations	Rapsyn anchors AChR to the membrane & interacts w/ MuSK	• Homozygotes present as neonates; may p/w arthrogryposis, arched palate, & fixed weakness • Mild cases subclinical until late childhood • ± mild ptosis/ophthalmoparesis • Improve w/AChEIs
DOK-7 "Downstream Kinase" mutations	Muscle cytoplasmic protein that interacts w/ MuSK for AChR aggregation	• Clinically identical to AChR deficiency • Onset < age 5;± reduced fetal movements, then static/ slowly progressive weakness • EMG/NCS identical to AChR deficiency • Response to AChEIs variable; ephedrine produces mild benefit
***AChR kinetic abnormality*: Slow-channel (SCCMS)**	SCCMS is a gain-of-function mutation increasing the time of channel opening	• AD inheritance w/ variable penetrance • Both fatigable & progressive weakness • Severe cases present in infancy, mild as adults • Neck & distal arm weakness predominates • Repetitive CMAPs w/ single stimulus & decrement of

		CMAP w/ fast > slow rep stim • Rx: quinidine & fluoxetine; w/o Rx weakness worsens. No response to AChEIs (may worsen)
Fast-channel (FCCMS)	FCCMS is a loss-of-function mutation decreasing time of channel opening	• Presents in infancy or childhood w/ ptosis, ophthalmoparesis, dysphagia, dysarthria, & exertional weakness; static/slowly progressive • Can resemble myopathies or AI MG • Decrement of CMAP w/ slow rep stim that corrects w/ exercise, fast rep stim, or AChEIs • Rx: AChEI & 3,4-DAP to stimulate ACh release

TOXINS THAT CAUSE NMJ DYSFUNCTION

Presynaptic: Botulinum toxin, corticosteroids, Mg, aminoglycosides, CCBs, aminopyridines, hemicholinium-3; venoms (Mamba, Australian Tiger snake, Panadinus scorpion, Conus marine snails, Multibanded Krait, Brazilian rattlesnake, Black/Brown Widow spiders), ticks.

Synaptic: AchEIs (e.g., edrophonium, pyridostigmine, neostigmine), organophosphates.

Postsynaptic: Curare & nondepolarizing agents, succinylcholine & depolarizing agents, tetracyclines, venoms (e.g., Banded Kraits, Siamese cobra, Conus marine snail).

BOTULISM

Overview: Rare, toxin-mediated illness 2/2 blockade of NMJ & cholinergic presynaptic neurons. Exotoxin produced by Clostridium botulinum; absorbed

via GI tract or wound & spread hematogenously; binds to the presynaptic nerve & internalized via endocytosis.

Si/Sx: Onset over hrs (days for wound botulism); n/v, ± diarrhea, dysphagia, diplopia, dysarthria, weakness of extremities, SOB, xerostomia, blurred vision, constipation. In infants: Variable sx (mild to sudden death); listless, ↓spontaneous mvmts, ↓ suck, hypotonia ("floppy baby"), ↓ DTRs. Drooling, CN weakness worrisome; 50% → ventilation. Weeks to recovery.

Exam: Ptosis, ↓ gag, dysphagia, dysarthria, facial diplegia, tongue weakness, ± nystagmus. ↓ DTRs, ↓ FVC. Autonomic: Ileus, urinary retention, ↓ pupillary response, ↓ BP, ↓ temp.

Dx: (1) EMG/NCS: ↓ CMAP amplitude; ↑'s incrementally to fast rep stim, ↓'s decrementally to slow rep stim (most prominent in proximal muscles). EMG variable depending on timing in course: ± pos sharps & fibs, ± MUAP's low amp/short duration, ± early recruitment & ↓'d interference pattern. (2) Culture: Se ˜50%-66% but results take time. (3) Toxin assay: Se ˜35%; can be done on gastric contents, stool, serum, wound aspirate, & suspected foods.

Rx: (1) Supportive: ↓ big ↓ in mortality. (2) Antitoxin: If administered w/in 24 h of sx onset. (3) Human botulinum IgG: ↓'s hospitalization duration & ventilation in infantile botulism; no role in adults. (4) GI lavage: Food borne & infantile botulism (controversial). (5) Wound debridement: For wound botulism. (6) If abx initiated, first give antitoxin to avoid sx worsening as bacteria lyse. (7) Food-borne illness: identify others exposed & test food.

TICK PARALYSIS

Epid: Children > adults (3:1). M > F. Peak incidence in spring & summer.

Pathophys: Varies by species; Ixodes holocyclus (Australia) ↓'s ACh release presynaptically. Other tics cause NMJ dysfunction or acute neuropathy.

Si/sx: Ascending wkness over hours-days; ophthalmoplegia, facial weakness, dysarthria, dysphagia, resp failure, sensory sx (pain, numbness, paresthesias, sensory ataxia); ↓ DTRs.

Ddx: MG, GBS, diphtheria, botulism.

Dx: Serology & CSF nl. EMG/NCS: ± slowed sensory nerve conduction. CMAP & motor velocities mildly ↓'s in paretic limbs. Pseudofacilitation on rep stim. EMG: Abnl recruitment.

Rx: Remove tick; supportive Rx for resp weakness; prognosis favorable if pt supported.

Myopathy

Intro: Can be inherited/congenital or acquired. Broad categories include: Inflammatory myopathies [dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM)], & Myopathies due to other causes (i.e., endocrine abnlities, infections, medications).

Approach to muscle weakness: History & exam: Establish whether true weakness versus subjective "weakness" 2/2 other causes, e.g., pain, joint dysfn, disabling systemic condition.

Evaluate for respiratory weakness: Tachypnea, consider mechanical ventilation if FVC < 15 mL/kg, NIF < 20 or rapid decline, evaluate for ineffective cough. Note: A normal ABG & oxygen saturation in a patient w/ tachypnea are not helpful in determining the need for mechanical ventilation. Diagnostic testing: Muscle enzymes, EMG/NCS, & muscle biopsy.

INFLAMMATORY MYOPATHIES

DERMATOMYOSITIS AND POLYMYOSITIS

Epid: Prevalence 1/100,000; 2F: 1M. Peak age 40-50 yr.

Dx: Symmetric prox weakness; ↑ CK; EMG w/ myopathic Δs; characteristic bx findings.

	DM	**PM**	**IBM**
Skin	Gottron papules, shawl sign, heliotrope rash, generalized erythroderma, mechanic's hands	Mechanic's hands (fissured, rough skin on the hands, resembling that of a manual laborer)	None
Sex/age	F > M, kid & adult	F > M; adult (common < 50)	M > F, adult (>50)
Weakness	Proximal > distal	Proximal > distal	Proximal & distal, esp hands & proximal legs
Other	Myocarditis,	Myocarditis,	Neuropathy

manifestations	interstitial lung dz, malignancy, vasculitis, connective tissue dzs	interstitial lung dz, connective tissue dzs	
CK	↑(up to 50×)	NI or ↑ (up to 50×)	NI or mild ↑ (<10×)
Biopsy	Perimysial, perivascular inflammation	Endomysial inflammation	Inflammation, rimmed vacuoles, inclusions, amyloid deposits
Rx response	Good	Good	Poor

(*Neurol Clin* 1997;15:615; *Semin Neurol* 2008;28:241.)

Association w/ systemic diseases: (1) Cancer: Risk increased 5-7-fold w/ DM; dx usu w/i 2 yr, either side of DM dx; 70% of cancers are solid tumors (cervix, lung, ovaries, pancreas, bladder, stomach). (2) Interstitial lung dz in 10% DM/PM (esp if antisynthetase Ab+). (3) Dysphagia 2/2 striated muscle weakness in upper 1/3 esophagus. (4) Myocarditis: Usu mild; check troponin I (more cardio-specific than CK-MB). (5) Other connective tissue dzs.

Ddx: IBM (often mistaken for PM; but IBM presents w/ a more insidious onset, lower CKs, inclusion bodies on biopsy; MR findings throughout whole muscle not just along fascial planes), hypothyroidism, HIV infection, drug-induced myopathy, ALS, myasthenia gravis, muscular dystrophy, inherited myopathies.

Dx: (1) History & full physical examination (including breast/rectal/pelvic exam). (2) Exclude drug-induced myopathy. (3) Labs: CBC, ESR, CRP, chem7, anti-Jo1, antisynthetase ab, CK, LDH, AST, ALT, PSA, UA, anti-Ro, Sm, RNP, HIV, TSH. CK may be increased up to 50×, but if long-standing dz, CK may be low despite active dz. (4) Autoantibodies: 80% ANA positive. Connective tissue disorders a/w myositis: Anti-Ro/Sm/RNP suggestive of overlap w/ connective tissue dz. Myositis-specific auto-Abs: In 30% of pts; likely pathophysiologic role, though not yet entirely clear (antisynthetase ab, anti-Jo-1 ab, anti-SRP ab, anti-Mi-2 ab). Anti-Jo-1 probably most important since a/w interstitial pulmonary fibrosis. (5) EMG/NCS: Increased membrane excitability (fibrillation potential activity & positive sharp waves in the active

stages prior to Rx) & myopathic motor unit potentials w/ early recruitment (may be nl in up to 10%) supports dx but is not diagnostic. (6) Consider MRI muscle (can show muscle inflammation, edema, myositis, fibrosis, calcification; may even use MR spectroscopy to look at muscle metabolism). (7) Biopsy of muscle (ideally open biopsy) or skin in DM. (8) CT chest/abdomen/pelvis for malignancy. (9) Ensure cancer screening is up-to-date (10) Maintain vigilance for underlying malignancy for 2-3 yr after DM/PM dx.

Predictors of poor outcome: Resp muscle weakness/interstitial lung dz; associated malignancy or cardiac involvement; dysphagia; delay in initiation of Rx for >6 mo after symptom onset; older age at onset (Am J Med 1993;94:379).

Rx: In general, DM responds better to steroids than PM; goal is to increase muscle strength. Treat w/ steroid taper ± steroid sparing agent until remission achieved, then attempt gradual taper, usu over 6-12 mo. Recurrent dz or dz resistant to therapies (see below) may need other options, including rituximab or intravenous immune globulin.

Steroids: Start at high doses, then taper to lowest effective maintenance dose. Initial dose: Prednisone at 1 mg/kg/day (but not >6 wk due to risk of steroid myopathy) ± steroid sparing agent (consult w/ neuromuscular specialist on preference/style). Assess response to Rx every few weeks by examining strength (more reliable than CK). If no response after 6 wk of high dose steroids, add steroid sparing agent (azathioprine or methotrexate) if not already added at beginning. If response, start tapering steroids as tolerated.

Azathioprine: (1) Test for TPMT (thiopurine methyltransferase) deficiency. Heterozygotes require lower doses & careful monitoring. Homozygotes (1/300) cannot metabolize drug leading to bone marrow toxicity (Ann Intern Med 1980;92:365). (2) Initial dose 25 mg/day; increase over weeks to 1.5-3 mg/kg/day; max dose 200 mg/day. (3) Side effects: Flu-like sx, fever, GI complaints; bone marrow suppression, liver toxicity, pancreatitis, possibly increased risk of malignancy. (4) Monitor CBC, LFTs initially every 2 wk, then monthly if stable.

Methotrexate: Only once weekly dosing; initial dose 15 mg/wk, ↑ by 5 mg/wk up to 25 mg/wk. Side effects: Stomatitis; GI symptoms, leukopenia, hepatotoxicity (don’t give to pts w/ liver dz or who drink alcohol), pulmonary toxicity. Can reduce risk of leukopenia w/ folic acid 1 mg/day.

INCLUSION BODY MYOSITIS

Introduction

- Most common myopathy over the age of 50 yr
- Prevalence of around 5-70 per million population; M > F

Clinical presentation: Insidious onset of weakness; usually asymmetric, affecting forearm finger flexor muscles in setting of well preserved finger & wrist extensors & weak quads w/ relatively spared hip flexors; Knee jerk often lost due to quad muscle atrophy; frequent myalgias; up to 50% w/ dysphagia.

DDx: PM, inherited muscle dzs w/ slow progression; drug-induced myopathies (e.g., colchicine); motor neuron dz.

Dx: (1) Labs: Nl or <10× elevated CK; usu nl ESR, ANA. (2) EMG/NCS: Myopathic pattern as in other myopathies. (3) MRI: Helps to distinguish IBM from PM (IBM in anterior muscle groups, more distally & more asymmetrical than PM). (4) Bx: Endomysial inflammation; basophilic rimmed vacuoles w/in muscle fiber sarcoplasm (on frozen bx only); eosinophilic inclusions, fiber size variation. Electron microscopy: Filamentous inclusions & vacuoles in 90% of pts. Muscle fiber inclusions w/ staining for β-amyloid deposits. Paired helical fibers by EM or immunohistochemistry.

Rx: Generally poor response to Rx, including steroids or immunosuppressants. IVIg w/ no real benefit in small studies to date. PT/OT.

HIV-ASSOCIATED MYOPATHY

HIV myopathy: Resembles PM. Symmetric proximal weakness, especially in legs; myalgias, muscle tenderness on palpation. May be a presenting feature of HIV infection. No correlation w/ CD4 count. Pathogenesis: Unclear; direct viral invasion versus immune-mediated.

Dx: Distinguish HIV myopathy from NRTI (nucleoside reverse transcriptase inhibitor) myopathy. May require trial of stopping NRTI. Muscle enzymes increased up to 10×. EMG/NCS: Myopathic changes, indistinguishable from PM. Muscle biopsy: Endomysial mononuclear cell infiltrate, less so around vessels or in interfascicular space.

Rx: High dose steroids (prednisone 1 mg/kg/day) should lead to improvement over 1-2 mo; then need to taper steroids. Watch response in symptoms & muscle enzymes.

NRTI myopathy: Proximal muscle weakness, severe muscle atrophy, myalgias, & muscle tenderness. Original description w/ zidovudine.

Dx: CK increased up to 10×; EMG/NCS w/ myopathic changes or nl. On

biopsy: No inflammatory infiltrate, variable muscle fiber atrophy.

Rx: Stop drug; if no improvement w/i 1-2 mo, consider HIV myopathy as a cause.

Muscle infection in HIV: Toxoplasmosis presents w/ diffuse muscle weakness, wasting, & tenderness. Often a/w CNS infection.

Dx: ↑ muscle enzymes. Bx: Necrosis, variable inflammation, intracellular T. gondii cysts.

Rx: Pyrimethamine & sulfadiazine.

ENDOCRINE DISORDER—ASSOCIATED MYOPATHIES

Hypothyroid myopathy: Weakness ± cramps/myalgia. More common in women. Broad range from asymptomatic elevated CK to disabling muscle weakness.

Dx: Elevated CK; EMG nl or w/ myopathic changes; muscle biopsy may not be necessary in the setting of longstanding hypothyroidism, weakness, and high CKs, but may show a range of myopathic changes correlating with duration of hypothyroid state but no evidence of inflammation.

Rx: Thyroid hormone replacement.

Hyperthyroid myopathy: Muscle weakness w/o atrophy & myalgia in 60%-80% of untreated pts. Usu prox weakness quads & hip flexors; rarely resp muscle dysfn; nl or ↑'d reflexes.

Dx: NI CK, biopsy nonspecific.

Rx: Treat underlying hyperthyroidism.

Cushing syndrome: Similar to exogenous cortisol excess. Weakness begins in the legs, then the arms & neck flexors; if weakness begins in the arms, reconsider dx.

Dx: Nl CK, EMG w/ features of myopathy. Biopsy: Type 2 fiber atrophy (esp type 2b high glycolytic, low oxidative potential).

Rx: Treat underlying dz.

Addison dz: Generalized weakness, cramping, fatigue, myalgia; usu improve w/ glucocorticoids.

Hyperparathyroidism: Proximal weakness in legs > arms, myalgia, hyperreflexia. Dx: Elevated Ca, ALP, PTH, nl CK. Biopsy: Mostly type 2 > type 1 fiber atrophy.

MYOPATHY DUE TO MALABSORPTION

Vitamin E deficiency: At risk: Celiac sprue or s/p gastric bypass surgery. Dx: Vacuolar myopathy w/ inflammation, CK nl. Rx: Vitamin E supplementation

Osteomalacia: Proximal weakness, often myalgia & bone pain. Often increased ALP, decreased vitamin D level, nl CK, EMG & biopsy not diagnostic.

Hypokalemic myopathy: Repeated episodes → vacuolar myopathy. Paralysis, e.g., in severe diarrhea, alcoholism, primary aldosteronism. Usu proximal muscle weakness, watch for cardiac arrhythmias. Rx: Replace potassium.

CRITICAL ILLNESS MYOPATHY

Intro: Most common form of ICU myopathy. Risk factors: IV steroid use, sepsis, intubation; use of neuromuscular blocking agents. May p/w flaccid quadriparesis & difficulty weaning from ventilator; diffuse proximal & distal weakness.

Dx: NCS w/ low amplitude motor responses w/ nl sensory studies; EMG w/ early/nl recruitment of brief, small, motor unit potentials; many patients will have fibrillation potential activity. Biopsy: Myopathy; myosin loss. CK variably elevated (elevated in first few weeks, then often normalizes even when weakness is pronounced).

Rx: ↓ steroids when possible. Rx underlying dz. Improvement over months but leads to increased duration of ICU stay.

TOXIN-INDUCED MYOPATHY

Intro: Many drugs may cause myopathy. Sx: Myalgias to severe weakness w/ rhabdomyolysis. Causes include EtOH, steroids, statins, antimalarials, antiretroviral drugs, antipsych drugs, colchicines. Damage: Direct (alcohol or cocaine) or immune-mediated myotoxicity penicillamine).

Myopathy due to glucocorticoid (steroid) use: Like Cushing myopathy. Any steroid type can cause it. Risk factors: Older age, cancer, negative nitrogen balance, inactivity.

Clinical features: Occur at any time during the treatment course. Usually involves proximal muscles. Respiratory dysfunction usually only in the context steroids use in the ICU and as such in the context of critical illness myopathy.

Dx: No definitive test: CK nl; EMG usually nl unless the weakness is pronounced. Biopsy: Nonspecific atrophy of type 2b fibers. 1 mo trial off of steroids to evaluate for improvement. Conundrum: Inflammatory myopathy patient treated w/ glucocorticoids complains of worsening weakness (i.e.,

inflammatory myopathy worsening vs. side effect of steroid therapy) If weakness worse w/in a month of starting/increasing steroids & muscle enzymes nl, suggests steroids as culprit. Reduce steroid dose if possible & look for improvement in sx w/in 3-4 wk).

Alcohol myopathy: Acute: Usu w/in hours after binge, common cause of nontraumatic rhabdomyolysis; toxicity worsened by hypokalemia & hypophosphatemia. Clinical

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si/sx: Cramps, muscle swelling; generalized but often calf muscles in particular. Dx: High CK; biopsy revealing necrosis. Rx: Stop alcohol, recovery over days-weeks. Chronic: Gradual onset diffuse, prox weakness over wks-mos, no tenderness, usu nl muscle enzymes.

Statin myopathy: Severe myopathy is rare (0.1% of treated pts) (JAMA 2004; 292(21): 2585). Mechanism of statin-induced myopathy unclear. ↑ risk w/: Cotreatment w/other drugs (esp Cyp3A4 inhibitors, such as cyclosporine, gemfibrozil, macrolides) & hypothyroidism. Most occur w/in 6 mo of starting statins but can occur at any time during Rx. Myalgias (10%): Proximal, symmetric muscle soreness & weakness; muscle enzymes can be nl. Labs: Baseline CK prior to statin therapy; no need for routine CK monitoring while on statin. Rx: Stop statin, encourage po fluids. When CK nl, consider restarting statin w/ less muscle toxicity or other agent. Possible prevention: 150-200 mg/ day CoQ10 supplementation (no controlled trials, anecdotal evidence). Toxicity mgt: If CK elevation & myopathy thought to be caused by statin, rather than other factors, especially if CK increased 10-fold, stop statin; encourage oral fluids, when CK back to nl, consider restarting statin a/w less muscle toxicity.

Cocaine: Variable presentation from asymptomatic CK rise to rhabdomyolysis. Mechanism may be due to sympathomimetic activity/vasoconstriction w/ muscle ischemia & infarction.

Antipsychotic drugs: Rhabdomyolysis may occur w/ neuroleptic malignant syndrome.

Colchicine: Especially myotoxic if pt has renal failure. Onset usually w/in 2 wk of rx (dose: 0.6 mg tid). Proximal leg weakness. CK elevated 10-20×. EMG/NCS w/ myopathic changes & mild axonal polyneuropathy, occasional myotonic discharges. Biopsy: Vacuolar changes of lysosomal origin. Rx: d/c drug → rapid resolution of symptoms; no need for steroids.

Penicillamine: Occurs in up to 1% of patients on this drug (e.g., w/ rheumatoid arthritis, SLE). No relationship to dose or duration of therapy. Dx:

Symmetric proximal muscle weakness; can see DM rash or dysphagia. Elevated CK. EMG w/ myopathic changes. Biopsy: Perifascicular cellular infiltrates, muscle fiber necrosis, & regeneration (similar to PM). Rx: Stop drug; consider high dose prednisone (40-60 mg/day).

Nerve Conduction Studies and Electromyography

INTRODUCTION

Purpose of electromyography (EMG)/nerve conduction studies (NCS): (1) Localization, (2) fiber type involved (mot/sens/both), whether dz is axonal or demyelinating, (3) determine injury extent, (4) determine dx & tx.

Common electrodiagnostic studies: NCS: Electrodes on skin, stimulate nerves w/ electrical impulses; EMG: Insert needle, measure the electrical activity of muscle; Repetitive stimulation: Nerve stimulated at different freq, consistency of motor response is measured.

Cautions w/ EMG/NCS: (1) Bleeding disorders/coagulopathy, (2) contraindicated w/ cardiac defibrillators, (3) caution w/ pacemaker: no electrical stimulation over pacemaker.

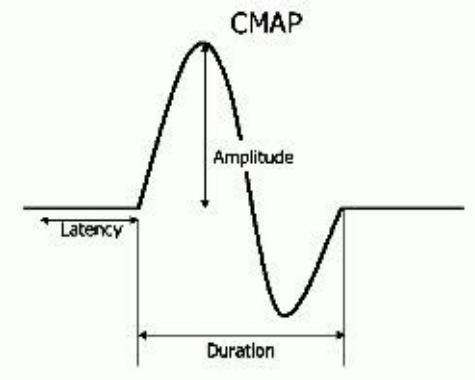
NERVE CONDUCTION STUDIES

Records large myelinated fibers. Small myelinated & unmyelinated fibers (autonomic & somatic pain nerves) are not as well recorded by this test.

Most common NCS: Compound muscle action potential (CMAP), sensory nerve action potential (SNAP), F-wave, H-reflexes.

Definitions: Conduction velocity: Speed in the fastest conducting nerve fibers; Latency: Time from stimulation to initial deflection of the CMAP or SNAP; Amplitude of CMAP or SNAP: Distance from baseline to negative peak (upward); Duration: Time from initial deflection from baseline to return; Antidromic: Stimulating toward the sensory receptor; Orthodromic: Away from the sensory receptor.

Motor NCS: CMAP: Summated record of synchronously activated muscle APs.



Sensory NCS SNAP: Represents sum of individual SNAPs.

- May be nl in neuropathies affecting only small fibers
- In lesions proximal to dorsal root ganglia, SNAPS are nl b/c dorsal root ganglia & peripheral axon are intact

Late responses: F-wave & H-reflex are used to assess the proximal nerve segments.

F-wave: Pathway: antidromic activation of motor neurons → anterior horn cells → orthodromic impulses traveling back along motor axons; response involving motor fibers only; may be absent in early Guillain-Barré synd. (initial demyelination may be only proximal).

H-reflex: Pathway: sensory Ia afferent, synapses → back down efferent α motor neuron.

- Tests some of the same fibers as ankle jerk, useful in assessing for SI radiculop.

NEEDLE ELECTROMYOGRAPHY

Needle inserted into muscle & electrical activity recorded. No electrical stimulation is given. Allows evaluation of motor unit action potentials (MUAPs).

Components of the EMG

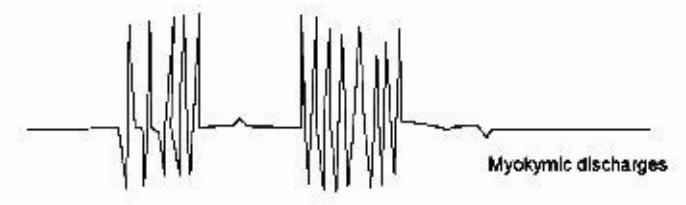
Insertional activity: Electrical activity associated w/ inserting or moving the needle

- Normal (nl): Lasts few hundred milliseconds
- Decreased insertional activity: ↓ Electrical activity on needle insertion & movement. Occurs w/ atrophied muscle.

- Increased insertional activity: Defined as electrical activity lasting longer than 300 ms. Occurs w/ neuropathic & myopathic conditions & is characterized by the presence of positive sharp waves & fibrillation potentials on insertion.

Examination of muscle at rest: Once the needle is in the muscle, evaluate for spontaneous activity. Nl muscle should not have activity at rest. Spontaneous activity typically means that there is pathology. Several types:

- Positive sharp waves: Brief init + burst, then long negative phase. In neuropathic & myopathic states. Equiv to fibrillation potentials: occur when needle tip in muscle fiber.
- Fibrillation potentials: Spontaneous depol of muscle fibers, which are firing autonomously. Also occur in presence of impaired innervation. Sound like “raindrops hitting a tin roof.” Occur in neuropathic & myopathic states.
- Complex repetitive discharges: Groups of spont firing action potentials; appear as runs of simple or complex spike patterns. Looks like a “muscular arrhythmia.” Occur in neuropathic & myopathic states, usually indicate longstanding injury (>6 mo).
- Myotonic discharges: Action potentials of muscle fibers firing in a prolonged fashion, “Diver bomber” sound. Occur in myotonic dystrophy, myotonia congenita, paramyotonia congenita, acid maltase deficiency, polymyositis, myotubular myopathy, hyperkalemic periodic paralysis, chronic radiculopathies, & neuropathies.
- Myokymic discharges: Groups of spontaneous motor unit potentials w/ a regular firing pattern & rhythm. Sounds like “soldiers marching.” May be seen in MS, Bell’s, polyradic. Clinical myokymia is described as “worm-like” movement of muscle. This is more often associated w/ neuromyotonic discharges on EMG.



P.237

Analyzing the motor unit: Analyze the MUAP morphology while pt contracts muscle slightly. Assess amplitude, rise time, duration, & phases. ↓ amplitude

may be seen in myopathy. ↑ duration in neuropathic processes while ↓ duration occurs in myopathic processes. ↑ phases (polyphasia) in neuropathic processes.

Recruitment: Defined as the orderly addition of motor units to ↑ the force of contraction. Neuropathic recruitment characterized by few motor units firing at ↑ rate. Seen in neuropathies, radiculopathies, motor neuron disease, nerve trauma. Myopathic processes exhibit early & ↑ recruitment.

COMMON PATTERNS IN DISEASE

Peripheral neuropathy

Demyelinating: 2/2 lesions affecting myelin sheath, such as entrapment or compressive neuropathies, Charcot-Marie-Tooth, or demyelinating forms of Guillain-Barré syndrome:

- NCS: Slow conduction velocity (slower than 75% lower limit of nl) & prolonged latencies (> 130% upper limit of nl). Conduction block: Focal demyelination so severe that action potential cannot propagate along that area. CMAP amplitude is ↓ by >50% from distal to proximal stimulation sites.
- EMG: Nl unless there is conduction block where there is decreased recruitment.

Axonal: 2/2 processes affecting nerve, typically caused by toxic, metabolic or genetic causes.

- NCS: CMAP amplitude may be ↓, depending on axonal injury severity. Conduction velocity & distal latency are nl or mildly slow. (Conduction velocities are never <75% of the lower limit of nl & distal latencies are not >130% of the upper limit of nl).
- EMG: Increased spontaneous activity w/ fibrillations & + sharp waves. MUAP morphology nl early on but after weeks-months, there may be ↑ duration, amplitude, & number of phases.
- Points to consider when planning the timing of studies for peripheral nerves: Abnl spont activity takes days-weeks to be detected; SNAPs & CMAPs ↓ several days after nerve injury & may appear nl in the first 3-4 days; at day 3-10, Wallerian degeneration occurs; when estimating recov period for peripheral nerves, keep in mind that axons regrow at a rate of 1 mm/day.

Motor neuron disease: NCS: Sensory NCS are nl. CMAP amplitude ↓.

Latency & conduction velocities are nl, except w/ severe axonal loss where there is mildly ↓ latency & decreased conduction velocity. EMG: ↑ spont activity: + sharp waves & fibrillation potentials. May see fascics, complex repetitive discharges. MUAPs may be of long duration, ↑ polyphasicity & large amplitude, indicating reinnervation. ↓ recruitment.

Diseases of the neuromuscular junction

Myasthenia gravis: Sensory NCS nl. Motor NCS nl. Repetitive nerve stimulation (RNS): Abnl in 50%-70% w/ generalized myasthenia but often nl in isolated ocular myasthenia. With 3 Hz RNS, > 10% ↓ in CMAP amplitude. EMG: nl, or unstable or short, small, polyphasic MUAPs; single fiber EMG: Jitter & blocking.

Lambert Eaton: Sensory NCS nl. Motor NCS: CMAP amplitudes are diffusely low or borderline at rest; rep stim: CMAP amplitude ↑ at 30-50 Hz RNS or after 10 s of exercise. EMG: Typically nl, although MUAP may be unstable, short & w/ small, polyphasic MUAPs. Single fiber EMG: Jitter & blocking.

Botulism: Sensory NCS nl. Motor NCS: CMAP amplitudes diffusely ↓ or absent. Rep stim: facilitation after 30-50 Hz RNS or 10 s of exercise. EMG: Fibrillation potentials, + sharp waves. MUAPs may be unstable & short, small, & polyphasic. NI or ↓ recruitment.

Myopathy: NCS: Sensory NCS are nl. Motor NCS usually nl, except in cases of myopathy involving distal muscle where CMAP amplitude may be ↓. EMG: MUAPs typically short duration, small amp, & polyphasic w/ early recruitment. In inflam myopathies, may see ↑ spontaneous activity: + sharp waves, fib potentials, myotonic disch, complex repetitive discharge.

Radiculopathy: NCS: Sensory & motor NCS are typically nl, except in case of a severe radicular lesion causing Wallerian degen distal to the lesion where CMAP may be ↓; NCS are useful in radic primarily to exclude other dx, such as a peripheral neuropathy. H-reflex: Assesses afferent & efferent S1 fibers (similar to the ankle reflex). Useful in distinguishing S1 from a L5 radic. EMG: Acute setting: fibrillation potentials & + sharp waves. Chronic setting: Abnl motor units, such as long duration or polyphasic motor units. Test two muscles supplied by the same root but different peripheral nerves, & one paraspinal muscle.

CNS disorders: NCS: Sensory & motor NCS are nl. EMG: MUAP morphology & recruitment are nl but there is ↓‘d activation.

Neuro-Rheumatology

Wide spectrum of musculoskeletal & systemic d/os affecting joints & periarticular or connective tissues. Most are autoimmune; expression depends on genetic, environmental, immunologic factors. Any organ system can be affected, including the CNS, PNS, & autonomic nervous systems. Neurologic si/sx can be 1° or 2° (e.g., to effects related to other organs or to Rx). Neurologic involvement → significant morbidity, may indicate increased dz activity. Sometimes neurologic si/sx = presenting manifestations of systemic rheumatological dz.

Clinical Sx Suggesting Systemic Rheumatological Dz

Constitutional	Fever, fatigue, malaise, wt loss, anorexia
Glandular	Dry eyes or mouth
Musculoskeletal	Joint pain or swelling, myalgias
Renal	Proteinuria, urinary cellular casts
Vascular	Unexplained DVT or PE
Cutaneous	Malar or discoid rash, photosensitivity, Raynaud's, psoriasis, oral or genital ulcers, petechiae, subq nodules, alopecia
Ocular	Uveitis, scleritis, conjunctivitis
Serologic	Elevated ESR or CRP

LABORATORY EVALUATION OF RHEUMATOLOGICAL DISEASE

Acute phase reactants (APR): ↑ or ↓ ≥25% during acute or chronic inflammatory state. ESR, CRP are most widely used indicators; not specific to any dz. (1) ESR = rate of RBC settling in a vertical tube; largely dependent on fibrinogen. (2) Causes of ↑↑↑ ESR (> 100) include infxn, systemic inflammatory dz (esp GCA), CA. (3) CRP not reliably elevated in systemic lupus erythematosus (SLE) but ESR may correlate w/ dz activity. (4) CRP or ESR may correlate w/ dz activity in RA. (5) ESR helps guide steroid taper in

GCA & Churg-Strauss.

Antinuclear abs (ANA): Target Ag include dsDNA, histones, RNA-protein complexes, other nuclear proteins. Found in multiple CTD (Se): SLE (93%), RA (41%), SS (48%), scleroderma (Scl) (85%), mixed connective tissue disease (MCTD) (required for dx), PM/DM; also in chronic infxn (hepC, TB, HIV, SBE), lymphoproliferative dz. Significant false ⊕ rate (32% 1:40, 13% 1:80, 5% 1:160) (Arth Rheum 1997;40:1601-1611). Increased suspicion for autoimmune dz w/ titer >1:640; follow for emergence of clinical sx. Ab to certain ANA antigens ↓ Se but ↑ Sp for individual dz: (1) dsDNA (97% Sp) in SLE (Arth Rheum 2002;47:546-555); titer fluctuates w/ dz activity. (2) Sm (55%-100% Sp) in SLE. (3) Ro/SSA & La/SSB most common in SLE & SS (1° > 2°). (4) Centromere (97% Sp) in Scl (↑ Se in limited Scl/CREST) & topoisomerase (Scl-70; 99.5% Sp) in Scl (↑ Se in diffuse Scl) (Arth Rheum 2003;49:399-412). (5) UI-RNP required for dx of MCTD; also found in SLE & limited > diffuse Scl.

Rheumatoid factor (RF) (Am J Med 1991;91:528): Targets Fc portion of IgG; IgM type measured in standard assays. Unclear role of RF in pathogenesis of RA or other autoimmune dz. Found in MCTD (Se): SLE (15-35%), RA (50-90%), SS (75-95%), Scl (20-30%), MCTD (50-60%), PM/DM (5-10%); chronic infxn (TB, SBE, syphilis, parasitic), pulm dz (sarcoid, asbestosis, silicosis), CA (leukemia, colon ca), 1° biliary cirrhosis, ↑ age independent of joint dz. Poor screening test for RA or other CTD; most useful in pts w/ clinical sx & moderate pretest prob of RA or in serial measurements in SS.

DIFFUSE CONNECTIVE TISSUE DISEASES

SYSTEMIC LUPUS ERYTHEMATOSUS

Neurol Clin 2002;20:151; Continuum 2008;14:94; Arth Rheum 1999;42:599.

Epid: Prev ˜40-50/100,000; more common: (1) F > M, (2) minorities, (3) young adults.

Dx of SLE (Arth Rheum 1982;25:1271 & 1997;40:1725): 11 criteria of American. College of Rheumatology. (ACR); ≥4, but not all simultaneously: Se 96%, Sp 96% w/ ≥4 criteria.

ACR Criteria for Dx of SLE

System	Criteria
Cutaneous/dermatologic	**1.** Malar rash (fixed erythema over malar eminences)

	2. Discoid rash (red raised patches w/ scaling & follicular plugging)
	3. Photosensitivity (skin rash from unusual reaction to sunlight)
	4. Oral ulcers (oral or nasopharyngeal, usually painless)
Musculoskeletal	**5.** Arthritis (nonerosive of >2 peripheral joints)
Cardiopulmonary	**6.** Serositis (pleuritis or pericarditis)
Renal	**7.** Persistent proteinuria (>0.5 g/day or 3+) or urinary cellular casts
Neuro/psych	**8.** Seizures or psychosis (no other cause identified)
Hematologic	**9.** Hemolytic anemia (w/ reticulocytosis) or leukopenia (<4,000/mm^3) or lymphopenia (<1,500/mm^3) or thrombocytopenia (< 100 k/mm^3 w/o offending drug present)
Immunologic/serologic	**10.** ⊕ anti-dsDNA or anti-Sm or antiphospholipid ab (elevated IgG or IgM anticardiolipin, positive LA, or false ⊕ syphilis)
	11. ⊕ ANA (in the absence of drugs a/w drug-induced lupus)

Neuropsychiatric SLE (NPSLE): Outside of ACR criteria, include 19 CNS/PNS syndromes; expands on no. 8 above. NPSLE replaces terms “CNS lupus,” “neurolupus,” & “lupus cerebritis.” Can present before or after clinical dx of SLE, including quiescent periods. Syndromes not exclusive to SLE; must r/o other conditions before dx NPSLE.

NPSLE syndromes (19 described; dx criteria, exclusions, associations, w/u on ACR website [http://www.rheumatology.org/publications/ar/1999/aprilappendix.asp]).

CNS: (1) Acute confusional state, (2) anxiety disorder, (3) aseptic meningitis, (4) cerebrovascular dz, (5) cognitive dysfunction, (6) demyelinating dz, (7) headache, (8) mood disorder, (9) movement disorder (chorea), (10) myelopathy, (11) psychosis, (12) seizures & seizure disorders; PNS: (13) AIDP, (14) autonomic disorder, (15) mononeuropathy (single or multiplex), (16) myasthenia gravis, (17) neuropathy, (18) plexopathy, (19) polyneuropathy.

W/u of NPSLE: Wide ddx; tailor w/u to specific syndrome. No single test Se and Sp. Some evidence antiribosomal protein P a/w SLE-related depression & psychosis.

Serologies to consider: CBC w/ smear, chem7, Cr, LFTs, C3, C4 CH50, anti-dsDNA, ESR, CRP, APLA (LA, ACL IgG/IgM, β-2 glycoprotein), lipid profile; ANA, dsDNA/Sm, antiribosomal P if SLE dx not definite.

Other considerations: LP: Abnl in 1/3 w/ CNS NPSLE; typically mild lymphocytic pleocytosis & protein elevation. Most useful to r/o meningitis. CSF ab testing (e.g., ANA, antiribosomal P,APL) still investigational. CSF IgG, oligoclonal bands often abnl but no definite clinical use in NPSLE. MRI: Periventricular & subcortical WM, cerebral atrophy; not diagnostic of NPSLE. Focal presentation may = infarct or ICH. (Note: consider APLA syndrome, may occur 2° w/ SLE; needs further vascular w/u; see chapter "Vascular Neurology".) Negative MRI does not r/o NPSLE. Electrodiagnostic testing—for PNS NPSLE, sz: EMG/NCS, EEG. Neuropsychiatric testing proposed battery for SLE on ACR website: http://www.rheumatology.org/publications/ar/1999/499apC.asp?aud=mem.

Rx of NPSLE: Symptomatic (e.g., Rx HA, sz) & immunomodulatory Rx. No specific immune Rx for NPSLE vs. SLE. Hydroxychloroquine: For mild SLE. Corticosteroids: ˜90% of SLE pts require long-term corticosteroids. Steroid-sparing agents (e.g., mycophenolate, cytoxan). Cyclophosphamide: Severe NPSLE refractory to other Rx.

RHEUMATOID ARTHRITIS

Neurol Clin 2002;20:151; Continuum 2008;14:120.

Epid: Prevalence ˜1/100; F > M (although more equal in RF⊕ dz); > w/ ↑ age.

Dx of rheumatoid arthritis (RA) (Arth Rheum 1988;31:315): 7 criteria defined by ACR; must meet 4 criteria for dx; Se 91%-94%, Sp 89% w/ ≥4 criteria.

ACR Criteria for Dx of RA

System involved	Criteria

Musculoskeletal	**1.** Morning stiffness, ≥1 h × 6 wk
	2. Arthritis >3 joints (PIP, MCP, wrist, elbow, knee, ankle, or MTP) simultaneously × 6 wk; observed by physician
	3. Arthritis >1 hand joint (PIP, MCP, or wrist) × 6 wk
	4. Symmetric joint arthritis × 6 wk
Cutaneous/derm	**5.** Rheumatoid (SQ) nodules observed by physician
Immunologic/serologic	**6.** ⊕ RF
Radiographic	**7.** Typical Δ on PA hand/wrist radiographs c/w RA (erosions or periarticular decalcification)

Neurologic manifestations of RA

1. Cervical spine dz (tends to spare rest of vertebral column) in 25%-70% of pts w/ adv RA.

Atlantoaxial subluxation: Increased separation of dens & anterior arch of atlas b/c involvement of C1/C2 joints. Sx: Asymptomatic → pain in neck & occiput → cord compression & myelopathy (often mild spastic quadriparesis, atrophy/sensory loss in hands/upper cervical dermatomes).

Atlantoaxial impaction: Progression from atlantoaxial subluxation: skull descends on C-spine, dens moves upwards. Sx: Dysfxn of pons/medulla including myelopathy, drop attacks, sudden death; lower cranial neuropathies including trigeminal neuropathy.

Subaxial subluxation: Involvement of facets below C1/C2; radiographic "stair-case spine." Sx: Asymptomatic → dermatomal pain → myelopathy. Dx: Plain XR w/ flexion/extension views. Cautions: R/o C-spine dz prior to intubation. Avoid maneuvers such as Dix-Hallpike in RA pts. Rx: Mild → observe, soft collar/PT; severe pain/myelopathy/spine instability → ?surgery.

2. Neuropathy

Compression or entrapment from synovitis/pannus/joint deformity; common in median, ulnar, peroneal, post tibial nerves. Rx: Mild → conservative,

severe → consider surgery.

Vasculitic usu severe RA w/ ↑ ESR & RF⊕; commonly mononeuritis multiplex or distal Sensory; Rx: immunomodulation.

3. Myopathy: Consider in pts w/ proximal weakness. Multiple causes: Disuse, steroids, vasculitic; ˜5% polymyositis or dermatomyositis.

4. CNS dz: Meningitis [rare, 22 histopath-proven cases (Neurology 2007;68:1079)]; Likely direct inflammation of CNS, usually in long-standing RF⊕ dz. W/u: LP (r/o infxn, DDx inflam CSF), MRI, consider meningeal bx. Rx: No RCT or consensus on optimal Rx,? immunomodulation.

SJÖGREN SYNDROME

Neurol Clin 2002;20:151; Continuum 2008;14:120.

Epid: Overall prevalence up to 3/100. More common in women & in middleage. Can be 1° or 2° (w/ another autoimmune dz; most common RA);˜50% split. 2/2 lymphocytic infiltration of salivary/lacrimal glands (large ddx). ˜1/3 systemic extraglandular involvement.

Dx of Sjögren syndrome (SS): 6 criteria (Am. Europ. Consensus Group (AECG); Ann Rheum Dis 2002;61:554). For 1°: 4/6 criteria (must incl. no. 4 or 6) OR 3/4 objective crit. (nos. 3-6); Se 96%, Sp 94%. For 2°: Presence of autoimmune dz + crit. # 1 or 2 & any 2 of #s. 3-5; Se 97%, Sp 90%. Exclusions: H/o head/neck XRT, hep C, AIDS, lymphoma, sarcoidosis, GVHD, anticholinergic use (w/in $t_{1/2} \times 4$).

AECG Criteria for Dx of SS

System	Criteria
Cutaneous/glandular	**1.** Daily, bothersome dry eyes × 3 mo, ⊕recurrent sensation of sand/gravel in eyes, or ⊕use tear substitute >3×/day.
	2. Daily dry mouth × 3 mo, ⊕recurrent/persist. salivary gland swelling, or freq. liquids to aid swallowing dry food.
	3. ⊕Schirmer test or Rose Bengal score.
	4. Minor salivary gland focal lymphocytic sialoadenitis on histopath (focus score >1).
	5. Decreased whole salivary flow, diffuse sialectasias on parotid sialography, or abnl.

salivary scintigraphy.

Serologic	**6.** ⊕ anti-Ro (SSA) or La (SSB)

Neurologic manifestations of SS

1. Neuropathy: Variety of presentations; may be present in up to 30%-60% of pts w/ SS. No definite findings to distinguish from neuropathies of other causes. Rx: No RCT or consensus on optimal Rx for pts w/ neuropathy & SS; no definite benefit of corticosteroids in small studies, except possibly where suspect path is vasculitis.

Peripheral Neuropathies Described in SS

Suspected pathology	Type/Sx	Special considerations
Ganglionitis (lymphocytic infiltration)	Sensory ataxia: distal paresthesias → severe joint position/vibration loss	Paraneoplastic (SCLC, anti-Hu)
	Trigeminal sensory: CNV distribution numbness; uni- or b/l	Mass lesion, MS, infarct
	Autonomic: Adie pupils, orthostatic hypotension, hypohydrosis	
Vasculitis	M. Multiplex: Sensory or motor dysfxn. in separate peripheral n	Lyme, hepatitis, TB, HIV, sarcoid, GCA, carcinomatous, mass lesion
	Multiple cranial neuropathies	
Small-fiber	Sensory w/o ataxia: painful distal dysesthesias & pain/temp loss	

Demyelinating	Sensorimotor poly. Dist > proximal	AIDP, myelopathy

(Adapted from *Continuum* 2008;14:124; Orig. data: *Brain* 2005;128:2518.)

2. CNS involvement: Not well-characterized; ?a/w MS-like CNS demyelination syndrome; a/w SS & NMO (optic neuritis, longitudinal TM); likely represents two diff. autoimmune syndromes. W/u, Rx: same as for NMO (see chapter "Demyelination").

SCLERODERMA (SCL)

Neurol Clin 2002;20:151.

Epidemiology (Primer Rheum Dis 1997;263). Rare; Incidence ˜17-19 cases/million/yr (some reports: up to ˜400 cases/million/yr). F > M; more common in middle age. Increased risk w/ certain chemical (e.g., silica dust) & possibly virus exposures (homologous regions to those of auto-g in feline sarcoma virus, CMV, HIV, HSV-1, EBV).

Dx of Scl: One major & three minor criteria defined by ACR; must meet one major or two minor for dx. Se 97%, Sp 98% w/ criteria (Arth Rheum 1980;23:581).

ACR Criteria for Dx of Scl

System	**Criteria**
Dermatologic	Major: Thickening/tightening/induration of skin on fingers extending prox. to MCP/MTPs
	Minor:
	1. Sclerodactyly— as above, but limited to fingers
	2. Digit pitting/loss of finger pad (2/2 ischemia/prolonged Raynaud's)
	3. Bibasilar pulmonary fibrosis

Divided into dz subsets based on degree of skin involved. Diffuse = thickening of dist/prox. limbs and/or truck; Limited = distal limbs & no trunk. Vascular & fibrotic complications occur in CV, pulm, GI, renal systems. Raynaud phenomenon common. Serologic studies (anticentromere &

topoisomerase/Scl-70) not required, but support dx.

Neurologic manifestations of Scl

1. Neuropathy: Cranial (most common), peripheral and/or autonomic.

Pathophysiology: Vasculopathy, compression, or antibody-related.

Trigeminal: (1) Most common of cranial neuropathies, although any may be affected. (2) Involves sensory > motor, often b/l, & assoc w/ painful dysesthesias. (3) Pathophysiology may be ganglionitis, similar to SS.

Compressive (commonly affected: median, ulnar, peroneal, posterior tibial; ilioinguinal & lat femoral cutaneous). Polyneuropathies: Sensory (most common), sensorimotor, mononeuritis multiplex, brachial plexopathy.

Autonomic: Decreased GI motility & impotence.

Neuropathy w/u: No specific findings distinguish Scl neuropathy from other causes. Rx: No RCT or consensus on optimal Rx for pts w/ neuropathy & Scl.

Corticosteroids or immunomodulation: Consider when suspect systemic vasculitis as etiology (e.g., mononeuritis multiplex); however, vasculitis rare in Scl so need to suspect different underlying dz including other CTD. No definite benefit of corticosteroids in trigeminal neuralgia a/w CTD (Neurology 1990;40:891).

2. Myopathy (Arth Rheum 1978;21:62) Consider in pts w/ prox weakness. Typical pattern: Nonprogressive, mild CK ↑, EMG: polyphasic motor units w/ nl ampl. & duration w/o e/o ↑ insertional activity or denervation, m. bx w/ fibrosis w/o inflam. Must distinguish from inflam myositis. W/u: see chapter “Myopathy”. Rx: None clearly indicated for stable myopathy; for inflam myositis/polymyositis, likely steroids ± steroid-sparing immunomodulation.

3. CNS involvement (Neurology 2008;71:1538) Ltd. Evidence; seen in craniofacial Scl (localized SCL en coup de saber w/ linear induration over frontoparietal bone or progressive facial hemiatrophy). Neurol. sxs and +neuroimaging described in localized SCL a/w focal epilepsy, HA & neuropsychiatric sxs. CNS MS-like inflam process in some pts w/gado-enhancing lesions & + oligoclonal bands. W/u: MRI brain w/ gado in pts w/ Scl & neurologic sxs suggestive of CNS dz; no consensus on indication for MRI in craniofacial SCL w/o neurologic sxs. If multiple T2 hyperintensities ± enhancing lesion → consider ddx of MS. Rx: Controversial; high-dose steroids for enhancing lesion, possibly immunomodulation.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Overlap syndrome w/ SLE, Scl, polymyositis (PM), & presence of high titer anti-U1RNP. More common in women & in young to middle-aged adults. Several sets of criteria proposed; most widely used Alarcon-Segovia & Cardiel: (1) Must meet # 1 + 3 of #s. 2-6 including either no. 4 or 5 (J Rheum 1989;16:328). (2) Se 62%, Sp 86% (J Rheum 1996;23:2055). Can take yrs to make dx as overlap sx often develop sequentially.

Dx of MCTD (6 criteria, from 4 categories): Immunologic/serologic: (1) anti-U1-RNP (> 1:1,600); Cutaneous/derm: (2) Swollen hands, (3) Acrosclerosis ± prox sclerosis; Musculoskeletal: (4) Synovitis, (5) Myositis; Vascular: (6) Raynaud's.

Neurologic manifestations of MCTD (Neurol Clin 2002;20:151): Present in ˜10% of pts; often similar to syndromes of predominant CTD at time of sx. Most common = trigeminal neuropathy; can be b/l & presenting sx of MCTD (J Clin Rheum 2006; 12:145). Rx: Similar to that in predominant CTD.

VASCULITIS

Definition: Inflammation, necrosis of the blood/lymphatic vessel wall. Etiology: Immune reaction against vessel wall; infxn of the vessel; antigenic cross-reactivity due to infxn, drug, etc. Pathophysiology: Inflammation → (a) aneurysm, which can rupture, (b) stenosis & occlusion, resulting in ischemia/infarct. Classification: Systemic vs. one organ; vessel caliber, type (larger vs. medium vs. small; arteries/veins); antibody associated (e.g., ANCA); infxn related (e.g., syphilitic). Epidemiology: 1:600, some less common. Sx: Fever, rash, fatigue, weakness, pain, wt loss Si: Oral/genital ulcers, hemoptysis, HTN, hematuria, palpable purpura, end organ failure, infarctions. Neurologic manifestation: HA, seizures, CVAs, encephalopathy, psychosis, hemorrhage, AMS, peripheral neuropathies.

Diagnostic modalities: (1) Biopsy involved sites (gold standard). (2) Angiography (look for sequential stenosis & dilatation, i.e., beading, aneurysms); Nonspecific: Atherosclerosis, fibromuscular dysplasia (FMD), post-XRT can appear similar. (3) Serologies. (4) EMG/NCS. (5) Laboratory features: Hypoalbuminemia; Anemia, ↑ plt, polys, eos; ESR > 100 mm/h, CRP > 10 mg/dL → r/o vasculitis if no infxn/CA; RF, ANA [circled minus] in 1° vasculitis. Other diagnostic testing: BCx, hepatitis serologies, HIV, CMV, Utox, TTE, Antiphospholipid ab, SPEP; CSF VZV, HSV. (6) DDx: endocarditis, hepatitis, drug abuse, malignancy, other infxn.

LARGE-SIZED VESSEL VASCULITIDES

Involves aorta, cerebral vessels (vertebral, temporal, carotid). Ddx: FMD, coarctation of aorta, radiation fibrosis, NF.

1. Primary angiitis of the CNS (PACNS): see “Central Nervous System Vasculitis” chapter.

2. Takayasu arteritis (aka pulseless dz): Pathology: Granulomatous inflammation of aorta, major branches ascend > descend. Etiology: Idiopathic. Epidemiology: Reproductive age women; F:M = 8:1; ↑ incidence in Asians. Sx: constitutional sx, HA, angina, vertigo; triphasic pattern (vague sx ˜ viral prodrome → vessel pain

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P.243

(e.g., carotidynia) & tenderness → bruits, ischemia). Systemic findings: Unequal pulses/BP, absent radial pulse, bruits, HTN, pulm HTN, MI, heart failure, sudden death, aortic regurgitation, CVAs. Neurologic features: Retinopathy, carotidynia, carotid stenosis, vertebrobasilar insufficiency, microaneurysms, CVAs, TIAs, sz, ICH. Exam: Bruits, focal neurologic deficits, HTN, encephalopathy, amaurosis fugax, retinal ischemia, microaneurysms, SAH, 2/2 HTN, sensorineural hearing loss, Cogan syndrome (interstitial keratitis + vestibulo-auditory sx). Serology: ↑ ESR, CRP, plt; anemia. Imaging: Gold standard = angiography, ⊕long segmental stenosis, occlusions, aneurysms. MRA + gado → wall thickening, stenosis, thrombus. PET⊕ in inflamed vessel wall. Bx: cellular infiltrate ˜ GCA but in the outer media, vasa vasorum, adventitia. Rx: (1) prednisone 20 mg tid, if no response add azathioprine, MTX, or cyclophosphamide; (2) BP control; (3) Antiplatelet, heparin, or warfarin for CVA prevention/treatment; (4) bypass graft for critical thoracic aortic stenosis.

3. Giant cell arteritis (aka Horton headache): Pathology: Granulomatous inflammation of temporal, cranial arteries. Etiology: Idiopathic. Epidemiology: >50 yo; mean ˜70 yo; ↑ risk w/ age; most common vasculitis in adults; F > M 2:1; Northern European descent higher incidence vs. other groups. Sx: New onset HA, temporal artery/scalp tenderness, blindness, jaw claudication, facial pain, arthralgias, wt loss, depression, fatigue, malaise.Si: Raynaud’s, anemia, symmetric shoulder, hip pain & stiffness worse in the a.m. (40% present w/PMR), FUO (1/3 of all GCA presentation), rigors, sweats. Neuro si: painless, sudden onset blindness (usually due to posterior ciliary artery necrosis), amaurosis fugax ± blurry vision (warning), optic neuritis, optic atrophy, diplopia, CVA/sz (rare as intracranial vessels do not have internal elastic lamina). Exam: nodular, enlarged nonpulsatile temporal artery (50%), subclavian bruit, scalp tenderness, blindness (15%), RAPD, CRAO. Serology: ESR > 100 mm/h; (normal if on prednisone already); anemia, ↑ plt, abnl LFT, ↑ CRP. Imaging: Doppler to guide bx (narrowing); extracranial GCA in 15 % have PET ⊕ aortic inflammation even if clinically silent; angiography to document extracranial GCA if bx [circled minus]. Bx:

Gold std = temporal artery bx (unilateral Se 85%;b/l 95%);⊕ even after starting prednisone for 1-2 wk); ⊕ giant cells, intimal proliferation, thrombosis. If posterior HA → superficial occipital artery bx. No need for bx in PMR w/o ⊕ temporal arteritis sx. Rx: 40-60 mg prednisone daily (blindness risk after initiating Rx 1%); sx improve in 24-72 h after initiation of Rx; gradual taper guided by sx, normalization of ESR; trial of azathioprine, MTX, or cyclophosphamide in steroid nonresponders. Complications: Blindness from optic neuritis (15%), stroke, complications related to long-term steroid Rx; thoracic aortic aneurysm, aortic dissection (late onset).

MEDIUM-SIZED VESSEL VASCULITIDES

Affects intracerebral vessels, intraorgan vessels. Ddx: Cholesterol emboli, atrial myxomas, thromboembolism, Ehlers-Danlos, FMD, NF, segmental mediolytic arteriopathy.

Polyarteritis nodosa (PAN): Pathology: Focal segmental necrotizing inflammation of medium/small arteries > arterioles, venules; fibrinoid necrosis, w/ disruption of the elastic laminae; ⊕ polys, lymphs, eos. Etiology: Idiopathic. Epid: M > F (2:1), 40-60 yo; ˜7% prevalence in Hep B associated PAN. Sx: Arthralgias, myalgias, rash, abd pain, angina, testicular pain. Si: HTN, testicular tenderness, palpable purpura, livedo reticularis, acral necrosis, renal dysfn. Neuro si: mononeuritis multiplex (50%-70%), weakness, paresthesias, sz, stroke, blindness. Associated conditions: Hep B, CMV, HTLV-1, parvo B19, EBV, Hep C, SLE, RA, DM, Cogan syndrome, allopurinol, sulfa, hairy cell leukemia. Exam: Weakness, sensory deficits, retinal hemorrhages. Serology: ↓ C3/C4 in active dz; ⊕ Hep B sAg (10%-50%), HBeAg, HBV DNA; ± ⊕Hep C, ↑ ESR, CRP, Plt; anemia, ↓ albumin; ANCA [circled minus]. EMG/NCS: Multifocal axon loss, asymmetric, generalized polyneuropathy. Imaging: Visceral angiogram if bx not amenable; ⊕ microaneurysms, occlusion, stenosis. Bx: Gold std = muscle, if abnl EMG/NCS → sural nerve bx (necrotizing arteritis, epineural inflammatory cells, multifocal axon loss), liver, skin, testicle or other symptomatic tissue; kidney bx ≠ specific for PAN. Rx: If [circled minus] HepB → High dose steroids, if severe, IV pulse dose methylprednisolone 1 g/day × 3 day, then prednisone 1-2 mg/kg/day divided; add cytotoxic agents, e.g., cyclophosphamide if unable to taper steroids. If ⊕Hep B & HBeAg ⊕ → prednisone 30 mg/day w/ rapid taper ⊕ plasmapheresis 9-12 over 3 wk ⊕ INFα_{2b} or lamivudine; Rx success = HBeAg ⊕ → [circled minus].

SMALL-SIZED VESSEL VASCULITIDES

General: Affects intraparenchymal arteries. Includes Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schonlein

purpura, cryoglobulinemic vasculitis, leukocytoclastic angiitis. Ddx: Infectious endocarditis, mycotic aneurysm,

cholesterol emboli, APLA, sepsis (GC, meningococcal), hemorrhage, cocaine, amphetamines, HIV, Hep C.

1. Wegener granulomatosis: Pathology: Necrotizing vasculitis of small to medium vessels (capillaries, venules, arterioles, small arteries); granulomas usually parenchymal. Etiology: idiopathic. Epidemiology: M = F; much more common in Caucasians; mean age ˜ 40 yo. Sx: sinusitis, epistaxis, ulcers, new ear infxns in adults, chronic cough, constitutional sx. Si: Chronic sinusitis, upper/lower respiratory tract granulomatous inflammation, & necrosis, renal failure & glomerulonephritis, HTN, subglotic stenosis, stridor, respiratory distress. Neuro si: Ocular findings (50%); PNS (15%) > CNS (8%) involvement; mononeuritis multiplex, retro-orbital pseudotumor (in 15%) → scleritis, episcleritis, uveitis, optic neuritis, conjunctivitis, retinal artery thrombosis, sz, CVA. Dx: ACR criteria (need 2/4): (1) nasal/oral ulcers, epistaxis, purulent discharge; (2) abnl CXR ⊕ nodules, infiltrates, cavities; (3) microhematuria, RBC casts; (4) granulomas in the vessel wall or peri/extravascular space. Exam: Periph neuropathy, proptosis, ↓ visual acuity, disconjugate gaze, CN palsies. CSF: Lymphocytic pleocytosis, ↑ protein, ↑ IgG. Serology: c-ANCA ⊕ (antiserine proteinase 3); Se 90% (in limited dz 40%), Sp 98%; dz activity correlation ˜60%; ↑ ESR, CRP, Plt; anemia, ↓, albumin. Imaging: MRI for retro-orbital infiltration, diffuse WM dz presumed due to vasculitis; cerebritis ↓ irregularly enhancing regions w/ edema. EMG/NCS: Acute ± chronic denervation, ↓ NCV, ↓ amplitude; myopathy; usu asymmetric involvement of nerves. Bx: Gold std = lung, sinus, less definitive if kidney (little to no Ig, immune complex, complement deposition); sural nerve bx ↓ vasculitis + noncaseating granulomas of small arteries, focal demyelination. Rx: Cyclophosphamide 2 mg/kg/day + prednisone 1 mg/kg/day; gradual steroid taper if responsive; maintenance of remission w/ MTX, esp if c-ANCA ⊕ despite clinical remission; fulminant dz ↓ start cyclophosphamide 3-5 mg/kg/day; TMP/SMX for PCP ppx; w/o Rx → < 1yr survival. Complications: Bacterial sinusitis (S. aureus), infxn 2/2 immunosuppression (PCP, HSV, mycobacteria, fungi, Legionella, S. pneumo), Rx related ↓ WBC, hemorrhagic cystitis, infxns, infertility.

2. Churg-Strauss syndrome (allergic angiitis & granulomatosis): Pathology: Eosinophilic necrotizing extravascular granulomas, necrotizing vasculitis of small to medium vessels (as for Wegener’s) + peripheral ↑ eos. Etiology: Unknown; Leukotriene receptor antagonist use a/w some cases. Epidemiology: Middle aged; M = F incidence. Sx: New onset/newly

progressing asthma (>95%), allergic rhinitis (70%), nasal polyps. Si: Triphasic evolution: (1) Prodrome → allergic rhinitis, asthma, polyposis. (2) Eosinophilia → ˜Löffler syndrome (transient pulm infiltrates, ↑ eos), chronic eosinophilic PNA/gastroenteritis. (3) Systemic vasculitis; sinus dz, purpura, nodules, eosinophilia, asthma, atopy, HTN, CHF, MI, ±renal failure; pulmonary nodules, infiltrates, hemorrhage, abd pain, bloody diarrhea. Neuro signs: Mononeuritis multiplex (˜75%), muscle vasculitis, panuveitis, keratitis, CVA vasculitis, optic neuritis, cranial neuritis. Dx: ACR criteria (need 4/6): Asthma, eosinophilia >10%, mononeuropathy, transient pulmonary infiltrates on CXR, paranasal sinus abnormalities,⊕ Bx. Exam: Paresthesias, weakness, atrophy, asymmetric sensorimotor polyneuropathy (legs > arms), AMS, cognitive changes, sz, SAH, intraparenchymal hemorrhage, psychosis. Serology: p-ANCA⊕ (MPO; Se 67%); anemia, ↑ ESR, ↑ IgE, ↑ eos > 10%. EMG/NCS: Myelinated, unmyelinated fibers affected in lower extremities > upper extremities; no conduction block (unlike in CIDP); ↓/[circled minus] SNAP. Bx: skin, lung, kidney; if abnl EMG/NCS sural nerve bx → vasculitic epineural necrosis; blood vessel ⊕ extravascular eosinophils. Rx: Prednisone 40-60 mg/day, w/ gradual taper over months; IV methylprednisolone for severe/refractory dz if immunosuppressants, e.g., AZT, MTX, cellcept, or cyclophosphamide fail; ESR & eos to follow dz activity, response to Rx in addition to clinical sx. Complications: CHF, MI.

3. Microscopic polyarteritis: Path: Pauci-immune, nongranulomatous necrotizing vasculitis (capillaries, arterioles, venules). Etiology: Idiopathic. Epidemiology: Mean age 30-50 yo; not a/w HBV (unlike PAN). Sx: Constitutional sx, rash, hemoptysis, abdominal pain, bleeding, arthralgias. Si: Pulmonary capillaritis ± rapidly progressing necrotizing glomerulonephritis, HTN, hemorrhage, palpable purpura. Neuro si: mononeuritis multiplex (˜60%), sz (˜10%), meningeal vasculitis (˜10%), ocular manifestations. Exam: Paresthesias, weakness, atrophy, wrist/foot drop, retinal hemorrhage, scleritis, uveitis, conjunctivitis, episcleritis. Serology: p-ANCA (MPO) ⊕ (80%); ± c-ANCA (proteinase 3) ⊕(40%); anemia, ↑ ESR,CRP. EMG/NCS: Multifocal axon loss, asymmetric, generalized polyneuropathy. Bx = gold std; Kidney, lung, muscle, skin (leukocytoclastic vasculitis), sural nerve (vasculitis of small vessels, axonal loss); rare microaneurysms. Rx: PDN 1 mg/kg/day + cyclophosphamide 1.5-2 mg/kg/day; PDN, MTX or azathioprine for maintenance IVIg, plasma exchange in pulmonary/renal failure; TMP/SMX for PCP ppx. Complications: Severe pulmonary hemorrhage.

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4. Henoch-Schonlein purpura: Path: IgA_1 deposition, complement activation via alternate pathway → vasculitis of small vessels, usu postcapillary; also

release of cytokines, inflammatory mediators. Etiology: Unknown; 2/3 ⊕antecedent URI by 1-3 wk; usu, self ltd, resolves over wks-mos. Epid: M:F 2:1; Mean age 5 yo; in adults & females can be severe, ↑ renal dz. Sx: Rash, arthralgias, arthritis, bloody diarrhea, colicky abd. pain, hematuria, constitutional sx. Si: Palpable purpura in dependent regions, symmetric arthritis, bowel ischemia/infarct, glomerulonephritis, nephritic syndrome, ARF, orchitis. Neuro si: ˜10%; HA, sz, AMS, focal deficits, behavioral Δs, brachial plexus neuropathy, GBS, mononeuropathies, vasculitis, episcleritis, keratitis, anterior uveitis, ↓ vision. Exam: BRAO, AMS, sz, behavioral changes, weakness, paresthesias (rare PNS involvement). Imaging: Cortical, WM CVA from vasculitis. Serology: ↑ IgA_1 (in 50%), ↑ IgA_1 circulating immune complexes, ↓ factor XIII (correlates w/ dz activity), ↑WBC, ↑ eos, ↑ plt, ↑ d-dimer, ↑ ASO titer (30%), ↓ CH50, ± ↓ C3, C4. Bx: IgA_1 deposits on direct IF, leukocytoclastic/necrotizing vasculitis; [circled minus] IgA_1 → r/o Wegener's. Rx: Supportive (avoid NSAIDs if GI/renal involvemt), prednisone if GI involvement, hemorrhage; ⊕ poor prognosis (nephritic syndrome, >50% crescents) → pulse dose steroids, cytotoxic agents.

5. Cryoglobulinemic vasculitis: Path: Reversible immune complex deposition at low temperatures in vessel walls; sequelae from thrombosis, hyperviscosity, immune activation.

Type I (25%) → mAb IgM >> IgG, IgA, ↑ serum levels, usu. Lymphoma, WM, MM; complement activation; sx 2/2 hyperviscosity syndrome, thrombosis

Type II (25%) → mixed; ⊕monoclonal RF, usu. mAb IgM against polyclonal IgG >> IgG-IgG, IgA-IgG; ↑ serum levels; MM, lymphoma, HCV, Sjögren's

Type III (50%)→ mixed polyclonal RF;± complement, lipoproteins; ↓ serum levels; infxns; 2/3 autoimmune → SLE, RA, PAN, SS, SCL, sarcoid, thyroiditis, HSP, Behçet's, PM, celiac dz

Etiology: 90% a/w ⊕ Hep C, 2/3 ⊕ chronic hepatitis; 5% ⊕ HBV; Other infxns, e.g., EBV, CMV, HIV, adenovirus, SBE, M. leprosy, Q fever, post-strep., syphilis, lyme, coccidioidomycosis, toxoplasmosis, malaria, schistosomiasis; autoimmune dz, lymphoma, CLL. Epid: ⊕ drug use,⊕ Hep C; F:M = 3:1; mean age 40-50 yo. Sx: Rash, ulcers, arthralgias, weakness (Meltzer triad in 25%-30% Types II, III), fever, abd pain, SOB, cough. Si: Recurrent lower extremity palpable purpura (Type II, III > Type I); ulcers (Type I), Raynaud's, nephritic/nephrotic syndrome (severity ∝ prognosis), HTN, arthritis, liver dz, HSM, hemorrhage, arterial thrombosis, abnl PFT, pulmonary infiltrates. Neuro si: Sensorimotor neuropathy (70%-80%) usu. Types II, III; retinal hemorrhage (Type I), pseudotumor cerebri, CVAs. Exam:

Pain, cold-induced paresthesias, weakness, foot or wrist drop, numbness, papilledema, impaired cognition, AMS, TIA/CVAs, impaired visuospatial fxn. Serology: collect at 37°C to avoid false neg;⊕ Hep C 70%-100%;[check mark] SPEP, UPEP; abnl LFT;⊕ hypergammaglobulinemia;⊕ RF (92%), ↑ESR,↑CRP,↓ CH_{50}, C3, C4. EMG/NCS: Distal symmetric progressive sensory > motor; isolated motor neuropathy in 5%; denervation pattern w/ nl. NCV. Imaging: MRI → multiple small WM lesions; Angiography → vasculitis/vasculopathy w/ focal narrowing, multiple irregularities, or occlusion. Bx: Intraluminal cryoglobulin deposits; leukocytoclastic vasculitis, fibrinoid necrosis, microinfarction, hemorrhage; sural nerve bx = loss of myelinated axons. Rx: ⊕ HCV → prednisone × 6 mo, PEG-IFN_a + ribavirin, if fail, trial of Rituximab; hyperviscosity → plasmapheresis, ± prednisone, cytotoxic agents to ↓ Ig production; malignancy → chemotherapy; autoimmune → prednisone, cyclophosphamide. Complications: Severe renal dz, systemic vasculitis.

BEHçET DISEASE

Path: Vasculitis of any size, arteries to veins. Etiology: Idiopathic. Epid: M = F; mean age 40 yo; Middle Eastern descent, Asians >> Caucasians, AA; HLA B51 association →↑ 6× dz risk. DDX: Infxn (viral/bacterial/fungal/PML), sarcoid, SLE, VKH, Sjögren's, MS, CA, (carcinomatous meningitis, lymphoma, glioblastoma cerebri). Sx: Oral ulcers, arthralgias, visual Δ, rash. Si: Aphthous ulcers, genital lesions, recurrent eye inflammation, erythema nodosum, folliculitis, skin ulcers, pulm hemorrhage due to aneurysmal rupture, painful scrotal/vulvar ulcers, ulcers of the GI tract ˜ IBD, migratory asymmetric arthritis, thrombophlebitis, ⊕ factor V Leiden 33%, arterial/venous thromboses, myo/pericarditis. Dx criteria: Recurrent oral ulceration ≥3/yr & ≥2 of the following: Recurrent genital ulcerations, eye lesions, skin lesions. ⊕pathergy test (sterile pustule at venipuncture site; common in Turkish, Japanese pts). Neuro features: 9% of Behçet's pts. M:F 3:1; mean age 20-40yrs. Eye (50%-80%): anterior uveitis—pain, photophobia, conjunctivitis, blurry vision, keratitis; posterior uveitis—blindness from retinal vasculitis (12% of acquired blindness in

Japan). Brain/spinal cord —parenchymal vs. nonparenchymal (Middle East/ France >> elsewhere); 40% mortality rate w/ CNS dz. Exam: ⊕ cells on slit lamp; retinal vasculitis; confusion, personality changes, ataxia, papilledema, weakness, pseudobulbar palsy, extrapyramidal signs. CSF: ↑ protein, leukocytosis, granulocytosis. Serology: ↑ serum IgG, IgA, IgM, CRP, ESR, α_2-globulin; r/o thrombophilia. Imaging: MRI T2 bright edema, MRV ⊕

thrombus. Bx: meningoencephalitis, multifocal necrotic foci, demyelination, gliosis, axonal injury. Rx: Mucocutaneous → topical steroids, colchicine, dapsone, thalidomide, levamisole, or IFN-α. Ocular/CNS → 1-2 mg/kg/day prednisone or IV 1 g/day solumedrol × 3 days; chlorambucil 0.1-0.2 mg/kg/day; AZT/CsA/cyclophosphamide/chlorambucil if life-threatening, severe ocular/CNS dz.

Key Features of Neuro-Behçet Dz (NBD)

	Parenchymal NBD	**Nonparenchymal NBD**
Neuro findings	Hemiparesis, hemisensory loss, sz, cognitive dysfxn, psychosis, encephalopathy, dementia, ataxia, sphincter dysfxn; pyramidal, brain stem, spinal cord signs (latter is rare, poor prognosis); diffuse meningoencephalitis (75%)	CVA ↑ICP (from VST), 25%→HA, papilledema, focal deficits, seizures, coma
MRI	**Mesodiencephalic junction**, brainstem, BG, subcortical hemispheric lesions, CBL, spinal cord (>2 vertebral segments) **T2 hyperintensities** reversible → edema; nonreversible → Wallerian degeneration Acute → ± contrast enhancement	Cerebral VST ± venous infarcts; aneurysms, extracranial dissection MRS →↑ lactate, ↓ NAA peak
CSF	PMN pleocytosis ± protein; rare OCBs	Wnl, except opening pressure
Pathophys	Inflammatory perivasculitis	Thrombus (venous sinuses, cerebral veins >> arteries); aneurysms of large arteries
Pathology	WM > GM involvement; multifocal necrotic foci,	Venous infarcts (WM ± GW jxn, w/

	meningoencephalitis; demyelination; gliosis, axonal injury in chronic lesions, atrophy (brainstem “cortical = chronic NBD)	hemorrhage); SSS thrombosis (b/l cerebral convexity WM; deep cerebral vein thrombosis (BG, thalami)
Rx	Methylprednisolone, immunosuppressive agents	VST → anticoagulation
Prognosis	Acute lesions ± reversible w/ steroids	Better if treated early

SERONEGATIVE SPONDYLOARTHROPATHIES (RF [circled minus])

ANKYLOSING SPONDYLITIS

Path: Chronic systemic inflammatory dz of the sacroiliac joints, spine, peripheral joints. Etiology: 1° vs. 2° (⊕ reactive arthritis, psoriasis, ulcerative colitis [UC], Crohn dz [CD]). Epid: Late teens—40s; M:F = 3:1 clinically; M = F radiographically; HLA-B27 association (90% Caucasians, 50%-80% others). Sx: Back pain, morning & nocturnal stiffness >1h; hip, shoulder pain, ↓ w/ activity, ↑ w/ rest. Si: Sacroiliitis, ↑ spinal mobility, ↓ chest expansion, discitis, enthesopathy, aortic insufficiency. AV conduction block, restrictive lung dz, IgA nephropathy, amyloidosis. Neuro si: Anterior uveitis (25%-30%), resolve over months, commonly recur; atlantoaxial subluxation (20%) → cervical myelopathy (86% males), cord compression; C-spine stenosis; epidural hematoma (deficits at higher level than fx); hemorrhagic cord contusion, intramedullary hematoma, cord transaction, cauda equina syndrome [⊕ h/o longstanding Ankylosing Spondylitis (AS)]; vertebral fx → nerve injury. Dx Criteria (New York): LBP ⊕ inflammation > 3 mo, L-spine ↓ motion in sagittal, frontal planes, ↓ chest expansion; b/l sacroiliiitis ≥ grade 2, unilateral sacroiliiitis > grade 3. Exam: Ocular →unilateral, painful ocular erythema, photophobia, ↑ lacrimation, blurred vision; Slit lamp—keratic precipitates, hypopyon, posterior synechiae, peripheral anterior synechiae, posterior subcapsular cataract, anterior vitreous cells, vitritis, retinal vasculitis. Neuro → neck pain from C-spine fx (usu. C5-6, C6-7); cervicothoracic kyphosis; loss of lumbar lordosis; back

pain ± radiation to legs = r/o CES; gradual onset leg pain, mild sensory sx, variable motor, bowel, bladder involvement, impotence; radiculopathies from foraminal stenosis, disc dz, fx; muscle atrophy. Serology: ↑ ESR, ↑ CRP ∝ dz

activity 75%; normocytic anemia; ↑ alk. phos., ± ↑ CK, ↑ serum IgA level; HLA B27 status; ANA, RF [circled minus];[check mark]VDRL, ACE, RPR, PPD. Imaging: Fluorescein angiography → retinal vasculitis; X-ray spine→ bamboo spine; symmetric sacroiliiitis, subchondral sclerosis; T10 vertebral osteitis (Romanus lesion, early sign); CT spine → asymmetric laminar, pedicular, spinous process erosion; MRI → thickened nerve roots, irregular widening of L/S thecal sac; dural sac arachnoid diverticulae; ⊕ Romanus lesion. EMG/NCS: Radiculopathy. Rx: NSAIDs; uveitis → topical corticosteroids, anti-inflammatories; vision impairment → systemic corticosteroids; if steroid-unresponsive → MTX, AZT, CsA, mycophenolate mofetil, cyclophosphamide, chlorambucil, or trial of TNF-α inhibitors; C-spine dz → halo for stabilization, immobilization in pre-fx position; Atlantoaxial subluxation + myelopathy→ fusion; Spinal stenosis + neuro sx → decompressive surgery.

REACTIVE ARTHRITIS

Path: Postinfectious sterile inflammatory synovitis ˜1 mo after urogenital/enteric infxns. Etiology: Chlamydia, Salmonella, Shigella, Yersinia, Campylobacter, Clostridium; self-limited, resolves in 3-12 mo. Epid: 20-40 yo; enteric M = F; urogenital M > F, 9:1; HLA-B27 ⊕ (75%); uncommon in African Americans. Sx: Dysuria, GU irritation, discharge, conjunctivitis, arthralgias, LBP, diarrhea, abd. Pain. Si: Constitutional sx, asymmetric arthritis, LE > UE w/ sparing of hands, wrists, infectious ileitis, colitis, urethritis, prostatitis (80%), epidydimitis, hemorrhagic cystitis, vulvovaginitis, salpingitis, cervicitis, circinate balanitis (30%), keratoderma blennorrhagicum (15%), painless oral ulcers (25%), dystrophic nails, IgA nephropathy, erythema nodosum, renal amyloidosis, thrombophlebitis, rare carditis, conduction block, aortitis. Neuro si: Ocular → sterile conjunctivitis (60%), anterior uveitis (20%) usu. unilateral, ⊕ HLA-B27, episcleritis, keratitis, corneal ulcers. Cranial: Cranial neuropathy, spondylitis (25%), rare C-spine involvement; rare encephalopathy, transverse myelitis. DDX: Arthritis due to gonococcal infxn, sepsis, psoriasis, IBD, RA, AS, rheumatic fever, gout/pseudogout, Lyme, Behçet, HCV, HIV. Dx: Serology: synovial WBC ↑, Gm. stain [circled minus], cx [circled minus], crystal [circled minus]; ↑ ESR, ↑ CRP (dz activity); normocytic anemia, ↑ WBC, ↑ plt; ↑ serum IgA level; HLA-B27 status; ANA, RF [circled minus];[check mark] Chlamydia PCR, HIV, HCV. Imaging: Asymmetric sacroiliitis. Rx: (1) Arthritis → ice packs, warm compress, exercise; NSAIDs, Rx Chlamydia w/ doxy/minocycline 100 mg bid × 3 mo; intra-articular steroids, refractory sx → sulfasalazine 2-3 g/day; trial of MTX, azathioprine, cyclophosphamide, TNF-α inhibitors. (2) Uveitis → ophthalmology eval; spondylitis & neuro complications → as above for AS. (3) transverse myelitis → sulfasalazine +

MTX.

ENTEROPATHIC (IBD-ASSOCIATED) ARTHRITIS

Path: GI tract inflammation → transmigration, deposition of Ag in other tissues → inflammation/autoimmunity due to molecular mimicry. Etiology: A/w Ulcerative Colitis (UC), Crohn Disease (CD); others include Whipple dz, celiac dz, microscopic colitis, intestinal bypass arthritis. Epid: M = F, 15-35 yo; ↑ US, Northern/Western Europe, HLA-B27 ⊕ = ↑ spondylitis risk 7×;⊕ 55%-70% in IBD. Sx: Abd pain, diarrhea, wt loss, arthralgias, back pain, stiffness ↓ w/ activity, ↑ w/ rest. Si: Peripheral arthritis, sacroiliiitis, spondylitis; UE predominance in UC vs. CD; migratory asymmetric nondeforming pauciarticular arthritis, enthesitis, hematochezia, pyoderma gangrenosum (UC), aphthous ulcers, erythema nodosum (CD), 2° amyloidosis, arterial, venous thrombosis. Neuro si (Neurology 1995;45:416): Eye: acute anterior uveitis (5%-15%); Vertebrae: Spinal arthritis, symmetric sacroiliiitis (10%; M:F, 3:1, does not correlate w/ IBD dz activity); NMJ/muscle: Myasthenia gravis; myopathy, myositis (CD > UC); PNS: Peripheral neuropathies (˜30% of all neuro sx)—AIDP (UC), GBS, sensorimotor polyneuropathy, mononeuropathy, brachial plexopathy, mononeuritis multiplex, cranial neuropathy, e.g., Melkersson-Rosenthal syndrome (CD)—facial nerve palsy, intermittent orofacial swelling, tongue fissuring; sensorineural hearing loss (UC), peripheral neuropathy pathophysiology axonal > demyelinating (70% vs. 30%). Spinal cord—progressive myelopathy (↓ B_{12} in CD), transverse myelitis (UC, Jo-1 ab ⊕); epidural, subdural empyema (CD). CNS—VST (UC > CD), CVAs (∝ dz activity), vasculitis, optic neuritis, MS (UC), encephalopathy (Wernicke's, selenium, vasculitis), seizures (usu complication of Rx). Exam: Anterior uveitis, conjunctivitis, sensory loss, paresthesias, HA, focal deficits, AMS, sz. Serology: Synovial fluid ˜50 K WBC, PMNs, [circled minus] crystals, cx; ↑ ESR, ↑ CRP, HLA-B27 status; ANA, RF [circled minus]; UC → ⊕ p-ANCA (60%; [circled minus] anti-MPO); Crohn's → ⊕ anti-S. cerevisiae ab (50%); anemia, ↑ plt; [check mark] coags, factor V Leiden, homocysteine, anticardiolipin ab, lupus anticoagulant; ↓ B_{12}, B_6; [check mark] antiendomysial ab, anti-TTG ab, HIV status. Imaging: MRI brain & spine if ? CVA, VST, MS. Rx: IBD extraintestinal manifestations → sulfasalazine,

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PDN; AZT, 6-MP, MTX, CsA, infliximab; avoid NSAIDs; Spondylitis → ˜ like AS; Uveitis → ophtho eval; correct nutritional deficiencies; thrombosis → anticoagulation; sz → AED, d/c offending agent.

PSORIATIC ARTHRITIS

Path: Inflammatory arthritis in pts w/ psoriasis inflamed synovium, ↑ vascularity, ↓ cellularity, hyperplasia vs. RA; ⊕ enthesitis. Etiology: Unknown. Epid: 5%-10% of pts. w/ psoriasis; 2% axial involvement; HLA B39 ˜ polyarthritis; HLADR4 ˜RA like; HLA B27 ˜ sacroiliiitis, spondylitis; M:F 3:1 for spinal involvement; else M = F; age 35-50; ↑ 1° relatives; ↑ in HIV ⊕. Sx: Rash, arthralgia, neck pain, weakness, numbness, eye pain. Si: Asymmetric oligoarticular dz (DIP, PIP, MCP, MTP, knees, hips, ankles), nail pits (90%), onycholysis, hyperkeratosis, discoloration, dactylitis (30%), psoriasis; more aggressive PA if ⊕ HIV; aortic insufficiency (late finding). Neuro si: Asymmetric sacroiliiitis, vertebral dz (20%-40%), atlantoaxial subluxation, T/L-spine usu spared; ocular dz—conjunctivitis (20%), bilateral, chronic uveitis ± posterior, iritis, (7%-33%)—a/w axial involvement; polyneuropathy (rare). Exam: Anterior uveitis, conjunctivitis, scleritis, papillitis, retinal vasculitis, chronic cervical/lumbar pain, weakness, numbness. Serology: ANA, RF [circled minus]; [check mark] HIV ESR, CRP, anemia ∝ dz activity; ↑ uric acid, HLA-B27 ⊕ 50%-70% in axial dz. Imaging: X-ray of phalanges → pencil-in-cup deformity; joint erosions, [circled minus] juxtaarticular osteopenia; C-spine instability, atlantoaxial subluxation. EMG/NCS: Chronic distal symmetric sensorimotor axonopathy. Rx: Arthritis → NSAIDs, intra-articular steroid injections; trial of TNF-α inhibitors; psoriasis → MTX; axial dz ˜ Rxfor AS; uveitis → ophthalmology eval, topical steroids.

IDIOPATHIC INFLAMMATORY MYOPATHIES

Includes dermatomyositis, polymyositis, inclusion body myositis. Can be 1° or 2°. See Myopathy chapter.

NEUROLOGIC COMPLICATIONS OF IMMUNOMODULATORY THERAPY

QJM 2006;99:6.

Allopurinol: MOA: Xanthine oxidase inhibitor; SEs: Paresthesias.

Azathioprine: MOA: Purine synthesis inhibitor; SEs: Vision Δs, potentiates NM blockade.

Colchicine: MOA: Antimitotic; blocks microtubule polym.; SE: Periph neuritis, myopathy.

Corticosteroids: MOA: Suppress CM & humoral immunity, induce apoptosis, anti-infl. (inhibit PLA2, COX-1, COX-2); SEs: Myopathy, psychosis, euphoria, depression, cataracts.

Cyclophospamide: MOA: DNA alkylating agent; SEs: Encephalopathy.

Cyclosporine: MOA: Calcineurin inhibitor, suppress T-cell function; SEs: Myopathy, myalgias, leukoencephalopathy, seizures, confusion, paresthesias.

Cytokine: Inhibitors [adalimumab (TNF), anakinra (IL-1), etanercept (TNF), infliximab (TNF)]: MOA: Inhibit actions of pro-inflammatory cytokines; SEs: Demyelination (TNF), sz/drowsiness (inflix), drowsiness/dizziness paresthesias/neuralgia (ada).

Dapsone: MOA: Folate synth inhibitor, immunosupp.; SEs: HA, psychosis, p. neuropathy.

Hydroxychloroquine (antimalarial): MOA: Interfere w/ antigenic processing by alkalinization of cellular compartments; SEs: Macular damage, ototoxicity, tinnitus, vertigo, psychosis, myopathy.

Leflunomide: MOA: Pyrimidine synthesis inhibitor; SEs: HA, dizziness, asthenia, paraesthesia, neuropathy.

Mycophenolate mofetil (cellcept): MOA: Purine synth inh; SEs: insomnia, HA, tremor.

NSAIDs: MOA: Nonselective COX inh; SEs: HA, dizziness, tinnitus, aseptic meningitis.

Pencillamine: MOA: ↓T-cell, mφ inhibition, ↓RF, ↓IL-1; SEs: RA or SLE-like synd, PM/DM.

Sulfasalazine: MOA: ↓ inflammatory mediator synthesis; SEs: ataxia, aseptic meningitis, vertigo, tinnitus, insomnia, depression, hallucinations.

Tacrolimus: MOA: FKBP12 inhibitor, calcineurin inhibitor; SEs: HA, insomnia, paresthesias, confusion, sz, tremors, blurred vision, depression, dizziness, convulsions, incoordination, encephalopathy, psychosis.

CONSIDERATIONS IN CHRONIC IMMUNOSUPPRESSION

↑ risk infxn (incl OIs—fungal, Listeria, JCV, CMV, VZV) & malignancy. Caution: Severe infxn can p/w low-grade temps, minimal sx or atypical presentation. Adrenal insufficiency w/ discontinuation of steroids. Vaccinations: Pneumococcal, influenza, Hep B; avoid live vaccines in pts on biologic agents. TB testing prior to initiation of Rx. Consider need to hold agents in surgery, severe infxn. Review pregnancy plans/birth control w/ reproductive age women.

Monitoring of Specific Immunotherapy

Drug	SE	Monitoring/Care
NSAIDs	GI bleed; inc. CV risk	GI ppx
Corticosteroids	HTN, hyperglycemia, osteopenia, ↑WBC	Routine BP, glucose; Vit D/Ca (+DEXA); GI ppx; PCP ppx
AZT, chlorambucil, cyclophosphamide, gold penicillamine, MTX, sulfasalazine	Myelosuppression	Periodic CBC, urine protein for gold/ penicillamine[a]; urine cytology for cyclophosphamide[b]; PCP ppx
Cyclosporine	Renal dysfxn, HTN, anemia, high K+	Routine BP, periodic CBC, creatinine, K+; PCP ppx
Cytokine inhibitors	Injection site rxn, ↓ WBC (IL-1), ↑ heart failure/LFT Δ	Routine CBC + LFTs for TNF)

[a] May cause proteinuria.

[b] May cause hemorrhagic cystitis.

Neuro-Oncology

Brain tumors: Si/sx: Usu nonspec, subacute, prog; 2/2 local invas, adjacent compress, ↑ICP. Depends on location, size, growth rate (not tumor type). Nl neuro exam (even no papilledema) does NOT exclude tumor. Can have: Localizing sxs: 2/2 cortical irritation/local dysfxn: partial szs, focal defs (aphasia, c/l wkns, visual field cut) False localizing sxs: Horiz diplopia (CN VI palsy 2/2 ↑ICP), i/l hemiparesis (uncal herniation).

Szs = most common focal sx. Partial or generalized, stereotyped. Cortical tumors >> infratentorial; low-grade > high-grade gliomas. Presenting si/sx in: 50% of melanoma mets, oligodendrogliomas, hemorrhagic tumors. More sz comps in brain tumor pts: prolonged postictal state (up to 24 h), perm neuro defs, ↑ICP from sz can → decompensation. Causes of szs in brain tumor pts: Tumor (new dx/ progression), radiation necrosis/encephalopathy, metabolic (hypo-Na, hypoxia, hypo-Ca, uremia, glucose), vascular (ischemic stroke, ICH, intratumoral hemorrhage, cerebral venous thrombosis), infxn (meningitis, encephalitis, UTI, bacteremia, PNA), occas chemo (methotrexate, cytarabine, L-asparaginase, taxol, ifosfamide, nitrosoureas, cisplatin).

HA (common, nonlocalizing): ˜50% of brain tumor pts. Caused by traction/pressure/ischemia/ invas of pain-sensitive structures. ˜17% have “classic” sxs from increased ICP: constant, prog, moderate-severe, holocranial, worse supine, worse in am, vomiting w/o nausea, increased w/ Valsalva. Beware: New HA in older patient, Δ in HA pattern or quality, “migraine” w/ persistent neuro def, “sinusitis” w/ neuro sxs/mult antibiotic failures/progression w/o fever.

Focal neuro defs: Often 2/2 edema, & resp to steroids. “Stroke-like” presentation: sz >> hemorrhage >> tumor embolus.

Syncope: Transient ↑ICP fol Valsalva→ LOC. Must disting from sz.

Altered mental status → Coma: ↑ICP, herniation; Emergency. Mech: Edema, venous/ventric obstr, nonobstr hydro.

Syndromes

1. Foster Kennedy, synd: Unilateral vision loss, contralateral papilledema. Cause: Sphenoid ridge tumor (often meningioma).

2. Parinaud synd: Light-near pupil dissociation, impaired upgaze, retraction-convergence nystagmus. Cause: Tectal compress/involvement from pineal

region tumor/tectal glioma.

3. Obstr hydro: HA, N/V, confusion, ataxia. Cause: p-fossa tumors: cerebellar astrocytoma/medulloblastoma/ependymoma.

4. Frontal Lobe Synd: gait apraxia, incontinence, memory loss, affect Δs. Bifrontal tumor/unilateral frontal tumor w/ contralateral compression.

Spinal cord tumors: Si/Sx: Depend on level & location (epidural/intradural; extramedullary/intramedullary). Most p/w prog pain & myelop. Fast-growing lesions (mets) don't localize as well as slow-growing lesions (primary tumors). Lesions may be several levels above clinical level.

P.250

Spec Si/Sx: Pain (common): >90% of epidural mets; less w/ intradural tumors. Local pain 2/2 ischemia/traction/compress. Classically: Worse lying/ w/ Valsalva; better w/ ambulation (unlike disc pain). Red flag: Thoracic pain (atypical for disc). Spinal tenderness/ instability (Emergency). Wkns: From cord/root compress. Root: Radicular (LMN) wkns at lesion level. Cord: Spastic paraparesis (UMN) wkns below lesion level: proximal leg wkns flexors > extensors, arms extensors weaker than flexors. Sensory loss: Distal → proximal (faster than periph neurop). Scalp numbness w/ C2-3 lesions. Sacral sparing w/ intramedullary lesions. Sensory loss w/o pain/wkns rare. Cord compress (late sign): Emergency if neuro compromise/radicular pain. UMN wkns, spasticity. ↓ rectal tone, bladder retention w/ overflow, sacral sparing. Cauda equina: Emergency. LMN leg wkns (distal > proximal), sensory Δ, sphincter dysfxn.

Ddx: Leptomeningeal cancer, paraneoplastic/radiation myelop, infxns (abscess, myelitis, fungal/TB meningitis), herniated disc, vertebral fracture, occas intrathecal chemo.

Workup and diagnostic studies

HPI/exam guides w/u. Despite imaging, generally need tissue for dx & Rx.

Imaging: MRI w/ gadolinium more sensitive than CT, enhances BBB breakdown, often reflects malig. Exceptions: Some benign tumors enhance vividly, some malig don't (˜40% nonenhancing gliomas are high-grade). MRS can help disting tumor from other process (↓ NAA (neuron terminals); ↑ choline (cell membrane); ↑ lactate (necrosis/anaerobic metab) tumor/stroke/infxn. FDG-PET may disting high vs. low grade/radiation necrosis. CT if pt unstable/suspect hemorrhage/MRI unavail.

- Imaging approach: Brain tumor: MRI with gado. Locations: Supratent = astros, menings. Infratent = vestib Schwannoma, ependymoma,

glioma/pineal = pineoblastoma, germ cell tumors. Sellar = pituitary adenoma, craniopharyngioma, meningioma. Spinal tumor: MRI entire spine (often >1 lesion AT OR ABOVE clinical level). Vertebral compress fxs may harbor tumor. Locations: Epidural: Seen better precontrast; more common; mets (breast, lung, prostate); p/w sig local/radicular pain. Intramedullary: Seen better postcontrast; ependymoma, astrocytoma, primary >> mets; p/w pain, sens loss, sphincter dysfxn (cord synd).

LP: CSF cytol for tumors that spread to CSF/meninges/cord: Lymphoma, medulloblastoma, pineoblastoma, germinomas, ependymoma, choroid plexus (CP). Mets to CSF sig affects Rx options & prog. Abnl CSF cytology highly spec, but nl CSF does NOT exclude tumor. Process CSF promptly (cells begin to lyse w/in 1 h, 40% lysed in 2 h).

Spec CSF findings: Primary CNS Lymphoma: ↑ protein, ↑ lymphs, nl glucose. Malig lymphoid cells in ˜30% pts. Flow cytometry & IgH gene rearrangement good for paucicellular CSF. Leptomeningeal mets: WBC mildly ↑(5-50), ↑protein, ↓ glucose. Se > 90% w/ three LPs, BUT nl/minimally abnl CSF does NOT exclude leptomeningeal tumor.

Biopsy: Bx alone if tumor highly sensitive to chemo (germ cell tumors, lymphomas).

Resect if surg curative or w/ minimal risk. Biopsy occas not necessary (e.g., known metastatic 1°, brainstem gliomas or optic pathway glioma (risks >> benefits), + tumor markers & characteristic imaging (i.e., germ cell tumors).

Systemic cancer w/u: Consider prior to biopsy (Pan-CT, PET, mammogram, colonosc). Avoid steroids prior to biopsy if consider lymphoma/infxn.

PRINCIPLES OF TREATMENT

Corticosteriods: Counteract VASOgenic edema by ↓ing permeability of BBB. Control sxs from peritumoral edema or ↑‘d ICP (sxs improve w/in hrs, peak effect in 24-72 h), days to ↓ ICP. Steriods ↓ enhance on MRI/CT. Direct transient cytotoxic effect on lymphoma. Before starting, look for infxn/osteoporosis/PUD/DM. Consider drug interactions (esp phenytoin).

Indications: (1) Symptomatic edema/herniation or radiographic mass effect. (2) Clin/radiographic cord compress. (3) Sx recurrence (double dose, slow taper). (4) Perioperatively (biopsy or resection); partic if sig mass effect.

Dexamethasone: Preferred steroid. Less mineralocorticoid activity = less fluid retention. Long half life (dosed bid-qid for GI tolerance). Typical start: 10 mg × 1 then 4 mg q6h.

Long-term side effects: Immunosuppression: ↑ risk of infxn, including PCP/PJP. Cardiovasc: Exac of CHF, HTN, edema. Endocrine: Impaired glucose tolerance, DM, wt gain, adrenal insuff. GI: Peptic ulcer dz, upset stomach/heartburn, constip. Psychiatric: Insomnia, agitation, psychosis. Neurologic: Tremor, myop, hiccups. Skeletal: Osteoporosis, compress fxs, aseptic necrosis. Dermatologic: Skin thin & breakdown, hair thin, flushing, night sweats.

Prophylaxis: PCP/PJP ppxfor >6 wk steroids: TMP-SMX SS PO QD or DS qMWF. GI ppx for perioperative/high dose steroids: PPI daily. Stress dose steroids occ required. Calcium + vitamin D may prevent osteoporosis.

P.251

Anti-seizure medications: Prophylaxis: No proven benefit of ppx AEDs in brain tumors; often used anyway. Used after craniotomy (limited data); taper after 1 wk. Hemorrhagic tumors/melanoma mets/oligodendrogliomas: consider ppx AEDs.

Symptomatic Rx: Initiate AEDs after first sz in brain tumor pts. High recurrent sz risk, high mort from status. Monotherapy preferred. If recurrent szs, ↑dose before new AED. Prefer AEDs that don’t induce P450 (if anticipating chemo): LEV, LTG, TOP, GPN, lacosamide; Avoid: PHT, CBZ, PBT.

Surgery: Decompress for mech compress causing acute sxs, Max resection for 1° CNS tumors/solitary mets. Except: Highly chemo-sensitive (lymphoma, germ cell tumors). Functional mapping & electrocorticography to avoid functional ctx/find sz focus. VP shunt/EVD to manage hydro/↑ ICP. Surgical fixation for spinal instability prior to radiation.

Radiation therapy (XRT): General principles: Tissue dx nearly always required prior to RT (imaging 10% FPR). Dose measured in gray (Gy), w/ units J/kg. SI unit of absorbed dose. Fraction = dose of each Rx. External-beam radiotherapy = photon or proton beams from external source. Brachytherapy = radiation source placed in/near tumor. Small <3 cm lesions can be Rx’d w/single fraction, larger require fractionated Rx (preserve nl tissue). IMRT = intensity modulated RT: computer optimizes configuration of moving apertures to conform dose to targets & spare critical structures. SRS = Stereotactic radiosurgery: 1-5 fractions of high intensity radiation: Gamma knife, CyberKnife, Linac (linear accelerator) based, & proton based approaches biologically equal effect on tumors. Head fixation crit for accuracy—usu req rigid head frame placed by neurosurg. Proton: Only few centers. Generally for pedi cases/difficult anatomy (cav sinus, skull base).

Typical dosing schedule: Whole brain: qd; 3 Gy × 10 (most common), 2.5 Gy

× 14, 4 Gy × 5 (leptomeningeal dz). High grade 1° brain (GBM): qd; 2.0 Gy × 30. Intermediate grade 1° brain (meningioma): qd; 1.8 Gy × 28-33. Acute radiation: Emergent XRT generally uses larger fields (exposing more nl tissue). Urgent tx for: tumor-related cord compress, new CN palsy, symptomatic brain mets. Usu Rx w/ steroids × 8-24 h before XRT.

Chemotherapy: General principles: CNS tumors seldom cured by chemo alone. Neoadjuvant chemo = prior to surgery/XRT. Concurrent chemo = during XRT. Adjuvant chemo= after surgery/XRT.

Common Chemo Regimens

Regimen	Setting	Common Side Effects
Temozolomide	Glioma	Nausea, HA, fatigue, myelosuppression, hepatotoxicity, constipation
Carmustine (BCNU)	Polymer wafer implant for glioma	Nausea, myelosuppression, pulm fibrosis, leukemia
PCV (procarbazine, CCNU, vincristine)	Oligodendroglial	Myelosuppression
Cisplatin, vincristine, & cyclophosphamide or CCNU	Medulloblastoma	Nausea, renal insufficiency, peripheral neurop, myelosuppression, hemorrhagic cystits

PRIMARY CNS TUMORS

Epid: 1° brain tumors = 2% of cancers = ˜11.5-14.1/100,000 person-yrs;↑ing. M > F (except meningioma). Caucasians > Latinos > African Americans (incl mening) > Asians & Native Americans. Glioma 50% > meningeal 20%-40% > pituitary 10%-20% > cranial & spinal tumors > PCNSL 3%-5%. Very rare to have systemic mets.

Risk factors: ↑ glioma in 1° relatives. HIV/immunosuppressed ↑ 1° CNS lymphoma. Several genetic synd a/w 1° BTs, prior XRT ↑ meningiomas, astrocytomas, sarcomas.

Classification: WHO system (named for cell of origin). Gliomas most

common (glial cells) Gliomas not easily biopsied are named for location (brainstem glioma, optic glioma, etc.). Tumors w/ more than one cell type = “mixed” (mixed gliomas: oligoastrocytoma, etc.) Grade based on appearance, & indicates tendency to spread/growth rate/prognosis. Unlike other tumors, not based on lymph node/metastatic spread (RARE for CNS tumors).

GLIOMAS

High grade: Glioblastoma (GMB) & anaplastic astrocytoma: (NEJM 2008; 359:492) Diffusely infiltrating, arise from glial cells, typically in white matter.

Epid: Most common brain tumors (70% of malig tumors, 5/100,000 people). ↑ing, unclear why (? improved imaging). Ionizing radiation is only nongenetic risk factor.

Dx: Presentation: Szs & HA common; also focal defs/confusion/memory loss. Imaging: Heterogeneously/ring enhancing mass w/ edema. MRI: Hypointense T1, inc T2 (edema & tumor). CT: Hypodense ± hemorrhage, ± central necrosis (hypodense).

Location: Typically found in cerebral hemispheres, brainstem, thalamus. Path: Grade based on most malig portion. AA/WHO III: Increased cellularity, moderate pleomorphism, no necrosis or vascular proliferation. GBM/WHO IV: Hypercellularity, pleomorphism, microvascular prolif, necrosis ± pseudopalisading.

Rx: Surgery → XRT ± temozolomide (Stupp NEJM 2005;352:987).

Surgery: Dx, improve sxs, max resect improves recurrence & survival (3-4 mo w/surg alone). Radiation: 60 Gy (1.8-2.0 Gy fractions 5 d/wk × 6 wk). Prolongs survival (7-12 mo w/surg + XRT). Recurrence often in XRT field, inc dose no benefit. Brachy/SRS/Proton no benefit. Chemo: (Temozolomide = TMZ = Temodar) GBM Rx (chemorad → adjuvant chemo). Dosing: During RT = 75 mg/m^2, after RT = 150-200 mg/m^2 × 5 d, q 28d × 6-12 cycles. MGMT (DNA methylation repair enzyme) silencing increases sensitivity to TMZ. Monitor liver function, blood counts, PCP/PJP prophylaxis while on TMZ + XRT. Recurrence: Almost all recur (median = 6.9 mo after XRT + TMZ). 1 mo MRI ↑ enhance in 40% = half “pseudoprogression” (vascular permeability from XRT).

Rx after recurrence: Repeat surgery in some cases (edema), anti-angiogenic therapy increasingly important (decreases vessel permeability, MRI enhancement). Bevacizumab approved for progression following standard therapy.

Prognosis: Age, grade, resection, performance status, MGMT status influence survival. Long-standing sxs, no AMS, small size may also improve survival. 90% recur at original site.

RPA Stages for Survival w/ GBM Treated w/ RT + TMZ

Stage	Characteristics	Median OS	2-yr OS
III	Age <50, PS 0	17 mo	32%
IV	Age <50, PS 1-2 Age ≥50, surgery, MMSE ≥27	15 mo	19%
V	Age ≥50, biopsy only *or* MMSE < 27	10 mo	11%

OS = Overall survival. *JCO* 2006;24:2563.

Gliomatosis cerebri: (J Neurooncol 2006;76:201) Rare, diffuse neoplastic glial infiltrate (≥3 lobes), monoclonal. Arise de-novo OR from pre-existing glial tumor.

Dx: Clinical sxs nonspec: sz, increased ICP, altered mental status, focal defs.

Ddx: MS, CNS vasculitis, leukoencephalopathy, encephalitis, PML, Behçet's. Can be astrocytic, oligodendroglial or mixed, usu Grade III (anaplastic).

W/U: MRI better than CT, but nonspec: asymmetric/heterogeneous hyperintense T2, nonenhancing, thickening of corpus callosum, loss of gray-white differentiation.

Rx: No standard Rx. Not amenable to surgery because of extent of spread. WBXRT-high rate of stabilization, impact on survival unclear. Up front chemo benefits some pts, may be preferred: Tx w/TMZ/PCV (procarbazine, CCNU, vincristine).

Prognosis: Median survival in large study = 14.5 mo (11 mo w/ no tx). Better prognosis: Young, high performance status, lower grade, male, oligodendroglial type. Poor prognosis: ↑ gray matter involvement (Neurology 2009;73:445).

Low-grade gliomas: (Oncologist 2006;11:681) 20%-25% of CNS glial tumors, less common than high grade. Median age at dx: 40s for adults, teens for pilocytic astrocytoma.

Dx: Szs common (85%) (vs. 69% in AA, 49% GBM). Imaging: MRI: Usu nonenhancing, little mass effect/edema. Low T1 signal, High T2 signal (best seen on T2). Arise in WM, extend to cortical surface (Exception: Pilocytic astrocytoma). Hypometabolic on PET (unlike oligodendrogliomas). Grade: WHO I: Pilocytic astrocytoma, subependymal gaint-cell astrocytoma (SEGA); WHO II: diffuse astrocytoma, PXA. ↑ MR perfusion may reflect transformation to high grade.

Rx: Optimal Rx unclear. Surgery: Controversy re: early resect versus obs & delay intervention. Surgery for large, symptomatic tumors; Max safe resection may improve survival. XRT: Given at dx; ↑ time to progress & ↓ szs but no survival benefit. Typical dose = 45-54 Gy. Obs if small, min. sxs. Oligodendroglial tumors more response to chemo, but role of chemo unclear. Szs: Mgt difficult, may require surgery.

Prognosis: 1p/19q deletion a/w superior survival in low-grade oligodendrogliomas. Most eventually transform to high grade tumors. Poor prognostic factors (1 point each): Age > 40, astrocytoma, >6 cm, crossing midline, neuro defs prior to surgery:

(0-2 = “low risk,” median survival 7.8 yr; 3-5 = “high risk,” median survival 3.2 yr) (JCO 2002;20:2076).

Recurrence: Sometimes difficult to disting from radiation necrosis (may require bx). Consider salvage surgery, radiation, chemo.

Pilocytic astrocytoma: WHO I, 2-6% of all 1° brain tumors. Earlier age of onset (generally <25 yo). Slow growing, less invasive, more favorable prognosis. Generally arise in cerebellar hemisphere (75%)/near third vent. Other locations: hypothalamus (precocious puberty), optic pathway (assoc c NF1, esp bilat), thalamus, cerebral hemispheres, corpus callosum.

Dx: Radiology: MRI: ↓T1, ↑T2. Well-demarcated (round/oval), vividly enhancing (94%), cystic (68%). ± enhancing mural nodule. Min. peritumoral edema. Mass effect common. Path: Scant extracellular fibrillary matrix, Rosenthal fibers are hallmark.

Prognosis: Surgery: 10 yr overall survival (OS) > 80% w/ resection alone. Cerebellar location best prognosis (more amendable to complete resection). XRT: Reserved for inoperable pts or recurrence. Malig degeneration may rarely occur (<5%). Seeding of subarachnoid space uncommon.

Subependymal giant-cell astrocytoma (SEGA): Almost exclusively in association w/ tuberous sclerosis (˜10% of pts w/TS). Near foramen of Monro (classic)/on ependymal surface of lateral ventricles. MRI: T1 iso, T2 hyper, common enhancement. Asymptomatic tumors do not require Rx. Surgical excision for symptomatic tumors.

Diffuse astrocytoma: (J Neurooncol 2009;92:253) Most common low grade glioma, WHO II, med age 30s. Diffuse, widely infiltr, slow growing, initially indolent on serial scans. Often → high grade after ˜5-7 yr of stability, ultimately incurable.

Dx: MRI: ↓T1, ↑T2, nonenhancing (if enhance = more aggressive). Path: ↑'d cellularity, enlarged astrocyte nuclei, no necrosis, mitotic activity, vascular Δs subdivided into fibrillary (deep), protoplasmic, & gemistocytic (cortical).

Rx: Surgery ↑'s survival (when possible) Postop XRT delays recurrence, ? prolong survival. Chemo: (TMZ) response in 50%-60%; 1p/19q deletion & silenced MGMT predictive.

Prognosis: Better if age <40, no enhancement, small tumor, sz at dx, ↓ proliferative index.

Pleomorphic xanthoastrocytoma: Adolescents & young adults, <1% of all astrocytic tumors, WHO Grade II. Uncommon, usu in temporal or parietal cortex. Bizarre histology, can be mistaken for GBM. Favorable prognosis, often curable w/ surgical resection, but can recur as GBM.

Brainstem gliomas: (JCO 2006;24:1266). 95% Astrocytomas; oligodendroglioma rare. Low to high grade. 80% pontine—mostly high grade tumors (WHO III/IV). 20% midbrain, medulla & cervicomedullary junction, mostly low grade. More common in young children.

Dx/imaging: MRI prefer'd for dx & f/u. Can't bx if intrinsic to brainstem; dx on MRI alone Ddx: Consider NFI (only risk factor). Mimics: Brainstem encephalitis (viral/autoimmune), brainstem encephalop (mitochondrial), vasc malformations, MS, hamartomas.

Oligodendroglioma & mixed gliomas: (JCO 2006;24,1246). Originate from oligodendrocyte. Uncommon: 5%-20% of gliomas, <5% of primary brain tumors. Usu single, sometimes mult lesions. Supratentorial subcortical (superficial, often infiltrate leptomeninges). Rare involve brainstem or cord. Young & middle aged adults (median 40-50 yo), less common in children.

Dx: Sz most common presentation (50%), szs eventually occur in 88%. Imaging: Anaplastic often enhance, low grade may not. CT: Well-demarcated hypodense subcortical mass; calcification common; sometimes hemorrhage. MRI: Irregular, ↓T1, ↑T2 (edema & infiltrate), 10% hemorrhage, ± patchy

enhance; ring enhance uncommon (worse prognosis). Path: Cystic ?, calcification, necrosis & hemorrhage. Uniform, closely packed swollen cells. Dark nuclei w/clear halo (“fried egg”). Capillaries in “chicken wire” pattern. Leptomeningeal spread may occur w/ tumor progression.

Majority have loss of 1p & 19q = prolonged nat hx, More responsive to chemo.

Rx: Surgery for dx, sx relief & prolonged survival. Adjuvant XRT/chemo for residual tumor/anaplastic tumors. Timing being studied (XRT + chemo vs. chemo + XRT). XRT felt to delay recurrence & prolong survival, typically given postop. Chemosensitive (due at least in part to 1p19q): PCV or TMZ effective, response up to 100% in 1p19q compared w/ 23%-31% in non-1p19q. Give one at progression, can give other following recurrence.

Prognosis: Better survival than astrocytomas. 1p19q codeletion most important prognostic factor. Often indolent course but ultimately fatal. Natural history = progression from low grade to high grade. High grade have much worse prognosis. Rare systemic mets.

EPENDYMAL TUMORS

Ependymoma: (Curr Opin Neurol 2008;21;754) Uncommon primitive glial tumors (<10% of CNS tumors,˜25% of spinal cord tumors). From ependymal cells lining ventricles. Children (median age 5 yo): 90% intracranial. Adults: 75% spinal (intramedullary). Infratentorial (fourth ventricle & subarachnoid) > supratent (lateral vent/parenchymal).

P/w: Depends on location. Post fossa = ↑ ICP (HA, n/v). Supratentorial = szs/focal defs. Spinal cord = Paraparesis, sensory level (cervical common, entire cord possible).

Dx: Imaging: Fourth vent tumor w/ calcification classic. CT: Hyperdense w/ homogeneous enhance, cysts & calcification common. MRI: ↓T1, ↑T2, prominent enhancement. Image entire neuraxis to r/o spinal mets. Spinal seeding more common w/infratent tumors (˜10%). Lumbar puncture: w/ CSF cytology for metastasis.

Surgical resection for dx & Rx. Path: Grade corr w/ prog: Myxopapillary ependymoma (WHO Grade I). Ependymoma (WHO Grade II). Anaplastic ependymoma (WHO Grade III).

Rx/prognosis: Surgery: Gross total resect improves survival, but often complicated.

XRT: Std Rx after resect, 54 Gy improves 5-yr survival 0%-20% →

50%-75% (consider SRS). Chemo: Role unclear, can allow postponing postop radiation in young children.

Even w/ surgery & radiation, prognosis poor w/ ˜50% local recurrence.

MENINGEAL TUMORS

Meningioma: (Neurosurgery 2005;57;1088): Most common benign BT (95%). 20% of all 1° brain tumors. 2.63/100,000 person-yrs; 25% of intracranial & 25% of intraspinal tumors. F > M (intracranial 2:1; spinal 9:1). Originate in arachnoidal cells. Most slow growing & benign (90%) = WHO Grade I. Atypical (5%-10%, WHO II), malig (2%, WHO III; more aggressive; more common in men). Usu single, but can be mult (familial synd/NF). Risk factors: Radiation, possibly hormone therapy & breast ca. Tumor size may ↑in pregnancy.

P/w: Depends on location. Often szs (30%-40%), HA (dural based), focal defs. Many found incidentally on imaging, incidence (˜1%) ↑‘s w/ age. Location: any meningeal tissue, esp dural reflections (falx, tentorium, sinuses).

Dx: Diagnosed by imaging. Biopsy not always required for Rx (RT vs. surgery). CT: Homog enhancing extra-axial dural-based lesion (“dural tail”); 15%-20% calcified, rare hemorrhage. MRI: ↓T1, iso-↑T2, (calcification ↓T2). Skull lumps over meningioma suggests invas. Path: WHO I = benign (90%; meningothelial/fibrous/transitional/psammomatous/angioblastic). WHO II = atypical (7%; choroid/clear cell. ↑‘d mitotic activity ≥4 mitoses/hpf/cellularity & ≥3 of: ↑ nuc: cyt ratio/prominent nucleoli/sheetlike growth/foci of necrosis). WHO III = anaplastic AKA malig (papillary, rhabdoid. ↑ degree of abnormality; malig cytology/↑ mitotic activity). Secretory meningiomas a/w ↑↑ edema.

Ddx: Lymphoma, dural mets, CNS sarcoid, extramedullary hematopoesis, chloroma.

Rx: (1) Observe: Asymptomatic/incidental meningiomas. (2) Surgery: Symptomatic or growing asymptomatic meningiomas, or young pts. Complete resection curative in 80%. Incomplete resect = 40% recur in 5 yr. Preoperative embolization may improve resection. (3) XRT: Definitive / following surgery. Can stabilize unresectable/recurrent. Recommended postop for atypical/malig/bone invas. Radiosurgery for <3cm lesions. Definitive XRT similar outcome to surgery. Postop XRT of SimpsonIV/high grade ↓‘s recurrence 2-4x. (4) Systemic therapy: Investigational: anti-angiogenic drugs & somatostatin analogs.

Prognosis: (1) Degree of resection: OS at 10 yr w/ Simpson I-III resection

80%. With Simpson IV risk of death increases by RR 4.2x. (2) Tumor grade: WHO I 15 yr OS = 80%. WHO II 15 yr OS = 50%.

Simpson Grading of Meningioma Resection

Grade	Completeness of Resection	Recurrence (10 yr)
I	Total resection + underlying bone/associated dura	9%
II	Total resection + coagulation of dural attachment	19%
III	Total resection w/o resection of dura or coagulation	29%
IV	Subtotal resection	40%

(*J Neurol Neurosurg Psychiatry* 1957;20;22)

Hemangiopericytoma: “Solitary fibrous tumor.” Aggressive, mening-based, classified as sarcoma. 2.5% of mening tumors; ave 40 yo; M > F. 70% supratent, 15% post fossa, 15% spinal.

Dx: Sxs usu < 1 yr (2/2 rapid growth). CT: Focal hypodensity, heterogeneous enhancement. MRI: Iso-T1 & T2 + flow voids, heterogeneous enhancement, 50% dural tail.

Rx/prognosis: Gross total resection; subtotal resection ↓ prognosis. Common local recurrence/distant mets. Late recurrence common. XRT (↑ local control & survival).

Hemangioblastoma: Uncommon, aggressive. Well circumscribed, vascular, typical cerebellum/cord. Most in children & young adults. 1%-2.5% of 1° intracranial tumors (7%-10% of post fossa, 4% of cord). 10%-25% occur in VHL (consider VHL if mult hemangioblastomas). ˜50% sporadic have inactivation of VHL tumor suppressor gene (chrom 3p).

P/w: Sx 2/2 compress, ↑ ICP, hemorrhage, paraneoplastic. Spinal lesions freq

p/w pain. Paraneoplastic erythrocytosis in 15%-20% from EPO-like factor secreted by tumor.

W/u: MRI w/ gado (CT inadequate; bone obscures posterior fossa/spinal canal). If no MRI, CT + conventional angio. Characteristic: Cerebellar cyst w/ enhancing mural nodule/homogeneous spinal lesion. Spinal lesions a/w syrinx/cord edema. Genetic screen for VHL if mult hemangioblastomas or single lesion in pt < 50 yo.

Rx: Surveillance. Surgery if tumor grows/causes neuro def/hemorrhage; SRS good alternative for smaller unresectable/mult tumors. Preoperative angiogram to identify feeding vessels of highly vascular. Embolization prior to resection of large lesions. Complete surgical resection often possible, ˜25% recur after surgery. Adjuvant XRT if +margins/incomplete resect. Surgery, XRT for recurrent/resistant cases.

LYMPHOMAS

Primary central nervous system lymphoma: (Lancet Neurol 2009;8;581) Rare tumor affecting brain, spinal cord & eyes. Intermediate-high grade non-Hodgkin lymphoma (most B cell). Responds to steroids, chemo, XRT, but relapse common. 2%-3% have systemic lymphoma (CXR, CT abd/pelvis).

Immunocompromise main risk factor.

Epid: Mean age 54 yo. 0.43/100,000 person-yrs; 4.1% of intracranial tumors. Any age; most commonly 50-60s; M > F (slightly).

P/w: Perivent WM, subcort/cortical, leptomeninges/CSF (40%), vitreous (20%). 50% mult. Sxs vary w/ location; Typical: HA, sz, focal defs. Others: personality Δs, lethargy, amnesia, confusion, psychosis, ataxia, myoclonus, floaters (vitreous); rarely RPD. Uveitis/vitreitis (10% cases); if+, usu precedes CNS tumor allowing early dx.

W/u: Definitive dx by biopsy/CSF/vitreous aspirate. Hold steroids preop (may ↓ bx yield). (1) Imaging: Image entire neuraxis. CT: Hyper/isodense; Homog enhance; Rare calcification/hemorrhage. MRI: Iso/↑T1, ↑T2, homog enhance. HIV-related: CT: Ring/patchy enhance; MRI mult nonenhancing ↑T2. (2) Biopsy: Path similar to systemic lymphoma; perivascular. (3) CSF: ↑ protein, ↑ lymphocytes; serial large vol LPs for dx by cytology. Send flow cytometry & IgH rearrangement. (4) Slit lamp exam for vitreous involvement. (5) Body imaging (CT chest/abdomen/pelvis) to r/o systemic dz. (6) Bone marrow biopsy. (7) EEG: Sym or asym diffuse slowing (nonspec).

Rx: (1) Dramatic temporary response to corticosteroids. (2) Resection does not improve prognosis, may worsen degree of def. (3) XRT: High responses & improved survival but short response duration & long-term neurotoxicity.

(4) Methotrexate-based chemo (often combined w/ other agents, occ followed by XRT) improves chances of durable remission.

Prognosis: No Rx ˜4 mo, WBRT 12-18 mo (contraindicated if >age 60 b/c dementia risk) Chemo Rx + WBRT >40 mo

SELLAR TUMORS

Numerous types: Craniopharyngioma, pituitary adenoma, meningioma, optic glioma. Visual impairment common presentation: Classic = Optic chiasm compress or invas → bitemporal hemianopsia. Hormone related sx also common → endocrine eval (pituitary / hypothalamus compress or involvement → hypopituitarism; pituitary adenoma → ↑ hormone production). Most tumors benign. Disability from proximity to other structures.

Craniopharyngioma: (J Neurooncol 2009;92:283; Horm Res 2008;69:193) In children/adol (30%-50%) 0.11/100,000 person-yrs; 0.9%-4% of BTs (5%-10% in children). Benign epithelial sellar tumor; often extends into surrounding structures.

P/w: Sxs from compress of optic chiasm, pituitary & third vent. Visual field defects, hormone aberrations, diabetes insipidus, hydro common.

Dx: Imaging: Sellar & suprasellar (70%), suprasellar only (20%), intrasellar only (10%). Commonly calcified. CT: Heterogeneous solid, cystic, calcified mass w/ heterog enhance. MRI: Heterog mass, iso/↑T1; ↑T2; solid/cystic rim enhance.

- Path: Encapsulated solid or cystic tumors. Micro: Sheets of epithelial, keratinized cells, connective tissue, cholesterol crystals, lamellar bone.
- Neuro-ophtho eval: Fundoscopy, formal visual fields & acuity.
- Endocrine eval: TFTs, GH, IGF-1, prolactin, FSH, LH, testosterone/estradiol.

Rx: May need pre-op EVD/shunt of hydro. Peri-operative stress-steroids, thyroid replacement. Surgery: Radical vs. subtotal resection via frontal/transsphenoidal approach. XRT: 54 Gy for subtotal resect. Conventional/intracavitary/fractionated/SRS.

Prognosis: Hypothalamic obesity synd, hypopituitarism, DI are risks of aggressive surgery. Subtotal resection + XRT = 80%-95% control.

Pituitary adenoma: (NEJM 2006;355:2558) Most common sella-region tumor.

1% population w/ sympt pit ad, 10% at autopsy. Microadenoma <1.0 cm; macro >1.0 cm.

P/w: Many subclinical. (1) Microadenoma: can be symptomatic from overprod of ant pituitary hormone. Hyperprolactinemia—galactorrhea & amenorrhea/hypogonadism (52%). Excessive growth hormone—gigantism & acromegaly (27%). ACTH—Cushing synd (20%). TSH-secreting (RARE)—hyperthyroidism. (2) Macroadenoma: sxs from compress of pituitary/stalk: Pituitary insufficiency. Mild hyperprolactinemia (disrupted pituitary stalk & lost hypothalamic inhibition). Chiasm compress—visual field defs. Cavernous sinus—oculomotor paresis. Traction on diaphragmata sella—HA.

Imaging: CT: Microadenomas: Low density mass in brightly enhancing pituitary. Macroadenomas: Isodense, enhance uniformly; more calcification/hemorrhage. MRI: Iso-T1, slight ↑T2, uniform enhancement.

Rx: Medical—hormone inhibition, esp for prolactinomas. Surgical—transsphenoidal resection; esp if visual field def. Gross total resect usu not possible. XRT—after subtotal resect. Monitoring—serial visual field testing. Long-term neuroendo f/u, supplementation.

PINEAL GLAND TUMORS

Epid: Very rare; 0.4%-1% of adult CNS tumors, 1%-11% of pedi. Subtypes: (1) Pineal parenchymal tumors/pinealomas (most <10 yo). (2) Germ cell tumors (most 10-14 yo). (3) Less common: Glioma, meningioma, lipoma, metastasis, pineal cyst.

P/w: Sxs from invas/compress/CSF obstruction. Hydro, visual Δ, nausea/vomiting, impaired ambulation. Classic is Parinaud synd (up to 75% = vertical gaze palsy, light-near pupillary dissociation, retraction convergence). Less common: Cranial neurop, hypothalamic dysfxn, leptomeningeal mets.

Dx: MRI/CT nonspec, don’t correlate w/ histology. MRI w/ contrast of entire spine, brain. CSF & serum for cytology & tumor markers preoperatively or 10-14 days postop. Biopsy prior to Rx. Open bx affords: visualization, CSF for markers, third ventriculostomy (if needed). Stereotactic bx. Surgery if bx inconclusive/shows benign tumor.

Rx/prognosis: Surgery: Benign, well encapsulated amendable to resection (few) XRT: Many subtypes respond. 5-yr survival 44 → 90% depends on type, age, extent of dz & Rx.

Pineocytomas: Def: Benign tumor of pineal cells. Epid: Adolescence to mid-life, slow growing, <3 cm. Only 1/3 w/ hydro. Dx: CT: Isodense; prominent homog enhance, cysts & calcification common. MRI: Sharply demarcated, ↓T1, ↑T2, variable intensity. Pathology: Similar to nl pineal gland. Rx: Often

surgically removed completely.

Pineoblastomas: Def: Primitive neuroectodermal tumor (PNET). Epid: Childhood to young adults, >3 cm. 90% w/ hydro. Dx: CT: Hyperdense; vividly enhance; calcification uncommon. MRI: Poorly demarcted, iso/↓T1, iso/↑T2, vividly enhance. Path: Hypercellular, small poorly differentiated cells (resemble medulloblastoma). Rx: Excision, adjuvant multiagent chemo & neuraxis XRT.

Intracranial germ cell tumors: (Oncologist 2008;13:690) Germ cell tumors from multipotent embryonal cells. Identical to extracranial GCTs: testicular seminomas & ovarian dysgerminomas. 90% before 20 yo; 3% of intracranial pedi tumors; M:F = 2-3:1. Pineal (60-80%) > sellar (20%-30%), 10% multifocal. Adults (germinomas more common): Suprasellar (F > M), pineal (M > F). Children (more nongerminomatous): Intracranial, sacrococcygeal; AFP/B-HCG-secreting (more aggressive) & nonsecreting tumors. Three main types: (1) Germinomas (60%-65%; less aggressive): Typically have nl levels of AFP & B-HCG tumor markers. Stain for placental alk phos (measurable in CSF). (2) Nongerminomatous germ cell tumors (NGGCT) (less common, more aggressive): Embryonal carcinoma, endodermal sinus tumor (yolk sac tumors), Choriocarcinoma, mixed tumors. (3) Teratoma (mature & immature); often considered separate category.

Epid: 12-40 yr; 0.09/100,000 person-yrs; 0.6% of intracranial tumors. 50% pineal region tumors are germ cell tumors. Pineal GCTs: M > F; Suprasellar GCTs: F > M.

P/w: Depends on location. Pineal: Hydro/ICP (25%-50%), ataxia, behavior Δ, Parinaud’s. Sellar: Hypothalamic/pituitary dysfxn, visual field loss.

Dx: Imaging: Well-delineated pineal or suprasellar masses. Heterogeneous (fat, cysts, calcification, hemorrhage). CT hyperdense; calcification (50%-70%), strong homog enhance. MRI: Iso-T1, ↑T2. Enhance heterog (if cystic). Imaging cannot disting germinomas & NGGCTs. MRI of spine for staging (10%-15% have leptomeningeal spread, esp NGGCT).

- LP: CSF & serum pre-op or 10-14 days postop (cytology & markers). Check CSF for cytology to diagnose leptomeningeal mets. CSF more sensitive than serum for tumor markers; send.
- CSF & serum: AFP—↑ in yolk sac tumors/immature teratoma; B-HCG—↑ in choriocarcinoma/immature teratoma/rarely germinoma; hpALP—↑ in germinoma.

- Biopsy: ↑ AFP sufficient to dx NGGCT; no bx needed. ↑ β-HCG → bx to disting choriocarcinoma/teratoma/germinoma (rarely). AFP & β-HCG negative → Must biopsy. Note: Small sample can result in inaccurate dx.

Rx & prognosis: (1) Germinoma: Sensitive to chemo & XRT; no indic for resection. Pure germinomas cured w/ XRT (>90% long-term progression-free survival). Regional XRT if focal (tumor & ventricles), cranio-spinal if spread. ↓ dose, add chemo b/c of long-term effects of XRT. Neoadjuvant chemo effective: bleomycin + etoposide + cis/carboplatin (but still need XRT). Salvage chemo/XRT for recurrence. (2) NGGCT: Chemo + XRT. Less sens to XRT (20%-40% survival w/ XRT alone). Neoadjuvant chemo + XRT improves outcomes (60%-70% long-term survival). Platinum-based chemo regimens: Cis/carboplatin + etoposide ± ifosfamide/cyclophosphamide. Regional XRT if focal (tumor & ventricles), cranio-spinal if spread. Unclear if extent of initial resection improves survival. Second-look surgery & resection after chemo-XRT may be beneficial. Prog poor if NGGCTs recur. Magnitude of AFP ← is negative prognostic indicator in NGGCTs. (3) Mature teratoma: Gross total resection curative. Recurrence risk factors: Multifocal, CSF cytology/tumor markers, embryonal elements.

EMBRYONAL CARCINOMAS

PNETs: Highly aggressive, spread via CSF (send CSF cytology). Tumors of childhood & young adulthood. Path: Small, blue, round cell embryonal tumors. Hypercellular, homog, small blue cells in dense sheets & rosettes. Related to other small blue cell tumors (Ewing's, Wilms), BUT not same; different behavior.

P/w: Depends on location: medulloblastomas, pineoblastomas, neuroblastomas, or ependymoblastomas. Variety of locations, identical histology: Cerebellum = medulloblastoma. Pineal = pineoblastoma. Retina = retinoblastoma. Hemispheres = neuroblastoma. Pineal & bilateral retina = "trilateral tumor." Location has major prognostic significance.

Rx: PNETs generally radiosensitive & chemosensitive.

Medulloblastoma: Most common PNET, generally post fossa. 50%-60% in 1st decade, peak in 20s. 1/3 CNS tumors in children—most common pedi CNS tumor.

P/w: Younger children: Increased ICP (HA, N/V, somnolence); truncal ataxia; Cerebellar vermis in children (midline sx). Adolescents/young adults: Ataxia, dysmetria; ↑ ICP later. Cerebellar hemispheres in adolescents & young adults (limb sx). Common spread via CSF; 20%-30% p/w CSF mets. 5% have systemic mets (long bones).

Staging: (1) MRI: Entire neuroaxis pre-op. (2) CSF cytology preop/2-3 wk postop. Risk stratification: (1) Avg risk (66%) (>3 yo, <1.5 cm^2 resid dz after resect, M0 by craniospinal MRI & CSF). (2) High risk (34%) [<3 yo, subtotal resect, >1.5 cm^2 residual tumor, M+; leptomeningeal seeding, located outside of post fossa (PNET)].

Imaging: Well-defined mass in roof of fourth ventricle/cerebellum. Cysts, hemorrhage, calcification common. CT: Hyperdense mass w/ homogeneous & vivid enhancement. MRI: ↓ T1, hetero-T2, enhancement = vivid & homogeneous, occ absent, particularly after Rx.

Rx: Surgery: Posterior fossa craniotomy, total resection is goal. CSF diversion only after surgery; 30% require VP shunt. Surgery alone almost all recur. Chemo + XRT: Standard of care in all risk groups. In young children, occas chemo alone to delay RT until older. Most adults treated as high risk. XRT: High turnover requires being finished in 45 days (o/w worse outcome). Avg risk: Craniospinal 23.4 Gy + boost 55 Gy to posterior fossa; High risk: Craniospinal 36 Gy + boost 55 Gy to posterior fossa. Chemo: Follows XRT, concurrent chemo being investigated. Mult agents active: Platinum, etoposides, cyclophosphamide, nitrosoureas.

Prognosis: Relates to dz extent. Most recur <2 yr. Poor risk factors: Residual tumor >1.5 cm, brainstem invas, CSF mets, cerebral involvement, age < 3 yo. Following RT, 5-yr dz free survival: 60%-70% in high risk pts, 70%-80% avg risk pts. Recurrence: Posterior fossa (50%), frontal lobes/cerebrum (20%), bone (15%). Long-term toxicity in children: Post fossa synd (20%), blindness, ototoxicity, endocrine, cognitive defs, second malignancy.

AT/RT (atypical teratoid/rhabdoid tumor): Highly malig embryonal tumors. Rare (<2%) 1° CNS pediatric tumor; majority in pts < 3 yr. Often p/w ↑ ICP/hydro: HA, n/v, lethargy. CNS variant of primary malig rhabdoid tumor can manifest in other sites.

Dx: Imaging: Bulky, solid & cystic w/hemorrhage. 50% in post fossa, 40% supratentorial, others: pineal, spinal, mult. MRI: ↓T1; iso-/↑T2, heterog enhance. 30% leptomeningeal spread: Image entire neuraxis, send CSF cytology. Difficult to disting from PNETs/medulloblastoma. Immunohistochem: Shows vimentin, EPA, SMA (medulloblastoma does not); INI-1 mutated in ˜80%.

Rx: Spec regimen not well established. Generally: (1) Max safe resection. (2) Alkylating agent-based chemotherapy (various regimens in literature). (3) Radiation 40%-60 Gy (even in young children). ↓ local recurrence &

development of leptomeningeal dz.

Prognosis: Refractory to tx; generally recurs in 6 mos, prognosis is poor (often months).

NEURONAL & MIXED NEURONAL-GLIAL TUMORS

Rare tumors, variable degree of neuronal differentiation: gangliomas & gangliocytomas, dysplastic gangliogliocytoma of the cerebellum (Lhermitte Duclos dz), cerebellar liponeurocytomas, central neurocytomas & glomus tumors (paragangliomas).

Ganglioglioma/gangliocytoma: Low grade, malig neuronal cells (w/malig glia in gangliogliomas). Occur in children & young adults (average ˜20 yo).

P/w: Epilepsy common. Often found incidentally in temporal lobectomy for epilepsy.

W/u: Imaging CT: Well-circumscribed, low/mixed density, min mass effect. MRI: ↑ T2 PET: hypometabolic. Typically supratentorial; TL/FL, ventricles, cerebellum. Intra or peritumoral cysts common (40%-50%). Occ erode inner table of skull. Histologically benign.

Rx/prognosis: Surgical resection generally curative. Rarely recur after resection; good prognosis even w/ subtotal resection. No role for radiation even w/ partial resection. Infrequently transform (˜10%) to more malig glial tumor. Radiation for anaplastic/recurrent tumor. Anaplastic transformation usu fatal in spite of chemo/radiation.

Central neurocytoma: Well-differentiated intraventricular tumors (˜50% of Intravent adult tumors). Typical lat/third vent, attached to septum/vent wall. Multicystic, calcified neuroectodermal w/ neuronal diff'n. Mean dx age ˜29 yo. Leptomeningeal spread rare.

P/w: ↑ICP, focal sxs uncommon. Occasional IVH.

Imaging: CT: Heterogeneous hyperdense intraventricular mass, moderate enhancement. MRI: ↑T1, variable T2, enhancing.

Rx & prognosis: Surgery: Complete resection → best prognosis. Prolonged survival even w/ subtotal resection (slow regrowth). XRT/SRS: Useful for incomplete resection/atypia. Benefit of chemotherapy controversial. Poorer prognosis w/ atypical lesions.

Dysembroplastic neuroepithelial tumor: Rare benign neoplasm. Dysplastic cortical neuronal organization w/ multinodular architecture & columnar structure perpendicular to cortical surface. Arise from granular cell layer. Typically children & young adults, possible familial predisposition.

P/w: Szs; rarely any other focal si/sx. Longstanding intractable focal epilepsy common. Must disting from low-grade gliomas (confused w/ oligodendroglioma).

Imaging: Expand cortex, extend into white matter but only rare mass effect. Occas w/adjacent skull molding. CT: Low-density, variably enhance (none vs. patchy multifocal). Mult nodular w/ occasional calcification (less than oligodendrogliomas).

Rx: Obs. Surgery for refractory szs (respond to surgery initially, but often recur).

Glomus tumors (paraganglioma): Aka paragangliomas/chemodectomas. Incidence 1/100,000. Arise from paraganglia tissue (extrachromaffin cells); most plentiful in carotid & aortic bodies. Slow growing, <5% malig potential. Highly vascular. Present in lung, neck, mid ear, skull base.

Dx: Depends on site. Carotid—painless neck mass; CN palsies (esp X, XII). Glomus jugulare—middle ear mass "red drum"; tinnitus, hearing loss, CN of jugular foramen. Vagal—painless neck mass; dysphagia hoarseness. Occ w/ endocrine activity similar to pheo (test urine VMA).

W/u: MRI: Enhancing, flow voids. CT/CTA: Occas can involve bone. Generally not biopsied for dx because of vascularity/characteristic imaging.

Rx: Surgery first line; risk of CN palsies, CSF leak. XRT: Inoperable/large can tx w/fractionated XRT (˜54 Gy) w/ ˜90% control rate; small inoperable tumors treated

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w/ SRS w/ similar results (>90%); Rx goal = to stop progression, not shrink (though ™40% shrink).

CHOROID PLEXUS TUMORS

Def/Epid: Ventricular tumors from CSF-producing CP. 0.5% of intracranial tumors (˜15% if <1 yo). Vent distribution proportional to choroid: 50% lateral, 40% fourth, 5% third, 5% multifocal. 2 types: (1) CP Papilloma (CPP) (80%) benign, resemble choroid, hamartomatous (WHO I). (2) CP Carcinoma (CPC) (20%) aggressive, invade parenchyma.

P/w: Most frequently p/w HA (↑ ICP). Hydro (↑'d prod/obstr/subclinical bleeding). Leptomeningeal seeding may occur (CPP/CPC).

Dx: (1) CPP: Imaging: CT calcified, enhancing (like ependymomas w/more calcification). MRI: Flow voids (vascularity), iso/↓T1, ↑ T2. Path: Uniform cells w/o atypia, MIB < 2%, microvilli & cilia. (2) CPC: Imaging: More

heterogeneous w/ areas of necrosis, invas & surrounding edema. Ddx: metastatic adenoca, teratoma, medulloepithelioma. Path: Dense cellularity, mitoses, pleomorphic, necrosis, lost architecture, invas.

Rx/Prognosis: (1) CPP: Complete resection: 85% 10 yr survival, rare recurrence. Prolonged survival even after subtotal resection: 56% 10 yr survival. XRT: No adjuvant role, may be useful for recurrent/inoperable. Rare reports of malig transformation to CPC. (2) CPC: Gross total resection difficult 2/2 invas. 5 yr survival ˜25% despite chemo/XRT.

DERMOID & EPIDERMOID TUMORS

Def/epid: Benign, slow growing developmental/congenital masses; not neoplastic. Uncommon: 0.3%-1% of all CNS tumors. Similar in behavior, development, histology & imaging. Slow sx onset (˜2 yr). Sx relating to location/mass effect (HA, visual sxs, cranial neurop, sz). Rare cyst rupture: asymptomatic or → chemical meningitis (can be fatal).

Rx: Obs if asymptomatic. Surgery if symptomatic; 86% in good condition postop. y.

Prognosis: Benign; very low risk of malig transformation. 20 yr survival = 92.8%.

PRIMARY SPINAL TUMORS

Epid: Uncommon; 0.11/100,000 patient-yrs, 2%-4% of primary CNS tumors, Location relative to cord important for dx: Intramedullary = Usu 1° cord tumors: 54% ependymoma (20-50s), 40% astrocytoma (children/young adults); occ mets (SCLC), usu in pts w/ diffuse mets. Intradural extramedullary = meningiomas & nerve sheath (schwannomas/neuromas). Spinal meningiomas common in T-spine. Extradural = mets (generally); often extend vertebral bodies, invade/compress. Occ 1° tumors: Sarcoma, chondrosarcoma, chordoma, Ewing’s, plasmacytoma, lymphoma, benign tumors (osteoid osteomas, osteochondromas/blastomas, giant-cell tumors, hemangiomas, aneurysmal bone cysts).

P/w: Sx from disruption of tracts in spinal cord; prog pain & myelop.

W/u: MRI spinal astrocytomas: Spinal cord enlargement, iso-T1, ↑T2: Areas of previous hemorrhage (↓T1/T2). Patchy & irregular enhance throughout cord. Spinal ependymomas: Isointense T1, ↑T2: Hemorrhage w/hypointense rim on T1 &T2; enhance intensely & sharply demarcated. Cellular ependymoma occurs in cervical/thoracic cord. Myxopapillary ependymomas occurs in conus & filum terminale. Mimic: MS plaques.

Rx: Surgery: Ependymomas: Attempt complete resection (can be curative).

Meningiomas: Complete resection often possible, curative. Astrocytomas: Diffuse astrocytomas often infiltrative, complete resection rarely possible. Pilocytic astrocytomas more amendable to surgical cure. XRT: Postop XRT for astrocytomas; esp recurrent/prog ependymoma. Chemo: Role undefined; similar regimens to astrocytomas.

TUMORS OF THE CRANIAL & PERIPHERAL NERVES

Optic nerve and chiasm gliomas: Glioma most common tumor of optic nerve/sheath. 3% of 1° brain tumors in children; 1% in adults. Peak incidence 2-6 yr. 10%-20% a/w NF1 (higher when b/l).

P/w: Depends on age & location in visual pathway. Intraorbital: Monocular visual loss, strabismus, proptosis, optic atrophy. Chiasm: Bitemporal hemianopsia. Hypothalamic: Dev delay, ataxia, precocious puberty, wt loss, overactivity, euphoria. Infants: Often large tumors invading hypothal early visual loss, poor prognosis. Older children & young adults: Tumors involve optic nerve > chiasm > hypothal. Vision better preserved, prognosis better.

Dx: Imaging: CT: Fusiform low-density enlargement of ON, 50% enhance, calcification rare. MRI iso-T1, ↑T2, 50% enhance. Path: Most histologically = pilocytic astrocytoma; also oligodendrogliomas/mixed gliomas/anaplastic astrocytoma/glioblastoma.

Rx/prognosis: Surgery radical resection if vision loss for exophytic/cyst decompress. XRT for unequivocal progression/hypothalamic involvement. Most progress after XRT. Can have endocrine abnlities, cognitive dysfxn (avoid XRT in young).

Chemo—aggressive regimens can delay need for XRT.

Survival: 10 yr survival 60%.

Optic nerve meningiomas: Slightly younger age onset than meningiomas elsewhere.

Sxs: Visual impairment, pain w/ eye movement, orbital HA.

Dx: CT: Tubular involvement of optic nerve sheath (enhancement around nonenhanced nerve). MRI: Isointense enlargement of optic nerve sheath, enhancement around nerve.

Rx: Resection if vision loss complete (cure). XRT risks radiation optic neurop, but tumor progression threatens vision more.

Vestibular schwannoma: Benign periph nerve sheath tumor. 8%-10% of intracranial tumors (most CN VIII). Schwannomas make up 25%-30% of

spinal tumors (intradural, dorsal > ventral roots). F > M (2:1), peak 30-50 yo; 1% population, <1% symptomatic. Risk factors: Acoustic trauma, parathyroid adenomas, NF-2. Usu slow growing (1-2 mm/yr); can shrink on serial imaging.

P/w: Involves CN VIII/adjacent CNs. Acoustic: Hearing loss & tinnitus (95%) Vestibular: Unsteadiness, vertigo (60%). Trigeminal: Facial numbness, paresthesias, pain (15%). Facial: Paresis, taste disturbance (5%). Posterior fossa: Ataxia (rare).

W/u: Confirm sensorineural hearing loss (Rinne & Webber); assess other CN. Dx based on imaging; bx often not nec. MRI: Enhancing, involves int aud canal “ice cream cone” sign.

Rx: Observe small asymptomatic tumors; MRI q6-12 mo. Surgery (combined ENT, NSU procedure) favored for younger pts. Middle fossa, retromastoid, translabyrinthine approach. Hearing preservation ˜50%, CSF leak ˜9%, CN palsy 5%. XRT: SRS for <2 cm. Hearing preservation ˜50%. Fractionated therapy (˜50 Gy). Hearing preservation 80%. Requires yrly MRI f/u (tumor generally remains but does not progress).

Prognosis: >95% control rate w/ surgery or XRT.

Neurofibroma: Benign periph nerve sheath tumors (mult cell types). Rarely affect CNs. All ages, no gender predilection. A/w NF1.

P/w: (1) Dermal (cutaneous) neurofibromas: A/w puberty; SQ nodules that ↑ in no. & size. Often asymptomatic; may produce wkns/numbness/pain. Slow growing, low risk of malig transformation. (2) Plexiform neurofibromas (essentially pathognomonic for NF1): Large, locally invasive & a/w nerves leading to pain, defs. 10% malign potential: (MPNST = malig peripheral nerve sheath tumor).

W/u: MRI w/ & w/o contrast. Dx often only established w/ excision.

Rx: Observation Versus. CO_2 laser: For asymptomatic/minor dermal lesions. Surgery: Consider for plexiform given malig potential. XRT: For inoperable/malig cases.

GENETIC SYNDS

(Neurol Clin 2007;25:925). Familial synds a/w ↑ incidence of nervous system tumors. Relatively uncommon. Genetic defects responsible for tumor risk have been identified in many cases. Majority are autosomal dominant germline mutations of tumor suppressor genes. Second somatic mutation results in tumor formation (“two hit hypothesis”).

Neurofibromatosis type I (NF1): Aka von Recklinghausen dz or peripheral

neurofibromatosis. A/w neurofibromas & gliomas. Most common neurogenetic disorder; incidence ˜1/3,000. Aut dom, complete penetrance but w/ variable phenotype. Mutation in NF1 gene on chromosome 17q11.2 (neurofibromin: silences p21-ras). Half are new mutations (no family history).

Dx criteria: NIH diagnostic criteria = at least two of the following**: (1) Neurofibromas (**≥2 or 1 plexiform neurofibroma); Present in 80% of NF1 pts by puberty (benign nerve sheath tumors; cutaneous/subcutaneous/deep; Spine common, intracranial very rare). (2) Gliomas (**esp optic pathway gliomas); 15%, ˜4% by 3 yo; Pilocytic astrocytomas of optic nerve, chiasm, tract, hypothalamus; 4% symptomatic (proptosis/visual loss/precocious puberty); Nonoptic gliomas: 100x increased freq. (3) Café au lait macules (**≥6); 99% by 1 yo. (4) Skin fold freckling (axilla/inguinal)**; 90% by 7 yo. (5) Lisch nodules (**≥2); >70% by 10 yo (hamartomas of iris, no visual sxs, NF1 spec). (6) Bony lesion* (dysplasia/thinning of long bones/pseudoarthrosis); ˜14% by 1 yo. (7) 1° relative w/ NF1**.

Other features: Common: Learning disabilities, HAs, hypertension, T2 changes on MRI, scoliosis. Uncommon: Szs, malig peripheral nerve sheath tumor, vasculopathy. Rare: Pheochromocytoma (2%), leukemia, high grade astrocytoma.

Genetic Synds A/w Nervous System

Synd	Inheritance	Mutation	Nervous S Tumor
NF 1	Dominant 50% sporadic 1/3,000	17q11.2 Neurofibromin	Neurofibro Gliomas (c brainstem, hemispheres)
NF 2	Dominant 50% sporadic 1/25-40,000	22q12.2 Merlin	Schwanno (CN VII) Meningior Spinal ependymoma

			Spinal astrocytoma
Tuberous sclerosis	Dominant 2/3 sporadic ~1/6,000	9q34 Hamartin 16p13.3 tuberin	Cortical tu Subependy nodules SEGA Glioma
Von Hippel-Lindau	Dominant 20% sporadic 1/36,000	3p25 pVHL	Hemangio blastoma
Cowden synd	Dominant 1/200,000	10q22 PTEN	Lhermitte-Duclos' Dz
Li-Fraumeni, synd	Dominant Very rare	17p13.1 P53	Astrocytor Medullobl PNET Neuroblast
Turcot synd	Variable Dominant/recessive	Several Astrocytoma	Medullobl Ependymoma
Gorlin' synd	Dominant 50% sporadic 1/57-164,000	9q22.1-3 Patched-1	Medullobl Meningior

W/u: (1) Full skin exam. (2) Ophthalmologic exam (annual 2-7 yr). (3) Monitor BP (essential HTN, renal vascular dz, pheochromocytoma). (4) Mutational analysis of NF1 gene: Identifies 95% mut in classic NF1. Not nec for pts who meet dx criteria.

Rx: (1) Neurofibromas: No spec Rx. Plexiform neurofibromas cause pain, erode, compress cord. Surgical resection if fxnl compromise. (2) Gliomas: Observe asymptomatic. Bx if growth or new sx. Rx high grade like sporadic glioma. Surgery: For painful proptosis/blindness/hydro. Chemo: For prog optic gliomas. Carboplatin & vincristine/TMZ. XRT: High-grade progression despite chemo.

Neurofibromatosis type II (NF2): Aka “central” neurofibromatosis. A/w mult tumors: Meningiomas, spinal gliomas & schwannomas. incidence 1/25,000-40,000. Aut dom, full penetrance, uniform in families. ˜50% w/new mutations in NF2 gene, chromosome22 (“merlin”: links cytoskeletal proteins). Inactivated NF2 in most sporadic schwannomas, 50%-60% of sporadic meningiomas.

Dx criteria: ≥1 of: (1) B/l Vestibular schwannomas. (2) NF2 FHx + (a) u/l Schwannoma/(b) 2 NF2-associated tumors.

P/w: Sxs 17-21 yo (prior to dx by 5-8 yr). Children: Cranial/periph nerve dysfxn, myelop, szs, skin tumors, cataracts, café au lait. Adults: CN VIII dysfxn (deafness, tinnitus, imbalance). (1) Vestibular Schwannomas (benign) invariable, hallmark of NF2 = prog hearing loss → complete deafness by adulthood. Freq other CN & spinal nerves.

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(2) Meningiomas (mult): 50% (optic sheath in 4%-8% → vision loss). (3) Spinal cord ependymomas (2/3 mult) or astrocytomas in ˜50% pts, C >T-spine >> brain/L-spine.

W/u: (1) Ophtho exam (lens opacities, retinal hamartomas, epiretinal membranes). (2) MRI+gado w/ thin cuts (IAC study). (3) MRI C-spine ± T&L-spine (depend on sxs). (4) Audiometry & auditory evoked potentials. (5) NF2 gene mutational analysis (ids 70% muts). Not necessary for pts who meet dx criteria.

Rx: Obs: Frequent follow-up, Serial: MRI, audiometry & evoked potentials. Surg: Consider early for: rapid growth, prog sxs (risk iatrogenic deafness). Minority of spinal tumors require surgery (extra intramedullary). XRT: for nonoperative vestibular Schwannomas (?risk transformation/second malign). Biologic Rx: Bevacizumab ↓ tumor volume & improved hearing for

nonoperative/RT pts (NEJM 2009;361:358).

Prognosis: Median survival 15 yr from dx.

Tuberous sclerosis complex (TSC): A/w benign hamartomas of brain, eyes, heart, lung, liver, kidney, & skin. Incidence ˜1/6,000. Aut dom, complete penetrance, variable phenotype. Mutation in TSC1 (chrom 9q34, hamartin) or TSC2 (chrom 16p13.3, tuberin); TSC1 mutations cause milder sx. 1/3 cases familial, 2/3 sporadic.

P/w: Variable; epilepsy & cogn disability common, related to tuber no.

Vogt triad (szs, mental retardation, facial angiofibromas) in <50% pts. Common si/sx: HA/nausea/vomiting/obstr hydro/focal defs/szs. (1) Szs in ˜80% of pts, usu before 2 yo. Infantile spasms common (25% of spasms =TSC). (2) Mult hamartomas (see Tuberous Sclerosis Diagnostic Criteria table) w/ risk of malig transformation: CNS: Subependymal nodules (can progress to larger SEGAs). SEGA: Benign slow growing periventricular glial tumor (predilection for foramen of Monro, 6%-9% symptomatic, typically 10-30 yo).

Tuberous Sclerosis Diagnostic Criteria

Dx = 2 Major Criteria OR 1 Major + 2 Minor Criteria

Major clinical features	Facial angiofibromas or forehead plaques
	Shagreen patch (connective tissue nevus)
	Ash leaf spots (≥3)
	Nontraumatic ungual or periungual fibromas
	Lymphangioleiomyomatosis (aka lymphangiomyomatosis)
	Renal angiomyolipoma
	Cardiac rhabdomyoma
	Mult retinal nodular hamartomas
	Cortical tuber
	Subependymal nodules
	Subependymal giant cell astrocytoma

Minor clinical features	Confetti skin lesions (mult 1—2 mm hypopigment macules)
	Gingival fibromas
	Mult randomly distributed pits in dental enamel
	Hamartomatous rectal polyps
	Mult renal cysts
	Nonrenal hamartomas
	Bone cysts
	Retinal achromic patch
	Cerebral white matter radial migration lines

W/u: (1) Skin exam, ophtho eval. (2) MRI (tubers, subependymal nodules, SEGAs, white matter lesions in 15%). (3) Renal U/S. (4) EEG if h/o sz: 75% epileptiform on routine EEG. (5) Malignancy screening q1-3 yr: Renal U/S, brain MRI. (6) Genetic counseling: Dx in child → workup parents (skin & ophtho exams, CT/MRI, renal U/S). (7) Mutational analysis of TSC1 & TSC2 (id 60%-80% mutations). Not necessary if meet diagnostic criteria.

Rx: (1) Szs mgt difficult. ACTH for infantile spasms. Carbamaz/oxcarb for partial szs. Ketogenic diet/VNS for refractory szs. (2) Surgery for causative tuber (c/b mult tubers). Complete resection of SEGAs curative but difficult. (3) Chemo: Sirolimus? (benefit in study).

Prognosis: Prog but variable. ↑ early death rate (SEGAs, status, renal dz).

Von Hippel-Lindau disease (VHL): (Lancet 2003:361;2059) A/W benign & malig tumors (young, mult). Incidence ˜ 1/36,000. Aut dom mutation in pVHL (Chrom3 tumor suppressor). New mutations ˜20%. Type I—no pheochromocytoma. Type II—high rate pheo (Type IIA—low risk of RCC; Type II B—high risk of RCC; Type II C—no RCC/hemangioblastoma).

P/w: Sxs childhood-early adulthood (ave 26 yo). Post fossa: Ataxia/dysmetria/hydro.

Dx criteria: Mult hemangioblastomas/hemangioblastoma + typical visceral lesions/FHx + hemangioblastoma or visceral lesion.

Tumors: (1) Hemangioblastoma (25% VHL, often mult, 75% sporadic): Benign vascular neoplasm w/ unpredictable growth. Most common VHL

tumor (60%-84%, ave 29 yo), cerebellum/BS/cord. MRI: Cystic w/ enhance mural nodule. (2) Retinal angiomas: Retina/ON hemangioblastoma; 60%, often bilat. Risk: Hemorrhage & vision loss. (3) Renal cell carcinoma in 2/3 pts, ↑ w/ age, high recurrence. (4) Pheochromocytoma (VHL type II), often asymptomatic. (5) Endolymphatic sac tumors ↑ hearing loss/tinnitus/vertigo/facial palsy. (6) Serous cystadenomas & pancreatic neuroendocrine tumors, usu asymptomatic. (7) Papillary cystadenomas of epididymis/broad ligament, asymptomatic.

W/u: (1) Genetic testing estab. dx (some false neg 2/2 mosaicism). Genetic counseling. (2) Surveillance for hemangioblastoma, RCC, pheochromocytoma, endolymph sac tumors. (3) Optho Exam annually. (4) Brain MRI annually after 10 yo. (5) Serum catecholamine annually, w/ abd CT after 10 yo. (6/7) Abd scanning for RCC in adults. (8) Baseline ENT & audiometry.

Rx: (1) Hemangioblastoma: Surveillance for asymptomatic lesions. Surgery if sxs; ˜17% recur. RT if inaccessible/to avoid mult surgeries. (2) Retinal angiomas: Early Rx w/ photocoagulation/cryotherapy. Salvage w/ XRT. VEGF inhibitors beneficial in small trials. (3) Renal cell carcinoma—monitor <3 cm, renal sparing surgery/laparoscopy/RFA >3 cm. VEGF abs/inhibitors being studied, ↑ survival in phase 3 trial.

RARE GENETIC NEURO-ONCOLOGY SYNDS

Cowdon synd: Aut dom, 1/200,000. PTEN (chrom10) Mutation. Hamartomas in mult organs; cutaneous hallmark=trichilemmomas. Predisposition to breast (25%-50%), thyroid (10%), endometrial cancer. Pathognomonic CNS feature in adults: Lhermitte-Duclos dz = Benign hamartoma cerebellar cortex (expanded granular layer), P/w: HA/n/v/ataxia/obstr hydro. MRI: Well-circumscribed nonenhancing ↑T2 enlarged folia (“tiger striped”). Surgery if prog growth; may recur XRT ineffective).

Li-Fraumeni synd: Mutations in TP53 gene in 70%. Early onset tumors: breast, sarcoma, leukemia, adrenocortical carcinoma & brain. Brain tumors (13%), ave 16 yo: astrocytomas, medulloblastomas & PNETs. Peripheral tumors: neuroblastoma. Dx: Sarcoma < 45 yo + 1° relative tumor < 45 yo + 1°/2° relative w/ sarcoma or other tumor <45 yo. Watch for secondary cancers after XRT/chemo.

Turcot synd: Rare association: primary brain tumors & colorectal polyposis (FAP / HNPCC). FAP: Medulloblastomas (60%), astrocytomas (14%), ependymoma (10%). HNPCC: Astrocytomas. ↑ risk of secondary malignancy following XRT/chemo.

Gorlin synd: Aka nevoid basal cell carcinoma synd. Aut dom, ˜1/60,000, 50%

sporadic. Mutation in PTCH gene on chrom9q. Basal cell carcinomas, jaw cysts, dural calcifications, rib abnlities & brain tumors including: medulloblastoma (3%-5%), meningiomas (5%). Predisposed to second malignancy after XRT.

NEUROLOGIC COMPLICATIONS OF SYSTEMIC CANCER

Brain mets: Neurologic sx = initial manifestation in 10% of systemic cancers. 10%-30% of cancer pts have brain mets at autopsy (35% lung, 30% breast, 70% melanoma). Distributed proportional to blood flow: 90% cerebrum; 10% posterior fossa, tend to involve gray/white jxn or in ACA-MCA-PCA border zones; pituitary mets often from breast, melanoma, germ cell. Single met = one met in brain (regardless of extracranial dz) "Solitary" met = only met in body.

W/u: Search for primary. (1) Exam (incl. skin, breast, testicular). (2) CXR, Pan-CT/PET. Balance need for palliative or definitive cranial tx. Primary can change Rx & dx approach. Tissue dx almost always required for XRT therapy.

Rx: Surgery: For single dominant/life threatening lesion. Solitary brain met: best results = resection followed by whole brain XRT (WBRT) ("Patchell Trial" (N Engl J Med 1990 Feb 22;322(8):494; Curr Oncol 2007;14:131): Median survival/local control/retained KPS > 70: (1) Biopsy + WBRT = 3.4 mo/48%/8 wk. (2) Resection + WBRT = 9.2 mo/80%/38 wk. XRT: WBRT ↓'s risk of: neurologic death, additional mets, recurrence. SRS boost ↑'s local control in pts w/ ≤4 lesions, but no improved survival. 30 Gy/10 fractions std regimen, 35 Gy/14 fx common. >3 Gy/fraction has more severe neurocognitive effects if pt lives >6 mo. Chemo: For responsive tumors (e.g. breast cancer).

Prognosis: Aggressive Rx for solitary met occas yields long-term survivors.

RPA Stages for Brain Mets (RTOG Trials 79-16, 89-05)

Stage	Characteristics	Median Survival
1.	KPS ≥ 70, age < 60, controlled primary, no extracranial mets	7.1 mo

2.	All others	4.2 mo
3.	KPS < 70	2.3 mo

Spinal mets: See “Acute Rx” section. Most mets to epidural space (85% from vertebral body, 10-15% through neural foramen). Hematogenous spread rare (occurs w/heme malig). Intramedullary mets rare (a/w brain mets). Increasing in breast cancer pts treated w/agents that do not cross BBB.

Rx: Medical Rx: Corticosteroids: For pain, assoc w/retained/regained neuro fxn. Temporizing only; must follow w/ definitive Rx; Analgesia: Narcotics; Foley, DVT ppx, preventative bowel regimen (stool softeners, suppositories). XRT: ↑ pain control, ↓ analgesic need, can ↑ neuro fxn if start soon after sxs. Surgery: For select pts, surgery → RT preferred to RT alone, may help retain ambulation (Patchell, Lancet 2005).

Leptomeningeal mets (carcinomatous meningitis): 3%-8% of cancer pts, incr as pts survive longer. Leptomeninges infiltrated by cancer cells. Primary dz dependent: Common: Breast, lung, melanoma, heme malignancies (non-Hodgkin’s lymphoma), brain primaries: malig astrocytomas, oligodendrogliomas, medulloblastoma, pineoblastoma, germinoma, primary CNS lymphoma.

P/w: Common si/sx: HA, AMS, n/v, ataxia. Multi-level nervous system dysfxn that is prog, unremitting: Brain: Personality changes, cognitive impairment, labile affect, ↓ alertness szs, HA. CN: Cranial neuropathies (VII most common). Spine: Radiculopathy, myelop, sensory loss, reflex loss, urinary or fecal incontinence.

Dx: MRI: Diffuse/patchy leptomeningeal enhance, ± small nodules (distinct). Nl MRI does NOT exclude. LP: CSF cytology; normal LP does NOT exclude, repeat × 1 or 2 to confirm dx.

Ddx: Mult mets, infxn, ↓ ICP (post-LP), postcraniotomy, recent head trauma.

Rx: Aim to palliate & extend survival; rarely curative. 50%-90% ↓ pain, improved defs. Advanced dz/unresp 1°: No benefit from tx of LM. Chemo: Intrathecal chemo in some, Ommaya reservoir preferred. Methotrexate 12 mg 3x/wk for leukemias, lymphomas, solid tumors. Cytarabine 40-50 mg 2-3x/wk for leukemia & lymphoma; liposomal for intrathecal use. Thiotepa: 10 mg 2-3x/wk. XRT: Helps focal defs Focal XRT or WBRT (including short course: 4 Gy × 5).

Prognosis: Mean survival 6 wk, varies w/: Primary histology (breast: 6 mo w/ Rx, 10 wk w/o), defs, performance status, CNS parench mets, control of

primary dz.

PARANEOPLASTIC NEUROLOGIC SYNDS

(NEJM 2003;349:1543; Lancet Neurol 2008;7:327; Curr Opin Neurol 2007;20:732)

Def: Rare cancer-related neuro synds (often develop prior to cancer dx). Can affect any part of the nervous system (brain/cord/periph nerve/muscle). Not a direct effect of tumor/Rx /vascular dz/coagulopathy. Immune-mediated; a/w antineural abs (see table below); new Abs being discovered. Cancer produces antigens normally present in neural tissue, abs cross-react → synd. Individual abs a/w spec synds (table). Immune response can inhibit tumor growth; often better cancer prognosis.

Epid: Rare, freq unclear, likely under-dx'd. Estimates: ˜0.01% of cancer, varies w/type: 3%-5% SCLC, 15-20% thymoma (esp myasthenia gravis), 3%-10% of B-/plasma-cell cancers, <1% of other tumors (breast, ovarian, Hodgkin's etc.).

P/w: (1) Generally subacute onset (days-months). (2) Most cause severe irreversible neurologic defs, can be fatal. (3) Affect one level of nervous system (except encephalomyelitis). (4) Most are painless (except: sensory neuronopathy, dermatomyositis). (5) Dx'd month-years before cancer (70%)/in known cancer pt/after "remission". (6) CSF typically inflammatory (WBC 30-40, protein 50-100, IgG, oligoclonal bands). (7) Discrete synds, but variable presentation (see below). (8) Individual synds a/w: various cancers/no cancer. Various abs/no (currently known) abs.

Dx: Based on synd, antibodies, cancer: Synds: Neuro synd required for dx (abs + cancer insufficient). Discrete presentations/synds, NOT just "unexplained neurologic sx". Classic synds (search for Abs & tumor; note: dx poss w/o either): Limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, encephalomyelitis, subacute sensory neuronopathy, Lambert-Eaton's myasthenic synd (LEMS), Dermatomyositis. Abs: In CSF & serum (can check either). May occur w/o synd or cancer; sig unclear. Common abs: Anti-CAR, CRMP5/CV2, Hu, LEMS, Ma/Ta, Ri, Yo, Zic4, VGKC, NMDA, Tr, amphiphysin. Cancer: Search for tumor in case of classic synd, which can guide cancer screening. Pan-CT/PET/mammography/U/S. If atypical tumor discovered, search for another tumor.

Rx: No established protocol for Rx. Objective is to stabilize, may not see improvement. Two approaches to Rx: (1) Removal/Rx of underlying tumor; often only effective Rx. (2) Suppress immune response: Ab-mediated

(extracellular Ag) → plasmapheresis/IVIg T-cell mediated (intracellular Ag) → tacrolimus, mycophenolate, rituximab. Both types of immunity may play a role; may be effective to use both approaches.

Prognosis: Varies by synd & cancer. Diff pathophys: Functional versus neuronal loss: LEMS/MG = Good response (NMJ can recover). Opsoclonus-myoclonus = good response (no apparent neuronal loss). CNS disorders = often poor response to tx (usu have neuronal loss).

Classic Paraneoplastic Neurologic Synds

Paraneoplastic Synd	Antibodies	Associated Cancer(s)
Limbic encephalitis	Anti-VGKC	SCLC, thymoma, NONE (in 80%)
	Anti-NMDA	Ovarian teratoma
	Anti-Hu (ANNA-1)	SCLC, others
	Anti-CRMP5/CV2	SCLC, thymoma
	Anti-Ma/Ta	Testicular, NSCLC, breast
Cerebellar degeneration	Anti-Yo	Breast, GYN
	Anti-Tr	Hodgkin’s dz
	Anti-VGCC, anti-Hu	SCLC
	Anti-GAD	No Cancer
	Any/No ab	
Opsoclonus-myoclonus-ataxia	Any ab	SCLC, breast, ovarian neuroblastoma (peds)

	Anti-Ri (ANNA-2)	Breast
Encephalomyelitis	Anti-Hu, others	SCLC (75%)
Sensory neuronopathy	Anti-Hu	SCLC
LEMS	Anti-VGCC	SCLC
Dermatomyositis	Mult ANA, anti-tRNA	Breast, lung, ovary, stomach, lymphoma
Stiff Person's synd	Anti-amphiphysin	Breast, SCLC

Limbic encephalitis: Limbic sys af (hippocampi, amygdala, frontobasal region, insula). Subacute onset (days-mos): "quietly confused": Mood disturbance: depression/irritability, hallucinations, sleep disturbance, short-term memory loss, szs.

Dx: Imaging MRI: T2/FLAIR hyperintensity medial temporal lobes (70%-80%); PET: hypermetabolism (>80%); EEG temporal slow/epileptiform d/c. LP: CSF w/↑ lymphs (80%).

Cancer: SCLC, testicular, thymoma, Hodgkin's, teratoma most common.

Antibodies determine synd subtypes: Anti-VGKC (voltage-gated potassium channel): Sleep disturbance, hypoNa, hypothermia, hypersalivation, pain. ↓ CSF inflamm/acellular. 20%-30% w/tumors (SCLC, thymoma). Most w/o tumor. 80% respond to corticosteroids, pheresis, IVIg. Anti-NMDA (NR1/NR2 heteromer): Stereotyped sx progression: HA, fever prodrome → prominent psychiatric sxs, memory loss, szs → catatonia, dyskinesia, hypoventilation → autonomic instability (BP/arrhythmia/hyperthermia). 65% w/tumors (usu ovarian teratoma). Rx: Tumor removal, immunotherapy; 65% w/near-full recovery. Anti-Hu: Extensive/multifocal encephalomyelitis. EPC (tongue/limbs). A/w SCLC, others. Anti-CRMP5/CV2: Not limited to limbic system: (mimics NMO-Devic's). Encephalomyelitis, sensorimotor neurop. Ataxia, chorea, uveitis, ON, OCD/behav Δs. A/w SCLC, thymoma. Anti-Ma/Ta: Affect hypothalamus, brainstem. Hypokinesis, rigidity, supranuclear gaze palsy, narcolepsy, cataplexy, REM-sleep abn, hyperphagia. A/w

testicular germ-cell tumors (microscopic), NSCLC, breast Ca. Responds to Rx: orchiectomy & immunotx (steroids/IVIg).

Paraneoplastic cerebellar degeneration: Most common paraneoplastic synd. 50% of pts w/ late onset cerebellar degeneration have tumor, other 50% w/o. >50% with tumor have cerebellar si/sx before tumor dx.

P/w: Rapid prog pancerebellar synd (<12 wk): Viral-like prodrome: dizzy/N/V; symmetric: gait then limbs; severe ataxia, dysarthria, vertigo, nystagmus, dysphag, diplopia. Noncerebellar sxs: Hearing loss;ΔMS, tremor, blurry vision, oscillopsia, transient opsoclonus.

Dx: MRI: Nl early/increased white matter signal/enhanced folia → atrophy (later: months). PET: Cerebellar hypermetabolism progressing to hypometabolism. Path: Early inflammatory infiltrate → extensive loss of Purkinje cells.

Cancer: Most common tumors: SCLC (1/3), ovarian (1/4), breast, Hodgkin's.

Antibodies: All known Abs reported: Anti-Yo (cdr2/PCA-1) = GYN/breast (fairly spec); most common, poor prog. Anti-Tr = Hodgkin dz (spec). Anti-VGCC = SCLC

(± LEMS). Anti-Hu = SCLC; poor prog. Anti-GAD nonneoplastic cerebellar degen: slower, milder, asymmetric, w/ transient muscle spasm, with endo dysfxn: DM/thyroiditis/ pernicious anemia. Others: Anti-CRMP/CV2, amphiphysin, anti-Zic1&4, anti-Ri. May occur w/o known abs.

Rx/Prognosis: Treat tumor (some partial & complete remission). Some benefit from plasmapheresis, IVIg, immunotherapy.

Opsoclonus-myoclonus-ataxia: "Dancing eyes-dancing feet." Opsoclonus = involuntary, nonrhythmic, multidirectional saccades. Cerebellar ataxia, vertigo, tremor, n/v, dysarthria. Myoclonic jerks, encephalopathy.

Imaging: fMRI: inhibited deep cerebellar nuclei (disinhibited fastigial ocular motor region).

Cancer: Most common SCLC, breast, ovary. 50% children have neuroblastoma.

Affects: 2%-5% of neuroblastoma pts.

Antibodies: All known abs reported (most ab negative; most have SCLC). Anti-Ri abs in breast cancer (may have rigidity & stimulus-sensitive myoclonus).

Rx/Prognosis: Rx tumor. Rx idiopathic w/ IVIg & steroids. Good response to

immunosuppression & tumor Rx. Often w/ residual motor & speech d/o.

Encephalomyelitis: Dysfxn at >1 level of CNS, depend on structures involved. Sx from single level predominate. Myelitis: Wkns & posterior column dysfxn, UMN & LMN signs. Limbic encephalitis: Confusion, anxiety, depression, amnesia, szs, hallucinations. Cerebellar degeneration: Dysarthria, vertigo, ataxia, nausea, tremor, nystagmus. Sensory neuronopathy (DRG): Sensory loss, dysesthetic pain, sensory ataxia. Bulbar encephalitis (rare in isolation): Lower brainstem: eye movement abnlities, vertigo, vomiting, UMN si/sx. Autonomic neuronopathy: GI dysmotility, neurogenic bladder, postural instability.

Dx: MRI: Often ↑ T2 signal changes in affected regions. Cancer: 75% assoc cancer is SCLC, many others reported abs: Majority Anti-Hu (Also: CRMP5, amphiphysin, Ri, others).

Rx: Early Rx important; sig neurologic improvement & survival benefit.

Subacute sensory neuropathy: Subacute onset nmbns, paresth, pain; all modalities ↓'d (vibratory first). Marked asym at onset ↑ b/l, spreads to all limbs (incl. arms, trunk), Proximal involvement (face, scalp) suggests paraneoplastic. Ataxia, pseudoathetoid movements, areflexia, ↓ hearing. Autonomic involvement: ileus, sicca, pupils, orthostasis. Strength relatively preserved. May progress to encephalomyelitis

Dx: EMG/NCS = no sensory potentials, ± mild motor neurop (axonal & demyelinating). In cancer pts, must disting from chemo-induced sensory neurop (Platinum & vincristine).

Cancer/antibody: 80% a/w SCLC, anti-Hu ab.

Rx: Cancer resection halts dz. Early IVIg/plasmapheresis ↑ brief remission.

Lambert Eaton myasthenic syndrome: Rare (1/100,000); M > F.

P/w: Proximal, lower limb wkns (hip girdle). Doesn't usu involve EOM / dysarthria. Often w/ numbness/paresthesias (hands, feet). Autonomic instability: Dry mouth, erectile failure, depressed reflexes. Some w/ cerebellar degeneration.

Clinically markedly different from Myasthenia Gravis: Fixed (NOT fatigable) wkns, strength may ↑ w/ effort/exercise.

Dx: EMG w/rep stim. CK nl 80% of pts. Cancer: 50%-70% paraneoplastic; almost all SCLC.

Antibodies: Anti-VGCC (presyn P/Q-type; ↓'s vesicle fusion → ↓ ACh @ NMJ).

Sox-1 abs in 45%-65% of paraneoplastic LEMS (may differentiate paraneoplastic/non).

Rx/prognosis: Rx w/ 3,4-diaminopyridine (K channel blocker; ↑‘s AP duration). Good response to immunosuppression & tumor Rx.

Dermatomyositis: Rare (<1/100,000); F > M (2:1) (peak age 40-50).

P/w: (1) Prog symmetric prox muscle weak, myalgias, dysphagia, cardiac involvemnt (↑ muscle enzymes). (2) Interstitial lung dz (10%). (3) Many skin findings (often at present): Gottron sign: Erythematous, scaly over MCP, IP joints, elbows, knees. Heliotrope rash: Violaceous eyelids; Shawl sign: Flat UV-ind erythema (chest & shoulders); Erythroderma: Flat erythema over malar, forehead.

Dx: EMG short, low-amplitude motor units w/ increased spontaneous activity. MRI shows muscle inflammation. Muscle biopsy: Perivascular B cell & plasmacytoid dendritic infiltrate; vessel immune complex deposits (complement-mediated): Perifascicular atrophy & fibrosis.

Cancer: 15% (↑‘s w/ age); most common: Breast, lung, ovary, stomach & non-Hodgkins.

Antibodies: Mult in ˜30%: ANA (anti-Ro,-La,-Sm,RNP), Anti-tRNA (anti-Jo,-SRP,-Mi-2).

Rx: Treat w/ steroids & immunotherapy.

Stiff Person synd: Axial muscle rigidity & spasms. (1) Anti-GAD abs < 5% paraneoplastic: thymoma. (2) Anti-amphiphysin; cancer more common—breast, SCLC.

Neuromyotonia (Isaac synd): Myokymia, cramps, delayed relaxation, wkns. Stiffness 2/2 continuous muscle activity. Often a/w anti-VGKC. Sx can → Morvan’s synd.

Retinal degeneration: Painless ↓ in visual acuity, night vision & color vision. Progresses to involve both eyes. Some have anti-CAR abs. A/w SCLCa, melanoma, GYN cancers.

Necrotizing myelop: Ascending sensory loss, sphincter dysfxn, paraplegia. Usu thoracic cord. Pain uncommon. Often → resp failure. No abs/markers, usu dx postmortem.

Motor neuronopathy: Lower motor neuron wkns of legs & arms. Painless, no sensory defs. Can mimic ALS. Hodgkin & non-Hodgkin lymphoma.

NEUROLOGIC COMPS OF CHEMOTHERAPY

DeAngelis LM, Posner JB, Neurologic Comps of Cancer; 2nd Ed., 2009.

Hard to disting from comps of tumor, c/b drug interactions, radiation; dx of excl. Peripheral neurop most common: platinums, taxanes. Most CNS toxic chemo: (1) Ifosfamide: 20%-30% encephalopathy (hours-days after tx), Rx: D/c drug. (2) Methotrexate (intrathecal/high dose): 10% aseptic meningitis (hours after tx) Rx: prevent w/steroids. Myelop less common,↑ risk w/ RT (hours-days after tx). Encephalopathy, szs, delayed leukoencephalopathy (w/ XRT). (3) Thalidomide: Somnolence (43%-55%), szs uncommon.

Symptom	Chemotherapy/Biologic Agents		
Neurop • Diffuse variants: 1. motor>sensory demyelinating resembling GBS 2. sensorimotor 3. pure sensory may reverse • Focal uncommon	5-Azacytidine Bortezomib Capecitabine Carboplatin (3) Cisplatin (3) Cytarabine Docetaxel (3) Etoposide 5-FU Gemcitabine	HMM Ifosphamide Interferon-alpha Misonidazole Nelarabine Oprelvekin Oxaliplatin (3) Paclitaxel (3) Pemetrexed Procarbazine	mal alka
Acute encephalopathy • Identical to metabolic causes • Most insomnia • ± Myoclonus • Occasional szs • *Risk for PRES	Asparaginase 5-Azacytidine BCNU Bevacizumab* Chlorambucil Cisplatin* Corticosteroids* Cyclophos.* Cytarabine*	Fludarabine 5-FU Gemcitabine* HMM Hydroxyurea Ibritumomab Ifosfamide* Imatinib Interferons*	

	Dacarbazine Doxorubicin Etoposide*	Interlukins Mechloramine Methotrexate	alka
HA	Asparaginase Capecitabine Cetuximab Cisplatin Corticosteroids Cytarabine Danazol Estramustine Etoposide Fludarabine Gefitinib	HMM Interferons Interleukins Ibritumomab Levamisole Mechlorethamine Methotrexate (IT) Nelarabine Octreotide Oprelvekin	
Subcortical dementia	BCNU Carmustine Corticosteroids	Cytarabine Dacarbazine 5-FU + levamisole	
Cranial neurop	BCNU (ototoxic) Cisplatin (ototoxic) Cytarabine	Ifosfamide Methotrexate	(ocu
Vision loss	BCNU (IA) Cisplatin	Etanercept Fludarabine	
Acute cerebellar synd	Cytarabine 5-Fluorouracil	Interlukin-2 Procarbazine	

	HMM Ifosfamide	Tamoxifen	alka
Leukoencephalopathy	Capecitabine Cisplatin Cytarabine (IT)	5-FU + levamisole Cyclosporin-A Methotrexate (IT)	mal
Aseptic meningitis	Cytarabine (IT) Levamisole	Methotrexate (IT)	
Myelop	Cisplatin Cladribine Corticosteroids Cytarabine	Doxorubicin Fludarabine Interferon alpha Methotrexate (IT)	(IT) (IT)
Vasculopathy/stroke	Asparaginase Bevacizumab BCNU (IA) Bleomycin Carboplatin (IA)	Cisplatin (IA) Doxorubicin Erlotinib Estramustine 5-FU	mes
Szs	Amifostine Asparaginase BCNU Busulphan Chlorambucil Cisplatin Corticosteroids	Etanercept Etoposide 5-FU Ifosfamide Interferon Inteleukin-2 Letrozole	

	Cytarabine Dacarbazine	Levamisole Mechloramine	alky
Syncope	Bevacizumab	Erlotinib	

(HMM = hexamethylmelamine; 5-FU = 5-fluorouracil; cyclophos = cycl
IA = Infraartorial; IT = intathecal. Newton HB, Jolesz FA. *Handbook of Neuro
Neuroimaging, 2008; DeAngelis LM, Posner JB. *Neurologic Comps of Cance*
D, Wen PY. *Cancer Neurology in Clinical Practice*, 2003.) IA = Intraarterial, I

NEUROLOGIC COMPS OF RADIATION THERAPY

Overview: Side effects depend on structures radiated, dose & fraction schedule. Often difficult to disting from dz progression.

Acute Effects

Symptom	Depends on	Onset	Likelihood
Fatigue	RT volume	3 wk	Common
Alopecia	Dermis > 40 Gy	3 wk	Common
Scalp erythema	Dermis dose	3 wk	Common
Wound infxns	Surgery date	Variable	Uncommon
HA	Unpredictable	1 wk	10%-20%
Nausea	Unpredictable	1 wk	10%-20%
Sz	SRS	1 day	Uncommon

Delayed Effects

Symptom	Depends on	Onset	Likelihood

Short-term memory	Temporal lobe dose	6-12 mo	Variable
Hypopituitarism	Pituitary dose	6-12 mo	Variable
Perm alopecia	Dermis dose	N/A	Variable
Somnolence/lethargy	Unclear	2 mo	Uncommon
Imbalance	Vestibular dose	3-9 mo	Uncommon
RT induced tumors	N/A	4-20 yr	Rare
Radiation necrosis	Dose	Variable	Rare
Leukoencephalopathy	MTX	Variable	Rare

Rx: Dexamethasone for XRT-related edema varies w/ doses & sched, depending on severity. Bevacizumab used off label for intractable radiation necrosis.

Principles: (1) “Memory loss” during/immed after XRT = fatigue, not perm XRT effect. (2) Microvascular changes thought to underlie XRT-related short-term memory loss take months to occur. (3) Hair usu grows back in 2-3 mo. (4) Skin changes typically improve 1-2 wk after completion. (5) Immune cells particularly sensitive to XRT. Optimal to start XRT 2-3 wk after surgery. (6) XRT related nausea & HA usually occurs in the hrs following Rx & improve during Rx breaks (wkends). (7) Cranial nerves relatively resistant; CN I, CN VIII most sensitive (anosmia, tinnitus, hearing loss). (8) Pituitary/hypothalamus: Endocrine abnlities common after XRT to pituitary/hypothalamus & whole brain XRT. Can cause aberration of one or more hormone pathway; evaluate all in w/u; GH most sensitive.

Spec cases

1. Somnolence synd: Early-delayed encephalopathy in children; can range

from drowsiness to exhaustion, may include low grade fever, nausea, & HA.

2. Leukoencephalopathy: White matter injury → mild-severe cognitive defs. Extent of white matter ↑T2/FLAIR doesn't correlate w/clinical severity. A/w concurrent MTX & RT or RT after MTX. Can cause communicating hydro; VP shunt may help.

3. Radiation necrosis: 3-4 mo to 20 yr post-XRT. Sxs localize to area of XRT. CT/MRI shows new area of enhancement, commonly ring-like; cannot distinguish from tumor recurrence on CT/MRI. PET shows hypometabolism. Important to determine if in prior XRT field; only occurs in high dose region. Definitive dx requires bx (can be difficult to interpret).

4. Radiation-induced tumors: 4-20 yr after XRT. New tumor in prior XRT field. Best-established examples: meningiomas, sarcomas, malig periph nerve sheath tumors, high-grade gliomas, patients with cancer predisposition synds at high risk.

Spinal cord & root radiation toxicity: Vascular dz & smoking ↑ risk of XRT toxicity. All plexopathies should be evaluated w/ MRI (tumor vs. XRT-related fibrosis).

Spinal cord: (1) Early: Acute radiation myelop: mild-moderate worsening neurologic def, self-limited, steroid responsive. (2) Early-delayed radiation myelop: 2/2 transient demyelination, peak at 4 mo. Sxs limited to Lhermitte sign usu (occasional neuro def), steroid responsive. (3) Delayed radiation myelop: Subacute-acute onset, dysesthesias paresis, sphincter dysfxn (bowel/bladder). Initially prog, then stabilization. Irreversible. Can be very challenging to disting from recurrent tumor.

Brachial plexopathies (most frequently after breast cancer Rx): Main consideration is recurrent tumor versus XRT injury. Brachial plexus must be confirmed to have been in the high dose radiation field. EMG often shows myokymia in muscles innervated by affected nerves. Tumor: Painful, upper plexus, prog (Horner synd: suspect cervical epidural tumor). XRT: Acute: Painful, reversible palsy that begins during XRT. Early-delayed: 4-6 mo, reversible; paresthesias & sometimes pain, mild to mod wkns. Late-delayed: Months-years, irreversible plexopathy, paresthesias but rare pain, paralysis.

Lumbar plexopathies: Tumor: Painful, direct infiltration, compress, uni/l usually. XRT: early/late delayed (as above); wkns >> pain, usu b/l.

Neurologic Comps of Chemotherapy

Sleep Medicine

SLEEP BIOLOGY

Stages of Sleep

Awake	Low voltage w/ fast frequency; α activity (8-12 Hz), prominent in parietooc-cipital areas, ↓ by eye opening and mental effort, muscle tone present
Drowsy	α dropout, θ activity (4.5-7.5 Hz) appears mixed w/ 15 to 25 Hz activity
Stage I	θ activity (3-7 Hz)
Stage II	Sleep spindle (12-14 Hz) lasts for ≤2 s, K complex (sharp negative wave w/slow positive wave last ≥0.5 s), slow eye movement, persistent muscle tone
Stage3	Δ activity (≤2 Hz) for <50% of each 30 s period examined, eye movements absent, muscle tone present
Stage4	Δ activity (≤2 Hz) for >50% of each 30 s period examined, eye movements absent, muscle tone present
REM	Low voltage, fast frequency, atonia except for rapid eye movements

Note: Stage III and IV have recently combined and now known as Stage III. (*Neurol Clin* 2005;23:967.)

Drug Effects on Sleep

Class	Category	Activity

Antidepressants	TCA	↑ daytime sleepiness, total sleep time. Stage 2 sleep; ↓ REM sleep
	MAOI	↑ daytime sleepiness (b/c ↓ total sleep time); ↓ REM sleep; MAOI withdrawal → REM rebound
	SSRI	↓ total sleep time, REM sleep; assoc w/ somnolence + insomnia; causes: slow eye movements during sleep, restless leg syndrome (RLS), periodic limb movement of sleep, REM sleep without atonia
	Trazodone	↑ daytime sleepiness, total sleep time
	Nefazodone	↑ drowsiness
	Venlafaxine	↓ total sleep time
	Mirtazapine	↑ daytime sleepiness, total sleep time
APS	Haldol	↑ sleep time, Stages 3-4 ↓ REM sleep, sleep latency
	Clozapine	↑ sedation
Sedative hypnotics	Benzodiazepines (BZD)	↑ total sleep time, Stage 2, abnormal sleep spindles; ↓ sleep latency, REM sleep, Stages 3-4; Diazepam, alprazolam: ↓ daytime sleep

		latency; short-acting benzos improve sleep in the first part of night but withdrawal in second part → sleep disruption, fragmentation	
	Barbiturates	↑ daytime sleepiness, total sleep time, Stage 2; ↓ sleep latency, REM sleep, Stages 3-4	
	Zolpidem	↑ sleep quality, Stages 2-4; ↓ REM sleep	
AED	Phenytoin		↑ Stages 3-4 sleep; ↓ REM sleep, daytime sleep latency
	Carbamazepine	↑ total sleep time; ↓ sleep latency	↑ Stages 3-4 sleep; ↓ REM sleep
	Valproic acid		↑ Stages 3-4 sleep
	Phenobarbital		↓ daytime sleep latency
Antihistamines	Diphenhydramine Loratadine	↑ Stages 2-4; ↓ REM sleep	
	Cetrizine	↑ sedation; ↓ sleep	

		latency
	Cimetidine Ranitidine	Insomnia;↑ somnolence (esp in elderly and renal impairment); ↑ Stage 3-4 w/ cimetidine
Others	Nicotine	↑ sedation, sleep disruption; smoking before bedtime → delay sleep onset; withdrawal → ↑ drowsiness, cortical arousal
	Alcohol	↑ Stages 3-4, snoring, sleep disordered breathing; ↓ REM sleep, sleep latency, b/c quick metabolism → rebound increase in arousals during the second part → sleep fragmentation Withdrawal: Insomnia (especially during DTs), ↑ sleep latency, REM sleep; ↓ Stages 3-4
	Caffeine	Insomnia, ↑ arousal frequency during sleep, sleep latency, Stage 1; ↓ REM sleep, Stages 3-4

(APS = antipsychotic drugs, AED = antiepileptic drugs. *Med Clin N Am* 2004;88:751.)

CIRCADIAN RHYTHM D/O

(Sleep 2007;30:1445, 146., 1484.)

Shift work disorder: Definition: Misalignment of circadian rhythms and sleep time caused by shift work. Workup: Sleep-wake diaries, actigraphy (monitors

rest/activity cycle), PSG to rule out other sleep disorders. MEQ scale, core body temp nadir, timing of melatonin secretion are of unproven usefulness in evaluation. Treatment: Planned

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P.271

napping before or during job can improve alertness. Timed light exposure during night shift and light restriction in morning can decrease sleepiness and increase alertness during night shift. Modafinil (FDA-approved), caffeine, methamphetamine (concern for abuse potential) can improve nighttime alertness. Melatonin (2-3 mg) before daytime sleep can promote daytime sleep. BZD can promote daytime sleep but can increase nighttime shift sedation.

Jet lag disorder: Definition: Misalignment of circadian rhythms and sleep time caused by traveling through multiple time zones. Workup: Sleep-wake diaries; actigraphy, MEQ, PSG of unproven usefulness in clinical evaluation. Treatment: Remaining on home-based sleep schedule when time at destination ≤2 days. Melatonin (0.5-5 mg immediate release). Unclear evidence for BZD.

Eastward travel: Before travel, go to sleep and wake up early. After travel, avoid bright light in the AM, then be outdoors as much as possible in the PM. Westward travel: Before travel, go to sleep and wake up later. After travel, exposure to AM sunlight.

Advance sleep phase disorder: Definition: Stable sleep schedule that is several hours earlier than the conventional or desired time. Workup: Sleep-wake diaries, actigraphy, MEQ. Treatment: Evening light therapy, avoid morning light, sleep hygiene.

Delayed sleep phase disorder: Definition: A stable sleep schedule that is substantially later than the conventional or desired time. Workup: Sleep-wake diaries, actigraphy; PSG not indicated; must r/o insomnia. Treatment: Morning light exposure, avoid evening light. Progressive delay of time of bedtime until desired sleep schedule reached (chronotherapy). Timed melatonin administration 1-2 h prior to intended sleep onset. Vit B_{12} not indicated.

Free-running circadian rhythm sleep disorder: Definition: Failure of entrainment with periods of light and dark, common in blind individuals when they lose their sight, occurs in sighted individuals <30 yo. Workup: Sleep-wake diaries, actigraphy, timing of melatonin section, core body temperatures. Treatment: Prescribed sleep/wake schedules. Timed light exposure in sighted patients (circadian phase shifting). Timed melatonin administration at bedtime

in sighted individuals (circadian phase shifting). Timed melatonin administration in blind individuals. Insufficient evidence for vitamin B_{12} in sighted individuals.

Irregular sleep-wake rhythm disorder: Definition: Relative absence of a circadian pattern to the sleep-wake cycle. Workup: Sleep-wake diaries, actigraphy. Treatment: Combination of bright light exposure + physical activity for all patients. Daytime bright light exposure, esp. for nursing home residents with dementia. Melatonin for children w/ severe psychomotor retardation.

SLEEP-RELATED BREATHING DISORDERS

Introduction

Apnea → cessation of nasal/oral airflow for ≥ 10 s. Central apnea → no respiratory effort. Obstructive apnea → respiratory effort. Apnea index → number of apnea per hour of sleep.

Hypopnea → ↓ airflow by ≥30% with desat of ≥4% for ≥10 s (but definitions are variable). Apnea-hypopnea index (AHI) → number of apnea/hypopnea per hour of sleep.

OBSTRUCTIVE SLEEP APNEA

Introduction: Up to 20% of population [if Obstructive Sleep Apnea (OSA) defined by AHI], or 3%-9% if OSA defined by AHI + daytime sleepiness. Prevalence ↑ with age and postmenopausal women. Sleepiness leading to ↓ alertness that interferes with daily ↑ activity. Due to upper airway obstruction (most commonly retropalatal and retrolingual). Severity: Mild: 5-15/h AHI. Moderate: 16-30/h. Severe: >30/h. Risk factors: FH, male, ↑ age/BMI, smoking, EtOH, anatomic factors.

Anatomic factors: Neck circumference > 17 in men >16 in women; Deviated septum, small oropharyngeal size, macroglossia; Large uvula, low-lying soft palate, large tonsils/adenoids.

Clinical features/diagnosis: Daytime sleepiness, witnessed apneas, awakenings with gasping/choking. Consequences: ↑ mortality, HTN →↑ risk with number of AHI and % O_2 desat (BMJ 2000;320:479), CAD, CHF, Stroke, GERD, insulin resistance. PSG: Gold standard for diagnosis, AHI with O_2 sat recorded; EEG after each apnea/hypopnea event shows brief arousal; Events often worse during REM. Neck MRI or CT: If surgery is considered.

Treatment: General measures: quit smoking, ↓ EtOH, lose weight (if 20-50 lb lost, repeat PSG), positional therapy (e.g.: if OSA worse in supine, prevent pt

from sleeping in supine position → tennis ball in back pocket, elevated head/trunk to 30 degrees). CPAP: If AHI > 15/h or for symptomatic pts with AHI ≥ 5/h; Improves sxs and nulls

consequences of OSA; Must be used daily, only 50% pts adhere to it. Oral devices: Well tolerated, for mild-mod OSA who don't tolerate CPAP; Pushes mandible and tongue forward. Upper airway surgery: If surgical cause found (e.g., deviated septum).

Upper Airway Problems

Snoring	Due to vibration or upper airway. Usually has no associated symptoms (minimal daytime sleepiness). More common in men. Risk factors: Sleep deprivation, obesity, smoking, avoid sedatives (EtOH, narcotics, BZD), supine sleeping.	*PSG*: Not needed, and is nl. *Tx*: Avoid sedatives, lose weight, nonsupine sleeping, oral devices, nasal surgery.
Upper airway resistance syndrome	Similar to OSA, but AHI < 5/h and no O_2 desat.	Tx: similar to OSA.

CENTRAL SLEEP APNEA

Introduction: Apneic episodes but without ventilatory effort. Rare, accounts for up to 15% of sleep related breathing d/o. Prevalence greater in middle-aged men. Features: insomnia, daytime sleepiness, repeated awakenings. Can be idiopathic [primary Central Sleep Apnea (CSA)] or secondary (e.g., CHF → 50% have CSA, opiate use). Pathophys: Respiratory drive → metabolic and voluntary systems. In NREM, only metabolic (hypercapneic ventilatory drive) system working. In CSA, CO_2 ventilatory drive ↓, i.e. more CO_2 needs to accumulate before ventilation stimulated. PSG: CSA usually during sleep onset and NREM Stage 1/2. Awake $PaCO_2$: nl.

Treatment: Treat underlying cause of CSA. Supplemental O_2 for select pts. CPAP (especially if CHF). Meds: Acetazolamide: Causes metabolic acidosis thus ↑ respiratory drive. Theophylline/medroxyprogesterone: Stimulates

ventilation. Hypnotics: Only in pts without significant O_2 desat, prevents arousal in sleep onset CSA.

Other Secondary CSA

Cheyne-Stokes respiration	Periodic breathing with ↑/↓ RR, separated by apneas/hypopneas. Due to long circulation time, ↓ $PaCO_2$ and ↑ hypercapneic respiratory drive. Secondary to CHF, neuro (stroke, tumor) elevation to high altitude, renal failure.	*PSG*: Usually occurs sleep onset and Stage ½. *Tx*: Improve CHF, supplemental O_2, CPAP.

Sleep-related Hypoventilation Syndrome

Obesity hypoventilation syndrome	BMI ≥ 40 kg/m^2 and hypercapnia ($PaCO_2$ > 45 mm Hg). Hypoventilation not due to anything else (e.g., lung disease). May have OSA as well. Sis/sxs: sleepiness, insomnia, awakenings. Hypercapnia due to respiratory drive, ventilation (due to restrictive effects of obesity).	*Tx*: Lose weight, CPAP.
Congenital central hypoventilation syndrome	Presents at birth, due to chemoreceptor disorder. Chronic course, death due to respiratory failure or cor pulmonale.	*Tx*: nocturnal or sometimes 24 hr ventilatory support (BiPAP).
Other causes of hypoventilation	Lung dz. Lower airway obstruction. Chest wall/diaphragm dz. Neuromuscular dz.	

EXCESSIVE SLEEPINESS

Introduction: Sleepiness leading to ↓ alertness that interferes with daily activity. 5% of general population. All excessive sleepiness treated like narcolepsy (naps, or stimulants) after ensuring adequate sleep duration and quality. Classification: Mild: Sleepiness at rest, with minor functional impairment. Moderate: Sleepiness during mild activity, with moderate impairment. Severe: During physical activity (eating, talking), marked impairment.

NARCOLEPSY

Introduction: 0.05% of population, onset in teens/early adulthood. Excessive sleepiness with intrusion of REM during wakefulness (cataplexy, sleep paralysis, hypnagogic

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hallucinations). Only ˜15% have all four symptoms (so consider narcolepsy even in pts with just sleepiness). Most cases sporadic, but familial pattern in up to 1/3.

Clinical Features

Sleepiness	Most common/disabling/first sx. ↓ after nap. *Sleep attacks*: Occur during inappropriate times, irresistible, generally short, can be preceded by drowsiness or occur suddenly.
Cataplexy	Present in 80% of pts (usually appears ˜1 yr after sleepiness). Bilateral abrupt, transient loss of postural tone. Precipitated by intense emotion (laughter, anger). Usually <2 min, gradually improves, severity varies (from mild to severe weakness). No changes in mental status, respiratory and oculomotor muscles spared. Thought to be intrusion of REM atonia into wakefulness. Pts can have narcolepsy without cataplexy.
Sleep paralysis	Inability to move at onset of sleep or awakening (despite being awake). Can be present in nl people. Again spares oculomotor and respiratory muscles and no change in mentation.
Sleep	30% of pts. Occur at sleep onset or awakening.

hallucinations	Usually fearful.
Sleep disturbances	80% have repeated awakenings and poor sleep quality.
Other features	Automatic behavior: inappropriate behavior (i.e. say something out of context) without memory of event.

Pathophysiology: Associated with HLA, DR2, and DQ1. Narcolepsy can be due to medical dz (brainstem or hypothalamic lesion, encephalitis, head trauma, PD). Hypocretin deficiency: Secreted by lateral hypothalamus, regulates sleep-wake cycle. ↓ levels of CSF hypocretin and (postmortem) ↓ hypocretin neurons → cause of narcolepsy with cataplexy. CSF hypocretin ≤ 110 pg/mL: highly specific (˜99%) and sensitive (˜90%) for narcolepsy with cataplexy (JNNP 2003;74:1667); not sensitive for pts with atypical, mild, or without cataplexy. Other theories: Cholinergic, noradrenergic, histaminergic, serotonergic, and dopamine dysfxn.

Diagnosis

PSG	Sleep fragmentation, frequent awakenings. Short sleep latency (i.e., falls asleep in <10 min). Sleep-onset REM period (SOREMP i.e., REM appears ≤ 20 min of sleep onset).
MSLT	Occurs after PSG and consists of 5 naps. Mean sleep latency ≤8 min. At least 2 SOREMPs (can be present in nl pts, sleep deprivation, other sleep disorders). False negative in up to 30%. Occurs at sleep onset.

Treatment: Improve sleep hygiene, scheduled brief naps (30 min) helpful.

Treatment

Sleepiness	Modafinil, dextroamphetamine, methylphenidate. If continued sleepiness despite meds, look for other sleep d/o.
Sleep disturbances	Sodium oxybate (λ-hydroxybutyrate): First line, ↓ awakenings; helps all REM related sxs.

	Other hypnotic agents can be helpful (BSD, zolpidem).
Cataplexy, sleep paralysis, hallucinations	Sodium oxybate. Meds that suppress REM sleep: SSRIs (fluoxetine, given during daytime since also has stimulant effect. TCAs (given at night, since causes somnolence. Other antidepressants (venlafaxine).

Medications

Modafinil	First line: Due to longer half life, low abuse potential, well studied (*Neurology* 2000;54:1166). Start at 100-200 mg in AM, add 100-200 mg at lunch if sleepiness occurs in late afternoon. Mild side effects (nausea, nervousness). Upregulates cytochrome P450 →↑ OCP metabolism. OCP must contain at least 50 µg of ethinylestradiol. Note: r-modafinil recently introduced, longer half-life than modafinil
Methylphenidate	Dopamine reuptake blocker. Dose range 10-100 mg, less abuse potential then amphetamines, tolerance can occur. Side effects similar to amphetamines but less severe.
Amphetamines	Promote NE and dopamine release. Frequent side effects: Insomnia, nervousness, arrhythmias. Rapid tolerance with potential for abuse.
Sodium oxybate	Helpful for all core sxs: Insomnia, cataplexy, daytime sleepiness, hallucinations (*Sleep* 2002;25:42). Start at 4.5 g: Divided into 2.25 g at bedtime, then 2.5-4 h later (when they spontaneously awake or by alarm) another 2.25 g. Dose can be ↑'d 9 g (total). ↓ risk of rebound cataplexy if med d/c'ed (*Sleep Med* 2004;5:119) → unlike antidepressants.

Other Causes of Excessive Sleepiness

Idiopathic hypersomnia	Severe, chronic, and constant excessive sleepiness without a known cause. Up to 10% of pts referred to sleep clinic. Begins insidiously in teens/early adulthood, may be preceded by viral illness. Pathophys unknown: ? failure of CNS to inhibit NREM sleep. Other causes must be excluded. PSG to r/o other dz. *MSLT*: Only reduced sleep latency noted. *Tx*: Stimulants (not very effective), improve sleep hygiene.
Insufficient sleep syndrome	Chronic, unintentional (but voluntary) failure to obtain sufficient amount of sleep. Sleeping less than actually needed, due to work, school, lifestyle. Leads to sleep deprivation. *Dx*: Hx, sleep log, PSG (not required). *Tx*: Sleep more!
Kleine-Levin syndrome	Hypersomnia (excessive sleep), binge eating, and hypersexuality. Occurs in adolescent men, remits by adulthood. Sleeping for > 16 h for days-weeks, recurring at least 2x a yr (Associated with binge eating, hypersexuality, disinhibited behavior). *Pathophys*: Unknown. Course is self-limited. *Tx*: Not been useful, dz self-limiting. *Recurrent hypersomnia*: Hypersomnia without other symptoms (i.e., binge eating).
Post-traumatic Hypersomnia	Occurs after head trauma (especially to hypothalamus, brainstem). Gradual improve over weeks-months. No Tx needed.
Other causes	*Idiopathic recurrent stupor*: Rare, without underlying cause, stupor last up to days, *Tx*: Flumazenil (BZD receptor antagonist) halts stupor. *Subwakefulness syndrome*: Rare, only ˜50 reported cases, chronic, pt c/o sleepiness, but studies nl. *Menstrual-related hypersomnia*: Sleepiness during premenstrual period, nl at other times, if disabling use OCP to stop ovulation.

	Medications: anticonvulsants, SSRIs, sedatives.
Secondary excessive sleepiness	*Sleep d/o*: Sleep apnea, restless leg, circadian rhythm d/o *Medical d/o*: Addison, hypothyroidism, chronic fatigue syndrome. Sleeping sickness: Due to protozoa *T. brucei*, spread by tsetse fly in sub-Saharan Africa, fevers (systemic sxs) with progressive sleepiness → coma/death (from encephalitis) if untreated. *Neuro d/o*: Dementia, PD, sleep related sz. Sleep related neurogenic tachypnea: ↑ RR during sleep → sleep disruption thus daytime sleepiness. Fragmentary myoclonus: adult males, asymmetric jerks of muscles of face or limbs, usually at sleep onset, pt not usually aware, leads to sleep disruption → daytime sleepiness. *Psych d/o*

PARASOMNIAS

Introduction: Parasomnias: Undesirable behaviors or physical acts during sleep. Classification: Disorder of arousal; Associated with REM sleep; Other.

DISORDER OF AROUSAL (SEE BOX BELOW)

Occur out of NREM (usually Stage 3/4) in the 1st third of night. Mostly in children, ↓ with age, rare in adults, + FH. Amnesia for event (in all cases in the table below). Risk factors: Fever, stress, sleep deprivation, EtOH, pregnancy, menstruation. Higher concordance for monozygotic twins. Ddx: seizure, restless leg, panic attacks.

Disorders of Arousal

Confusional arousal	Episodes of confusion, disorientation, inappropriate behavior → after arousal from NREM (usually). Lasts 5-15 min (can last hours). *Two subtypes*: **(1)** Severe morning sleep inertia → occurs in AM. **(2)** Sleep-related abnl	*PSG*: ± alpha rhythm, microsleeps, NREM sleep Stage 1 (during episode). *Tx*: TCA, BZD,

	sexual behavior → masturbation, sex.	scheduled awakenings (wake up 15 min before nl time, then let child fall back asleep).
Sleep terrors	Sudden awakening from NREM with fear (with confusion, crying).	*Tx*: Safe sleep environment, if child gets injured → TCA, BZD, SSRIs.
Sleepwalking	Rare in adults (usually had it as kids). Arousal from NREM, leading from simple to complex motor behaviors (driving a car). Eyes usually open, pt not interactive with environment, incompletely awake. HLA DQB1*05 implicated. SPECT during episode → activation of thalamocingulate pathway, with other pathways deactivated (*Lancet* 2000;356:484).	*PSG*: Usually not needed, arousal from Sage 3/4, first NREM-REM cycle (multiple disordered arousals, ↑ delta activity prior to arousal). *Tx*: Usually not needed, BZD (taper after 5-6 mo).

PARASOMNIAS ASSOCIATED WITH REM REM sleep behavior disorder (RBD)

Introduction: < 1% of population, 90% males, ˜60 yo. During REM, muscles paralyzed (i.e., sleep atonia). In RBD, during REM pts act out dreams (simple to complex motor behaviors). Dreams often violent/scary → leading to violent behavior (96% of pts report injury to themselves or partners). Pts often recall dreams, occur in latter half of night, when REM is more frequent. Most often due to neuro dz (PD, MS, dementia, brain tumor, stroke). Strong association with Lewy body disease. 38% of pts developed Parkinson disease by 3 yr and >80% at long-term follow-up. RBD + PD → more frequent cognitive impairment or hallucination. MSA: 90% have RBD, and in about

half (44%) RBD preceded. Pathophys: REM sleep atonia due pedunculo-pontine nucleus (PPN) + other brainstem structures; In PD, PPN affected, leading to RBD.

Diagnosis: Video PSG (± EMG on UE): REM sleep with motor activation. In PD pts, movement during REM not bradykinetic, slow, but ballistic (movement bypasses BG).

Treatment: Safety: Remove dangerous objects, place cushions around bed (in case pt falls). Clonazepam: Doesn't re-establish sleep atonia, but ↓ motor activity; Other BZD not as effective; Stop med → RBD recurs. Melatonin: Second line, re-establishes sleep atonia; Start at 3 mg 30 min before bedtime (titrate qwk to 12 mg/night). Dopamine agonists (since RBD associated with PD): Little evidence for its use.

Other Parasomnias

Enuresis	Involuntary bed-wetting in kids > 5 yo, more common in boys. *Primary* if always had bed-wetting (more common), *secondary* if no bed-wetting for 6 mo (˜15% of cases, can be due to stress, abuse). Due to failure to arouse to bladder fullness, → urine production in sleep. *Tx*: desmopressin (enhances renal water reabsorption), TCA (anticholinergic effect), behavioral therapy (enuresis alarm system).
Exploding head syndrome	More common in women. Occurs on falling asleep or wakening up. Sensation of explosion or loud noise. Benign, though frequent attacks cause insomnia. Worsen with stress/fatigue. Improves with time. *Tx*: Clomipramine.
Nocturnal eating (drinking) syndrome	Repeated arousal from sleep with involuntary eating/drinking (daytime: nl eating behavior). Pt completely or partly unaware. Rare, more common in women. *Risk factors*: stress, mood d/o, EtOH withdrawal, smoking. *Tx*: SSRI, BZD, dopaminergic agonists.
Nocturnal leg cramps	Painful spasms in leg, wakes pt up. Occurs in most adults (more common in elderly, DM/endocrine d/o, fluid/lytes imbalance, exercise, pregnancy, OCP, PVD,

	NMJ d/o, PD). Labs: TSH, BMP. *Tx*: Only if cramps cause insomnia, quinine (avoid in pregnancy/liver failure), baclofen.
REM sleeprelated sinus arrest	Rare, asystole can last ˜9 secs. Usually in healthy young adults with nl CV. Possibly due to autonomic dysfxn. *Tx*: usually not indicated, but pacemaker may be needed.

P.276

INSOMNIA

Introduction: Most common sleep disorder, 1/3 of all adults with occasional insomnia, W > M; Pts c/o fatigue, difficulty with cognition, slow mentation; Often subjective tests nl (e.g., PSG, MSLT), but pts with altered perception concerning their sleep (i.e., sleep little, when in fact sleep nl); Many different factors lead to insomnia: stress, new job, poor sleep hygiene, anxiety.

Insomnia Classification

Duration	*Acute*: Few days up to a month. *Chronic*: > 1 month.
Temporal profile	*Sleep-onset insomnia*: Trouble falling asleep. *Sleep maintenance insomnia*: Multiple or prolonged awakenings. *Terminal insomnia*: Early awakening. *Nonrestorative sleep*: Not feeling refreshed.

Evaluation of insomnia: Consider onset, duration, and consequence of insomnia. Obtain list of meds; Habits: caffeine intake, lights out, awake, naps. Sleep log for 1-2 wk helpful. PSG: Usually nl, not indicated; May be abnl as pt is sleeping in new locale → “first night” effect; May be nl in pts with psychophysiologic insomnia (as sleep lab not associated with anxiety).

Acute/transient insomnia

Etiology of Transient Insomnia

Adjustment sleep disorder	Acute stressor (divorce, death, physical illness) → difficulty sleeping. Usually older women (but any age

	group or men). Brief course, sleep nl once stressor resolves.
Jet lag	Resolves spontaneously in few days. Westward travel → early waking (due to time now earlier). Eastward travel → difficult falling asleep (due to time now later than used to).
Shift work sleep disorder	Due to shift work outside normal times (e.g., night shift). Sleep affected and misaligned from environmental/social cues.

Chronic insomnia: Many different etiologies: Medical to neurologic, and primary insomnia (not caused by other sleep or medical disorder).

Primary Insomnia (Causing Chronic Insomnia)

Psychophysiologic insomnia	15% of chronic insomnia, young adults, usually women. Due to maladaptive behavior preventing sleep (e.g., stressor causes insomnia, stressor removed but insomnia persists due to fear of insomnia). Pts anxious/concerned/preoccupied with sleep. Often have conditioned arousal → can sleep better in other places than their own bed. *Dx*: By Hx, PSG generally not helpful.
Paradoxical insomnia (sleep state misperception)	Pt c/o extreme sleep loss, but daily fxn of pt and PSG nl. Women, early- to mid-life. Insomnia can persist for years.
Idiopathic insomnia	Long-standing, starts in childhood, no underlying etiology. Insidious onset, chronic course, often refractory to Tx. Possibly secondary to CNS dysfunction slee-pwake cycle disruption.

Other Causes of Chronic Insomnia

Parasomnias	Sleepwalking, RBD.

Circadian-rhythm d/o	Biological and environmental clock not in sync (see above).
Medical causes	*Pulmonary*: OSA. *Cardiovascular*: CHF, CAD, nocturnal cardiac ischemia. *GI*: GERD, peptic ulcer, sleep-related abnl swallowing syndrome (pt with difficulty swallowing saliva during sleep). *Pain*. *Pregnancy*: Menstrual associated sleep d/o (insomnia during premenstrual period, cause unknown), pregnancy associated (improves after delivery).
Neurologic	Dementia, Parkinson's, Huntington's, seizures, sleep-related HAs.
Psychiatric	Strong correlation with insomnia. Mood disorders, personality disorders, anxiety, panic, PTSD.
Meds	Alcohol, steroids, OCPs, nicotine, Anti-HTN, Bronchodilators, AED, anticholinergic, some Parkinson meds.
Behavioral	*Poor sleep hygiene*: Spend too much time awake in bed, going to bed at different times, frequent daytime napping. *Sleep-onset association disorder*: Usually child, refusing to fall asleep without certain condition (e.g., pacifier, toy), 15% of boys 6 mo-3 yr. *Nocturnal eating* (*drinking*) *syndrome*: Awakening to feed though not hungry, due to learned behavior.
Environmental	Adverse sleeping conditions: loud, bright, snoring bed partner. Food Allergy Insomnia → children, frequent arousals with other sxs of allergies (e.g., rash, GI upset). Toxin-induced → different toxins can produce insomnia. Altitude insomnia → insomnia for ascent, due to periodic breathing with central apnea from hypoxia/resp alkalosis.

Treatment: Prompt Tx of acute insomnia before it develops into chronic due to learned behavior.

Nonpharm Tx

Sleep hygiene/habits	Same bedtime (even on weekends). Awake at same time. No daytime naps, No smoking, EtOH, or smoking near bed time. No strenuous exertion late in evening. Exercise beneficial (but not 3-5 h within bedtime). If can't sleep in 30 min, leave bed and do quiet relaxing activity (reading). Clocks: if causes anxiety, turn off. Rooms should be dark/quiet. Bed use only for sexual activity and sleeping.
Light therapy	Tx for circadian rhythm d/o.
Behavioral techniques	Most insomniacs benefit, but may take wks. *Relaxation*: Progressive relaxation, visualized pleasant environment. *Cognitive behavioral therapy* (*CBT*): Address unrealistic beliefs with sleep. *Paradoxical intention*: Instruct pt to remain awake as long as possible. *Sleep restriction*: Limit time in bed to actual total sleep time, causes sleep deprivation but improves sleep efficiency, e.g., spends 9 h in bed, but sleeps 6 h → should only spend 6 h in bed, then adjust time in bed according to sleep efficiency (total sleep time/time in bed = 100%); If efficiency < 80%, ↓ time in bed by 15 min, if > 90% ↑ time in bed by 15 min.

MEDICATIONS FOR INSOMNIA

Should only be used for short term (or very select pts with chronic insomnia). Hypnotics → improve sleep, but not daytime performance. Taper BZD slowly (consider adding CBT with taper).

Medications

Non-BZD receptor agonist	Zolpidem, Zopiclone, Eszopiclone, Zaleplon. Unlike BZD, no anxiety or antiSz effect, ↓ risk of tolerance and rebound insomnia.
BZD	Most given at bedtime. Triazolam, estazolam, temazepam, flurazepam. Side effects: Cognitive

	impairment, rebound insomnia once med d/c'ed, withdrawal symptoms, tolerance, dependency.
Antidepressants	Trazodone: 25-100 mg at bedtime. Mirtazapine, nefazodone, TCA.
Other meds	Ramelton: Melatonin receptor agonist. Antihistamines (diphenhydramine): Few studies proving effectiveness for insomnia. Melatonin: Helpful for circadian rhythm disturbances (jet lag, shift work). Herbal supplements: Little evidence.

RESTLESS LEG SYNDROME

Introduction/symptoms

Criteria for dx: An urge to move legs ± associated with unpleasant sensation, worse at periods of rest, relieved by movement, worse at night. Unpleasant sensation: Deep in limbs, can be bilateral, can involve arms in progressive dz. Symptomatic causes of RLS: Iron deficiency: Most common cause of RLS, usually associated with low ferritin (often no anemia is detected). Renal failure, rheumatoid arthritis, fibromyalgia, pregnancy.

Periodic limb movement of sleep: Periodic jerking during sleep that often accompany RLS; Pt unaware of movements; Usually doesn't need treatment unless associated with daytime sleepiness (if sleepiness, treat like RLS); Discovered on PSG.

Diagnosis: EMG/NCV if associated neuropathy/radiculopathy; Ferritin (most sensitive test for iron deficient anemia) all pts; Ddx: Neuropathy/radiculopathy (no urge to move and not usually worse at night), neuroleptic induced akathisia (i.e., motor restlessness, from antipsychotics that block dopamine receptors).

Treatment: Sleep hygiene, iron supplement and underlying cause for pts with low ferritin (<50 is cutoff). Dopaminergic drugs are 1st line, then opiates, anticonvulsants (gabapentin), and BZD (clonazepam because long acting). Tx close to onset of Sxs. Start at lowest dose, titrate slowly. Mild or intermittent dz → levodopa. Moderate or severe dz → dopamine agonists.

Tx complications: (1) Augmentation: Sxs earlier, more severe, involves other body parts, due to dopaminergic meds, Tx by d/c med for severe cases or adding an early dose for milder cases. (2) Rebound: i.e., withdrawal from med, sx appear at med half-life, occurs in AM.

Pregnancy Neurology

IMAGING IN PREGNANCY

Balance the risks and the benefits to both mother and fetus. Both CT and MRI entail potential danger to the fetus.

When scanning the mother during pregnancy: Involve patient and family, obstetrician, and radiologist in discussion, and document this. Modify MRI and CT exams under the direction of radiology to be as informative as possible with as little exposure as possible (e.g., minimize sequences, contrast exposure, etc.). Avoid all imaging in the first trimester if possible, and delay elective imaging until after the delivery. Consider alternate imaging modalities (e.g., ultrasound) or diagnostic approaches (e.g., LP). MRI generally a safer option than CT. Abd shielding during CT head is of questionable benefit for fetal protection, but may help reduce maternal anxiety. Gadolinium is a category C drug in pregnancy, and should be avoided. Iodinated contrast is a category B drug.

Head CT: No human studies for ionized radiation, but there is risk for pregnancy loss, malformations, carcinogenic effects, growth/developmental delays. Fetal radiation exposure during maternal head CT is very minimal. And at that level of fetal radiation, there is no evidence for fetal malformation, development/growth delays, or pregnancy loss. Risk of CA in the fetus, controversial, but generally felt that the risk is unlikely to be greater than 1/1,000 children exposed (Obstet Gynecol 2004;104:647). Iodinated contrast can be used during pregnancy.

MRI: Safe to use, no reported harmful effects. Gadolinium: Due to long half-life and limited data, do not use unless benefit outweighs risk.

THE NEUROLOGY OF PRE-ECLAMPSIA/ECLAMPSIA

Epidemiology: Pre-eclampsia/eclampsia → leading cause of maternal death in the US, affecting up to 8% of pregnancies. Eclampsia in one pregnancy predicts 46% risk in subsequent pregnancy. Overall mortality is ˜9%-23%, highest early in the pregnancy.

Clinical features: Hypertension in pregnancy → BP ≥ 140/90 after 20 wk gestation. Proteinuria in pregnancy → 1+ protein reading on a random urine test dipstick. Pre-eclampsia → ↑ BP and proteinuria after the 20th wk of pregnancy. Severe pre-eclampsia → considered to be present with one or more of the following criteria: BP ≥ 160/110 (on two occasions); Proteinuria

(3+ or more on two random urine samples); Oliguria < 500 mL/24 h; Pulmonary edema; Diffuse peripheral edema; Abnormal LFTs; Thrombocytopenia; Impaired fetal growth; HELLP syndrome. Eclampsia → Sz+ Pre-eclampsia (exclude other causes of Sz → venous sinus thrombosis, stroke, and ruptured aneurysms). Relation to delivery: >70% occur prior to delivery, 25% before labor, 50% during labor, 25% after delivery. Eclampsia before 20 wk rare, and suspicion should be high for molar pregnancy, multiple pregnancy, or noneclamptic neurologic disease. HELLP syndrome → Hemolysis, elevated liver enzymes, and low platelet counts (below 100,000 to 150,000/mm^3).

Cerebral pathology: Mechanism of pre-eclampsia/eclampsia: unclear. Cerebral pathology due to vascular injury from ↑ BP and predisposition to coagulopathies. Entire neuroaxis subject to potential ischemia, edema, or hemorrhage.

P.279

Imaging: MRI preferable, with similar findings to PRES.

Management: Therapeutic goals: Protecting the fetus (with delivery if possible); Controlling hypertension to within the normal range for the individual patient; Suppressing seizures.

Seizures: Magnesium sulfate mainstay of management, not traditional antiepileptics. Mechanism of action for magnesium sulfate → antivasospastic effect. If Mg fails, add antiepileptic drugs of proven efficacy: lorazepam or phenytoin. Blood pressure: HTN associated with eclampsia often adequately controlled by stopping seizure. Goal diastolic blood pressure < 110 mm Hg. Meds: Hydralazine, nicardipine, labetalol, nifedepine. Avoid ACE-I because of potential toxicity to the fetal kidneys. Avoid diuretics in eclampsia, unless indicated for maternal symptoms (e.g., pulmonary edema), because these pts often intravascularly depleted.

Neurologic prognosis: ˜ 10% of patients have repeated seizures without treatment. Up to 56% of patients with eclampsia may have transient deficits, including cortical blindness. ICH usually associated with BP > 170/120 mm Hg, and responsible for up to 20% of eclamptic deaths. Ischemic stroke accounts for 5% of pregnancy-related maternal deaths in the U.S. Range of increased perinatal mortality is 5% (for history of pre-eclampsia) to 45% (for abruptio placentae). Seizure duration has not been associated with increased perinatal mortality.

CEREBROVASCULAR DISEASE IN PREGNANCY

Ischemic stroke: Stroke in young patients due to: Heart disease, substance

abuse, coagulopathies, arterial dissection, early atherosclerosis. Pregnancy and the postpartum period ↑ relative stroke rate, with up to 35% of strokes between ages 15 and 45 being related to pregnancy. Overall risk of stroke in pregnancy generally low and largely the result of background risk factors. The postpartum period: greatest risk. The major specific risk factors are pre-eclampsia/eclampsia and hypercoagulability. Standard stroke imaging should be pursued under the guidelines discussed in the “Imaging in Pregnancy” section of this chapter.

Treatment: Acute arterial occlusion: Standard stroke treatment employs the use of IV tPA, not well studied in pregnancy. Potential complications include: uterine or fetal hemorrhage, pregnancy loss, hemorrhagic complications in the mother. Use of thrombolysis has largely been free of major adverse effects and fetal tPA exposure is likely very low. Consider thrombolytic therapy for potentially disabling strokes, but have OB service on alert in the event of the need for emergent delivery of the fetus. If emergent delivery needed within 24 h of tPA, then effects of tPA need to be reversed. IA therapy should also be considered (risk to the fetus likely minimal).

Imaging in pregnancy: U/S and MRI preferred over ionized radiation (see above).

CEREBRAL VENOUS THROMBOSIS

Introduction: Young to middle aged pts (˜75% women), ˜80% of pts with good outcome. Poor pts with age > 37 yo, male, coma, altered mental status, GCS < 9, ICH on admission, DVT, CNS infection, and CA (Stroke 2004;35:664). Recurs in 2% of pts.

Etiologies: Genetic: Antithrombin III, protein C/S deficiencies, factor V Leiden, prothrombin gene mutation, homocysteinemia. Acquired: Pregnancy/puerperium, nephrotic syndrome, antiphospholipid syndrome, homocysteinemia, malignancy. Infection: Sinusitis, otitis, mastoiditis, meningitis. Rheum. Meds: OCP, hormone replacement therapy, asparaginase, tamoxifen, steroids. Trauma: Neurosurgery, IJ central line, LP.

Clinical manifestations: Highly variable; HA (90% of pts) gradual in onset usually (may be thunderclap in some cases); Neurologic si/sxs develop in 50% of pts; Seizures in 40% of pts (half of which are focal/limited). ICH: 40% of pts, even prior to anticoagulation. Cavernous sinus thrombosis: proptosis, periorbital edema, chemosis, and CN III, IV, V palsies.

Diagnosis: Consider dx in younger pts with no risk factors with stroke sxs, unusual HA, ICH, intracranial hypertension. MR or CT venography (angiography if CT or MR negative).

Risk factor workup: Most pts have identifiable risk factors (˜50% have multiple ones), ˜13% cause of SVT unknown (Stroke 2004;35:664). Following labs in all pts (since pts can have multiple risk factors): Antiphospholipid syndrome (including lupus anticoagulant), prothrombin G20210A gene mutation, Factor V Leiden, protein C/protein S/antithrombin III deficiencies, homocysteine. LP: If pt febrile. Look for malignancy in older pts without risk factors.

Treatment: Anticoagulation: Heparin (even if ICH present) goal PTT 2-2.5× baseline, bridge to warfarin for 6 mo or longer with INR goal 2-3.2 main trials: First trial: 20 pts, long treatment delay, avg. 4 wk, stopped early due to significant benefit with heparin (based on a SVT scale, authors argue other stroke scales do not account for all sxs of SVT) (Lancet 1991;338:597). Second trial: 59 pts, SC LMWH used, no statistical difference but trend toward better outcome with LMWH, possible imbalance at baseline favoring placebo group (Stroke 1999;30:484). Meta-analysis of both trials: nonsignificant trend toward fewer death and dependency, anticoagulation safe with no new ICH occurring in either trial (Cochrane 2004;4:CD002005).

Endovascular: Reserved for pts with poor prognosis and worsening pts despite heparin, limited evidence. Administration of urokinase or rt-PA or mechanical disruption.

Seizures: AED in pts with both seizures and parenchymal lesions on imaging —edema, ischemic/hemorrhagic infarct → these pts have higher risk of szs (Cerebrovasc Dis 2003;15:78); Otherwise no AED; Tx for a year.

Intracranial HTN: Rare complication. LP: for pts with worsening vision and intracranial hypertension, no heparin for at least 24 h after procedure, remove enough CSF to normalize closing pressure. Consider acetazolamide 500-1,000 mg daily. Surgery: If above measures fail, VPS or fenestration of optic nerve; Other Tx to consider: Mannitol/hyperventilation.

Future pregnancy: No contraindication for future pregnancy in pts with prior cerebral venous thrombosis (CVT). Anticoagulate during pregnancy with h/o CVT only if prothrombotic condition or other thromboembolic event (PE, DVT), dose-adjusted heparin or LMWH (with factor Xa monitoring) in third trimester up to 8 wks postpartum.

HEMORRHAGIC STROKE

In pregnancy, hemorrhage is usually associated with pre-eclampsia/eclampsia and AVMs.

HEADACHE IN PREGNANCY

Primary Headache Disorders
Migraine
Tension
Cluster
Hemicrania continua
Primary thunderclap headache

Secondary Headache Disorders

Blood	CSF
Intracerebral hemorrhage	Idiopathic intracranial hypertension
Ischemic stroke	
Vascular malformation	Hydrocephalus
Subarachnoid hemorrhage	Spontaneous intracranial hypotension
Subdural hematoma	
Cervical artery dissection	**Parenchyma**
Pituitary apoplexy	Primary neop|asm
CVT	Secondary neoplasm
Retroclival hematoma	Brain abscess
Pre-eclampsia	Encephalitis
Vasculitic syndromes	Meningitis
Reversible cerebral vasoconstriction syndromes	

Referred Head Pain

Otitis media

Sinusitis

Temporomandibular joint syndrome

Trigeminal neuralgia

Acute angle-closure glaucoma

Cervicogenic headache

MIGRAINES

Migraine prevalence higher during the reproductive years and shows a variable pattern during pregnancy. As a rule of thumb, 1/3 of patients improve, 1/3 worsen, and 1/3

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remain unchanged. Medication discontinuation should be attempted before conception. If not possible, then those rated as safest by the FDA should be used. Clomiphene may increase the risk of migrainous infarction and so should be avoided in any patient with a complicated migraine history. Migraine → no increased risk of malformation in infant but ↑ risk of maternal complications during pregnancy.

Treatment: The risk of migraine therapy in pregnancy largely anecdotal and conjectural because of the absence of randomized studies.

Acute treatment for migraine: Triptans—FDA pregnancy Class C. Ergots—Absolutely contraindicated (can cause fetal growth retardation). NSAIDs—Ibuprofen is the best choice and can be used in the first trimester at a dose of 200-600 mg PO q6h (avoid aspirin, indomethacin, and other potent prostaglandin synthesis inhibitors because of the risk of constriction or closure of the fetal ductus arteriosus). Acetaminophen— FDA pregnancy category B and an excellent choice. Narcotics—Combinations with acetaminophen can be safely used. Magnesium sulfate—The preferred treatment when it is difficult to distinguish between pre-eclampsia and migraine or when the two overlap.

Acute treatment for associated symptoms (e.g., N/V): Phosphorylated

carbohydrate solution 15-30 mg PO q 15min (for mild cases). Metoclopramide (Pregnancy Class B); Chlorpromazine (C); Promethazine (C); Prochlorperazine (C); Prednisone (C).

Prophylactic therapy: Justified if frequency and severity of migraines are disabling. Begin with nonpharmacologic therapy such as biofeedback and relaxation therapy. If medication is required, first line should be: Propanolol (fetal growth should be monitored for risk of intrauterine growth retardation). Folic acid supplementation (1-5 mg daily) crucial for women using valproic acid as preventive therapy. Also consider magnesium supplementation for prophylaxis in difficult cases.

Lactation: Migraine treatments that are safe for both breastfeeding and pregnancy include: Triptans; acetaminophen; caffeine; opioids; propanolol; metoclopramide is highly concentrated in breast milk and should be used with caution postpartum.

MULTIPLE SCLEROSIS IN PREGNANCY

Reproductive issues in multiple sclerosis

Contraception: Condoms: safe and effective choice. Oral contraception agents ↑ DVT risk, and should be used with caution in patients with ↓ mobility and spasticity. IUDs not advisable because sensory abnormalities may impair detection of IUD migration. Barrier protection (diaphragms and sponges) may be difficult if patients suffer sensory changes and impaired fine motor control.

Sexuality: Sexual dysfunction (vaginal dryness, changes in sensation, and failure to achieve orgasm) affects 50%-90% of women (and men) with multiple sclerosis (MS).

Genetics: Majority of patients have no family history of MS. Risk for developing MS is close to 4% if one parent has MS; If both parents affected, risk approaches 20%.

Pregnancy with MS: Considerable controversy. Likely ↓ MS relapse rate in pregnant patients and ↓ disease-related disability during pregnancy. No clear association exists between disability and the following: Total number of term pregnancies, timing of pregnancy relative to onset of MS, onset or worsening of MS during pregnancy, epidural anesthesia use, breastfeeding. 20%—40% of patients have relapse within 3 mo after delivery. Postpartum MS relapse is correlated with: ↑ relapse rate in the year before pregnancy, ↑ relapse rate during pregnancy, ↑ Expanded Disability Status Scale (EDSS) score at the onset of pregnancy. Delivery can proceed per the preferences of the obstetrician (i.e., C-section or vaginal). Patients with MS marginally more likely to deliver infants of low birth weight, potentially due to neuronal

dysfunction in pelvic organs producing suboptimal intrauterine conditions.

Management

Disease activity: IV steroids: For acute relapses. No association with fetal malformations, and intravenous steroids safe in the second/third trimesters of pregnancy. Placental passage allows transient neonatal effects (leukocytosis with dexamethasone, immunosuppression with methylprednisolone). Intravenous immunoglobulin (IVIg); acute relapse. Low rate of maternal side effects and no adverse effect on the developing fetal immune system. Breastfeeding is not contraindicated during IVIg therapy. Immunomodulating agents (Interferons B/b and B/a and glatiramer acetate) cause fetal loss in human pregnancy (40% compared to 5% in the first trimester). Should the pregnancy hold, no fetal malformations have been described. Azathioprine: FDA designated as a category D medicine, but a large body of data exists in pregnant patients with other pathology (autoimmune or transplant related) without clear evidence of teratogenicity. Consider its use in the chronic setting for patients

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with intractable disease. Dose is 1 mg/kg daily for 6-8 wk, then increase. Cyclosporine A: crosses the placenta easily, but its use has not been associated with dramatic fetal effects. As such, consider it in later trimesters of pregnancy for difficult cases. Dosage is 7-9 mg/kg/day. Methotrexate and cyclophosphamide: both carry FDA designation as category X agents. They are contraindicated in pregnancy due to risk of CNS defects.

EPILEPSY IN PREGNANCY

Epidemiology: Epilepsy most common neurologic disorder in pregnant women, affecting 3-5 births per 1,000 in the U.S.

Reproductive issues in epileptics: Sexuality: ˜33% to 50% experience some degree of sexual dysfunction. Contraception: AEDs ↓ efficiency of oral contraception by enzyme induction. Higher dose OCPs (containing 50 µg of ethinyl estradiol) recommended for patients taking AEDs that are associated with enzyme induction.

Precautions with Hormonal Contraception	**Safe with Hormonal Contraception**
Phenytoin	Ethosuximide
Carbamazepine	Valproate

Oxcarbazepine	Gabapentin
Phénobarbital	Lamotrigine
Primidone	Lamotrigine
Topiramate	

Risk of epilepsy in offspring: The overall risk of children developing epilepsy higher if the mother has epilepsy (8%) compared to the father (2%), probably due to genetic contributions. Seizure profile in pregnancy: pts should be warned that breakthrough seizures are more likely due to altered bioavailability in the face of physiologic changes in gut motility, hepatic clearance, expanding plasma volume, and altered protein binding. Optimize AED therapy before pregnancy. Good seizure control prior to pregnancy predicts control during pregnancy. Seizures and the fetus: an individual seizure carries risk to the fetus due to placental hypoperfusion and potential trauma. Ictally, fetal effects could include: spontaneous abortion; fetal bradycardia; fetal hypoxia with resultant acidosis; fetal intracranial hemorrhage; intrauterine death. Repeated seizures (five or more) have been associated with lower verbal IQ in the child.

Antiepileptic medications: Individualize choice of AED. Most AEDs are rated by FDA as category C (valproate, carbamazepine, and phenytoin are category D). Always request free AED levels to reflect the changes in pharmacokinetics during pregnancy. AED dose should be adjusted to achieve a serum level appropriate for the patient to maintain seizure freedom.

Drug	**Free Level**	**Total Level**
Valproate	Little change	Decreases markedly
Phénobarbital	Decreases markedly	Decreases markedly
Carbamazepine	Little change	Little change
Phenytoin	Decreases slightly	Decreases markedly

Lamotrigine	Decreases variably, levels must be checked every 2-4 weeks	
Oxcarbazepine	Decreases slightly	Decreases markedly

Pre-pregnancy sz-free drug level, should be used as target during pregnancy. For women with well-controlled seizures, check AED levels before conception, and at 1 mo intervals with dose adjustments to maintain a therapeutic level (lamotrigine levels should be checked more frequently, because of the marked increase in clearance for some women).

Peripartum care: 1%-2% of patients with epilepsy will have tonic-clonic seizure during labor, and another \%—1%-2% will experience one during the 24 h after delivery. Most will have normal vaginal deliveries. Serial seizures during labor may be managed with lorazepam. Elective cesarean section is appropriate if frequent seizures occur in the last weeks of pregnancy or if any concern for eclampsia exists. Serum AED concentration monitoring continued after delivery, with a return to prepregnancy states, typically noted within 2 mo.

Teratogenesis: Increased risk of major congenital malformations due to intrauterine AED exposure. Major congenital malformations are defined as structural abnormalities with medical, surgical, or cosmetic importance. Valproate → increases risk by 3—4×

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compared to other AEDs. Carbamazepine and phenytoin: lower major congenital malformation rates than valproate and phenobarbital. Lamotrigine: has the most data and appears safe in pregnancy.

Dosing and breastfeeding: AED levels transfer into breast milk at variable concentrations depending on agent. Benefits of breastfeeding far outweigh these risks, and patients should be strongly encouraged to breastfeed their infants. Monitor infant for excessive sleepiness and subsequent poor feeding. Phenytoin, valproate and carbamazepine are so protein-bound that they are not present at high concentrations in breast milk. Lamotrigine, topiramate, and levetiracetam have low protein binding, permitting breast milk transfer.

Supplementation and prevention: Vitamin K: AEDs that induce the hepatic cytochrome P450 (CYP) enzymes can induce vitamin K metabolism and reduce the effectiveness of vitamin K-dependent clotting factors. Folate: AED (phenytoin, carbamazepine, and barbiturates) use may reduce folate levels →

neural tube defects; Tx: Folate supplementation.

NEUROMUSCULAR DISEASES IN PREGNANCY

FOCAL NEUROPATHIES

Bell palsy: As with nonpregnant patients, usually due to a viral infection; Treatment is generally supportive with use of prednisone for severe cases.

Carpal tunnel syndrome: Incidence increased due to fluid retention during pregnancy. Treatment: conservative first line (splints, PT, salt restriction); local steroid injection; surgery rarely needed.

Lumbosacral radiculopathy: Back pain is a common symptom during pregnancy, affecting over half of all women. Contributing factors: ligamentous laxity, exaggerated lumbar lordosis, postural stress, direct pressure from growing uterus. Conservative therapy: analgesics, PT, modification of activity.

Lumbar disk disease: Usually affects the L5-SI segments → back pain + radicular findings. Delivery method is debatable → C-section suggested to avoid disk herniation during vaginal delivery. Central disk herniation (can produce cauda equina syndrome) requires immediate surgery and reports of successful lumbar laminectomy and discectomy during pregnancy exist.

Epidural anesthesia: Iatrogenic injury may occur from: drug toxicity, direct injury to nerve root by spinal needle, chemical arachnoiditis or radiculitis, epidural hematoma/abscess, compromised spinal vasculature (usually anterior spinal artery).

Spinal imaging: Best achieved with MRI (clinical correlation essential because half of pregnant patients have disk disease in L3-S1).

Myalgia paresthetica: In 80% condition unilateral. Predisposed by: increased abdominal girth from gravid uterus; lumbar lordosis; thigh flexion during delivery; direct injury, e.g., from retractor during C-section. Expectant treatment is usually all that is required. For severe pain: local treatment: lidocaine patch, local anesthetic.

Obturator and femoral neuropathy: Uncommon in pregnancy; typically associated with nerve injury during vaginal or operative delivery. Lesions are typically demyelinating and recovery w/in 6 mo or less should be expected.

Peroneal neuropathy: Produces a postpartum foot drop. Typically occurs in perineal nerve injury (from compression, usually peripartum). Treatment is supportive (consider ankle foot orthotics). Full recovery in 3-6 mo. More severe injury → axonal damage → slow/incomplete recovery.

INHERITED POLYNEUROPATHIES

Charcot-Marie-Tooth: 50% risk of exacerbation during pregnancy, presumably from perineurial edema and pressure from the gravid uterus; 65% of patients will not recover to pre-pregnancy baseline following delivery. Pregnancy outcome is unaffected, however.

Heredity neuropathy with liability to pressure palsy: Prone to develop any of the compressive neuropathies discussed above, particularly postpartum foot drop.

MYOTONIAS

Myotonic dystrophy Type I: Fertility variable; Higher incidence of pregnancy wastage, polyhydramnios, and prematurity. Not uncommon for women to be first diagnosed peripartum. In symptomatic pts → all stages of labor may be affected (needing assisted delivery and increasing risk of postpartum hemorrhage). Tocolytics may worsen myotonia and induce rhabdomyolysis and should be avoided, as should neuromuscular

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blocking agents. Condition autosomal dominant → suspect fetus to be affected when reduced fetal movement, polyhydramnios, and preterm labor.

Myotonic dystrophy Type II: Different than Type I in that no congenital form exist, and does not appear to cause polyhydramnios; risk of preterm labor; pts may develop sxs in pregnancy.

MUSCULAR DYSTROPHY AND CONGENITAL MYOPATHIES

Usually no increased incidence of pregnancy or labor difficulties but beware of increased respiratory complications if kyphoscolosis contributes to restrictive lung disease in the mother.

AMYOTROPHIC LATERAL SCLEROSIS

Delivery can proceed per the preferences of the obstetrician and anesthesiologist, depending on potential for respiratory compromise.

GUILLAIN BARRÉ SYNDROME

GBS in pregnancy closely resembles that in the general population. Maternal infections carry the risk of placental (and therefore fetal) infections. Termination of pregnancy has no effect on duration of illness in the mother and normal fetal activity persists despite maternal paralysis, suggesting the placenta is an effective barrier to the immune process producing the disease. Uterine contractility is unaffected by the disease. Deliver vaginally if possible. As with the general GBS population, succinylcholine should not be used due to the risk of hyperkalemia. Plasmapheresis or IVIg have similar

efficacy and can both be used in pregnancy with the usual precautions and associated risks.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Pt may experience worsening during pregnancy particularly in the third trimester or the immediate postpartum period; Tx: Intravenous steroids, IVIg, and plasmapheresis (can all be used). Generally, steroid-sparing therapies contraindicated, but consider azathioprine. Like GBS the neonate appears unaffected by the disease.

MYASTHENIA GRAVIS

Disease course during pregnancy variable, but long-term outcome remains unchanged. Increased risk of disease exacerbation in pregnancy: diagnosis within 1 y of becoming pregnant; pre- or postpartum infections. Maternal mortality increased with: respiratory failure; Magnesium use with pre-eclampsia, or eclampsia; postpartum hemorrhage. Overall risk of death to the mother is 4%. Unlike GBS and CIDP, perinatal mortality is 5× that of uncomplicated birth.

Labor: Uterine smooth muscle unaffected by the disease, but skeletal muscle use in labor may fatigue in stage II, necessitating assistive delivery.

Fetal and neonatal complications: Fetal complications include neonatal myasthenia and arthrogryposis congenita. Neonatal myasthenia affects up to 20% of infants born from myasthenic mothers (usually within the first 24 h after delivery). Treatment for severe cases of neonatal myasthenia → plasmapheresis, but the majority supportive therapy and anticholinesterase medications.

Maternal treatment: Proceeds along the usual lines. Thymectomy should be pre-formed electively before a planned pregnancy, and preferably early in the period after disease diagnosis. Anticholinesterase medications (category C) should be continued. Severe exacerbations can be treated with IVIg and plasmapheresis, but avoid azathioprine and cyclosporine if possible.

DERMATOMYOSITIS AND POLYMYOSITIS

For pts in remission, risk during pregnancy small with typically good outcomes. With active disease, as many as 43% of pregnancies reported to be complicated by fetal death; Intrauterine growth retardation occurred in as many as 33% of fetuses of actively affected mothers. During pregnancy, maternal strength and respiratory functions should be followed; serum CK → an unreliable marker of disease activity. Delivery by cesarean section desirable in patients with active disease. Neither polymyositis nor

dermatomyositis transmitted to the fetus. Treat active disease with corticosteroids: prednisone up to 2 mg/kg/day. In steroid resistant cases, use IVIg.

MOVEMENT DISORDERS IN PREGNANCY

Chorea gravidarum: Hemichorea during pregnancy, usually after the first trimester. Patients that manifest this need a full evaluation for connective tissue disease (SLE and antiphospholipid syndrome specifically) as well as rheumatic fever (historically

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the commonest cause). Severity of chorea decreases toward term and one-third of patients experience resolution after delivery. Treatment only needed for severe chorea (marked by features such as hyperthermia, rhabdomyolysis, myoglobinuria) → haloperidol preferred (pregnancy category C).

Restless leg syndrome: Relatively frequent during pregnancy (up to 26%) (Neurology 2004;63:1065). Dopamine agonists first-line.

Essential tremor: Pre-pregnancy, warn families that inheritance is autosomal dominant in half of affected patients. The majority of cases during pregnancy do not require treatment as this condition is not dangerous and medication exposure may have deleterious effects on the fetus. If necessary, treatment should be initiated with propanolol and fetal growth should be monitored. Other available agents include primidone, topiramate, and gabapentin.

Focal dystonias: Treatment commonly involves local botulinum toxin injection; type A and B are category C drugs but type B has been more convincingly shown to be safe and should be used preferentially for muscle injection if a choice is available.

Parkinson disease (PD): PD extremely rare in pregnancy.

Wilson disease: Higher rate of pregnancy complications. Chelation therapy throughout pregnancy controls hepatic disease and decreases risk of hemolytic anemia in the mother. Chelation also controls copper accumulation in the placenta and limits possible liver damage in the fetus. Penicillamine the preferred agent despite known teratogenic risks (pregnancy category D). Remember to supplement with pyridoxine 25 mg daily.

Huntington disease (HD): All patients with HD should be offered prenatal counseling (condition is autosomal dominant). Only a minority of people at risk for HD (in some reports as low as 5%) chose to be tested in the absence of treatment. Therapy for HD is purely symptomatic: Chorea: Haloperidol (pregnancy category C); Behavioral disturbance: Lorazepam (D); Depression:

Nortriptyline (D); or Fluoxetine (C).

NEUROSURGERY IN PREGNANCY

If possible, wait until after delivery for any neurosurgical procedure. During surgery, fetal monitoring should be performed. All agents used should be screened by the OB anesthesiologist.

Intracranial hemorrhage: Risk of rebleeding in the same pregnancy is 27%; AVMs usually bleed before 24 wk and aneurysms after 30 wk. Mannitol for elevated ICP unsafe due to risk of uterine hypoperfusion from maternal hypovolemia. If needed, 23.4% hypertonic saline bolus for ICP emergency.

Hydrocephalus: Pregnancy-related shunt malfunction can occur in as many as 50% of patients (present up to 6 mo postpartum) due to changes in intra-abdominal pressure. Depending on the cause of the patient's hydrocephalus, consider amniocentesis to diagnose neural tube defects between 13 and 24 wk gestation.

Brain tumors: In pregnancy, hormonal changes may cause enlargement of pituitary adenomas and meningiomas. Pituitary adenomas may enlarge or undergo apoplexy during the third trimester. If surgery needed, wait for at least second trimester.

Trauma: Typically this is treated as in the nonpregnant woman. For severe cases in early pregnancy, consideration should be given to pregnancy termination for consideration of the mother's health.

Neuro-Ophthalmology

AFFERENT NEURO-OPHTHALMOLOGY

AFFERENT EXAMINATION OVERVIEW

(1) Acuity: Check w/ correction (>40 yo require near correction). Pinhole occluder (or paper w/ pinhole) to exclude refractive error. (2) Color vision (color plates, red desaturation). (3) Pupillary response to light & near; look for APD (detectable w/dim stimulus). (4) Visual fields, each eye separately—laser pointer a great bedside test; have pt fixate central target, move/flash red stim in areas of interest. (5) Funduscopy: Use dilating drops; if not possible, try small light at dimmest setting to ↓ glare;

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examine right eye w/ your right eye & left eye w/ your left eye: color & quality of optic disc & neuroretinal rim, degree of cupping, arteries & veins, venous pulsations at edge of optic cup, quality of nerve fiber layer (NFL) (best seen w/ green light), peripapillary changes (hemorrhage, swelling, infiltrates), & macula.

ANATOMY OF THE AFFERENT VISUAL PATHWAY

Retina: Photoreceptors (outer-) → retinal ganglion cells (inner-) → unmyelinated NFL (innermost retina); NFL axons travel to optic disc. Retinal projections: mainly lateral geniculate nucleus (LGN), also pretectal nucleus (pupillary light reflex pathway), superior colliculus (fixation, saccades, vergence, smooth pursuit), & hypothalamic suprachiasmatic nucleus (circadian rhythms). NFL axon paths: Foveal NFL → to optic disc (maculopapillary bundle); temporal retina NFL above & below fovea → disc in arced path (as arcuate bundles), respects horiz. meridian; nasal retina NFL axons → directly to disc. Arterial supply: Ophthalmic a. (ICA branch) travels w/ ON in optic canal, branches into central retinal artery (travels in ON to supply inner retina) & long & short post. ciliary arteries (supply ON head, ciliary body, choroid, outer retina); 1/3 people have cilioretinal artery (from post ciliary circulation) to supply central macula. Venous drainage: Veins follow retinal & ophthalmic a., exiting orbit through sup & inf orbital fissures → cav. sinus & pterygoid plexus. Field defects: dzs of temporal retinal NFL & optic disc & retinal arterial supply may respect horiz. meridian; primary retinal d/o's do not. (Prechiasmal dzs respect vertical meridian).

Optic nerve (ON): Where retinal NFL axons converge. Axons become

myelinated post. to lamina cribrosa. Four portions: intraocular, intraorbital, intracancicular, intracranial. Blood supply: (1) anterior nerve & disc—post. ciliary arteries via ophthalmic artery; (2) post. nerve—pial circulation & central retinal/ophthalmic artery. Topographic representation of retina is preserved in ON. Exits orbit through optic canal (w/ ophth. artery & oculosympathetics). Subarachnoid space surrounds ON (anterior limit is lamina cribrosa).

Field defects 2/2 ON dz can be global or regional; divided by affected area: (1) temporal retina—horizontal altitudinal, arcuate, central, & centrocecal; (2) nasal retina—step-like; enlarged blind spots occur when optic disc swells, displaces adjacent photoreceptors.

Optic chiasm (OC): Produces crossed fibers from nasal- & uncrossed fibers from temporal-retina. Blood supply: Hypophyseal artery branches inferiorly (via ICA) & ACA branches superiorly. Located above pituitary/sella. Field defects: Divided by affected area of OC: (1) midsagittal region—inf, sup, or full bitemporal hemianopia (field defect begins near vertical midline, not peripherally); (2) anterior chiasm—junctional scotomas w/ i/l ON-type defect (e.g., central scotomas) & c/l chiasm-type defect (e.g., superotemporal defect).

Optic tract: Info from c/l nasal- & i/l temporal-retina. Blood supply: Ant choroidal a. (via ICA) & PComm. lesion → c/l incongruous homonymous hemianopia (w/o central sparing).

LGN: 6-Layered thalamic nucleus; gets input from optic tract. Blood supply: Ant choroidal artery (ICA branch) → med & lat LGN; post choroidal artery (PCA branch) → hilum of LGN. Field defects (in stroke): c/l incongruous hemianopia, sectoranopia (postchoroidal stroke); quadruple sectoranopia (ant choroidal stroke).

Optic radiations: Post-LGN tracts divided superiorly (occipito-parietal) & inferiorly (occipito-temporal; Meyer’s loop). Blood supply: Anterior radiations, via ant. choroidal & MCA; superior radiation via superior MCA; inf & postradiations via MCA & PCA. Field defects: c/l congruent homonymous hemianopsias: inferior division lesion: c/l superior homonymous hemianopia (“pie in the sky”); superior division: c/l inferior homonymous hemianopia.

Primary visual cortex (striate cortex): Target of optic radiations. Blood supply: OL: PCA, occipital pole: PCA, MCA (dual supply). Lesions → c/l congruent homon. hemianopsia; rare ant. mesial OL lesion → c/l monocular peripheral crescent-shaped field defect. Macula represented at occipital pole → lesions ant. to pole spare macular vision.

Visual association cortex: “Where” visual stream is superior (OL/PL). Lesions yield visuospatial deficits (e.g., visual attention, spatial organization). “What” visual stream is inferior (OL/TL). Lesions → semantic deficits (e.g., object recognition, color). Blood supply: OL/PL regions via superior MCA branches; OL/TL regions via PCA & inferior MCA branches.

TRANSIENT MONOCULAR VISUAL LOSS

Def: Can be ischemic or non-ischemic. Epid: Ischemic transient monocular visual loss (TMVL) usu in elderly.

P/w: (1) Ischemic: Usu painless, acute-onset & brief (sec-min); often horizontal altitudinal; w/ ICA atheroembolism, ±transient language Δs, c/l wkness/numbness. (2) Non-ischemic: Sx often vague; common mis-Dxs: blurring, ↓ w/ blinking/artificial tears → dry eyes; visual obscurations w/ bending forward → optic disc swelling including papilledema; eye pain → angle-closure glaucoma; ↓vision w/ eye mvmts→ orbital tumor; HA → migraine.

DDx: (1) Ischemic TMVL: Ophthalmic, central or branch retinal, or posterior ciliary artery dz. ICA atheroembolization/in-situ thrombus of ophthalmic, central retinal or branch retinal arteries (can be 2/2 GCA) or veins (i.e., impending CRVO/BRVO). Posterior ciliary a. thrombosis or inflammation via impending anterior ischemic optic neuropathy (AION) (can be 2/2 GCA). (2) Nonischemic TMVL: Dry eyes, angle- * closure glaucoma, anterior segment dz (e.g., dry eyes, hyphema), retinal detachment, ON compression (orbital tumor), optic disc swelling including papilledema & drusen, migraine (may evolve into ischemic TMVL).

Dx: (1) Obtain prior ophth. history & vascular risk factors (including carotid & cardiac dz). (2) Eye exam: Non-ischemic TMVL: Routine eye exam (r/o anterior segment dz & ↑intraocular pressure). Ischemic TMVL (aka amaurosis fugax), may see refractile emboli w/in retinal arteries on funduscopy (Hollenhorst plaques). (3) R/o giant cell arteritis (ophthalmologic emergency) via CBC, ESR, & CRP. (4) Vessel imaging from aortic arch to ophthalmic arteries (e.g., head & neck CTA or MRA, or ultrasound); carotid bifurcation of special interest for atheroembolic dz. (5) Cardiac ultrasound (ejection fraction, valves, presence of PFO, r/o thrombus). (6) Consider hypercoagulable panel in pts w/o vascular risk factors & nl vessels. (7) Consider fluorescein angiogram: delayed choroidal filling suggests GCA; sluggish venous flow suggests impending CRVO/BRVO.

Rx: Ischemic TMVL: Secondary stroke prevention w/ risk factor modification. Nonischemic TMVL: Ophthalmologic or neurologic care based

on etiology.

Prognosis: In cases of ICA atheroembolism-related TMVL, 25% chance of stroke over 3 yr in significant carotid stenosis; 4% annual risk of death (NEJM 2001;345:1084).

ISCHEMIC OPTIC NEUROPATHIES

Def: ↓ blood supply to any portion of ON—posterior ciliary arteries w/ anterior ON ischemia & branches of pial vasculature as well as central retinal & ophthalmic arteries w/ posterior ON ischemia. Classified based on (1) location of dz: AION = anterior optic dz; posterior ischemic optic neuropathy (PION) = posterior ON. (2) Underlying cause: "arteritic" or "non-arteritic." "Arteritic" synonymous" w/ GCA-related ischemia. AION & PION are not believed to be embolic in etiology.

Epid: (1) Non-arteritic AION (NA-AION): Typically >50 yo (but can occur at any age). A/w small optic cups (cup-to-disc ratio < 0.3). Controversial risk factors: HTN, DM, hyperlipidemia, ischemic cardiomyopathy, peripheral vascular dz, sleep apnea, smoking, labile (fluctuating) blood pressure, acute ↑ intraocular pressure. (2) Arteritic AION (A-AION): Age >50 yo, a/w GCA; often +PMR. (3) PION: Typically in setting of severe blood loss (cardiac or spine surgery) or prolonged ↓ BP; rarely related to GCA (i.e., arteritic).

P/w: (1) NA-AION: Acute onset loss of monocular vision (mild to severe); often worst at onset, but may reach nadir in days to weeks; may notice inferior field defect; rarely binocular or sequential unless GCA-related; usu painless (but mild pain may be reported). (2) A-AION: as w/ NA-AION, but often w/ prodromal TMVL; ±sx of GCA & PMR: Jaw claudication, HA, head tenderness, malaise, wt loss, fevers, sweats, hip, & shoulder aches. (3) PION: Rapid-onset or awakes from surgery w/ severe binocular (or monocular) visual loss.

Dx: (1) Si/sx of optic neuropathy—↓ acuity, dyschromatopsia, APD, edematous hyperemic optic disc (pallor w/ edema in A-AION), inf. altitudinal field defect; disc pallor chronically. (2) w/ NA-AION, other eye w/ small cup-to-disc ratio (<0.3). (3) Palpate for nodular, thickened, pulseless, & firm temporal arteries. (4) CRP, ESR, & CBC (anemia & thrombocytosis in GCA). (5) Temporal artery bx; b/l bx ↑'s sensitivity (6) ±brain & orbital MRI w/ gado: eval ONs; typically nl in acute phase; may show DWI/ADC abnlities in PION; chronically ↑ T2 signal of ON in AION & PION (also helps r/o other causes of optic neuropathy).

DDx: Optic neuritis—F > M, younger pts, pain w/ eye mvmts, a/w MS; tends to improve. ON infiltrative/infectious/compressive lesions; slower course if neoplasticrelated.

Rx: NA-AION: no proven Rx. A-AION: IV methylprednisolone (up to 1 g/day, for 2-5 days), then PO prednisone (start at 80-120 mg daily) to protect fellow eye (rare involved eye improvement). PION: No proven Rx; consider A-AION Rx regimen if GCA suspected.

Prognosis: NA-AION: Affected eye recurrence <5%; other eye ˜15% at 5 yr; poor visual recovery. A-AION: Progressive visual loss of involved eye; visual loss of fellow eye in ˜40% if untreated; risk of MI & stroke; can recur if steroids are tapered too quickly; recurrences yr after tx are exceedingly rare; poor visual recovery. PION: Poor visual recovery.

	A-AION	**N-AION**	**Optic Neuritis**
Age	>50	Typically >40	Typically 20s-30s
Pain	HA, jaw claudication	Usu not	Yes, w/ eye mvmts
Dx	HPI/exam, ESR/CRP, TA bx	HPI/exam	HPI/exam
Pathogenesis	Vasculitic	?Ischemic	Immune-mediated
↓ acuity, APD, dyschromatopsia	Yes	Yes	Yes
Disc edema	Yes (±pallid edema)	Yes (may be sectorial)	Only 1/3 of pts
Disc hemorrhages	Yes	Yes	No
Optic cup of fellow eye	NI	Small	NI
Visual field	Any ON type	Typically	Any ON-

defect	defect	inferior altitudinal	type defect; central/arcuate defects common
Rx	Steroids w/ slow taper	Risk factor modification	Consider IV steroids
Prognosis	Severe visual loss; risk of further/fellow eye visual loss w/o Rx	Variable visual loss, static; 15% fellow eye involvement in 5 yr	Most recover; risk of developing MS

OPTIC NEURITIS & DEMYELINATING OPTIC NEUROPATHIES

See “Optic Neuritis” section in “Demyelinating Diseases of the Central Nervous System” chapter.

HEREDITARY,TOXIC, & METABOLIC OPTIC NEUROPATHIES

Def: Various ON dzs, most often affect central vision (via maculopapillary bundle).

P/w: Insidious, binocular central visual loss (unless otherwise noted).

Dx: Exam: Symmetric, ↓acuity, dyschromatopsia, central visual field defects, disc pallor.

Labs: Serum for LHON & dominant optic atrophy (DOA) mutations; B_{12}, homocysteine/methylmalonic acid. Rarely 2/2 deficiency of: B_1, B_2, B_6, niacin, thiamine.

Imaging: Brain & orbital MRI w/ gado to exclude compressive lesions.

Specific causes:

B_{12} deficiency-related optic neuropathy: Def: Malnutrition-related demyelination of ON stemming from maculopapillary bundle. Epid: Pernicious anemia, enteritis or small intestine resection, veganism. DDx: DOA, chiasmal lesion (occasional bitemporal field defects). Dx: Optic pallor, centrocecal field defects, memory dysfxn, ↓ vibratory & position sensation, macrocytic anemia, ↓ B_{12} & ↑ homocysteine/methylmalonic acid, brain MRI w/ white matter dz. Rx: IM hydroxycobalamin. Prog: Visual stability w/ Rx; variable improvement.

Methanol-related optic neuropathy: Def: Toxin-mediated white matter dysfxn. P/w: Lethargic; HA; vomiting abdominal pain; blindness. Epid: Homemade ETOH, methanol-containing industrial products. Dx: Disc swelling; metabolic

acidosis; brain MRI w/ putamen hemorrhage and infarct. Rx: Ethanol or fomepizole IV, bicarbonate IV. Prog: Poor visual recovery.

Tobacco-alcohol amblyopia: Def: Presumed additive malnutrition & toxin-mediated optic neuropathy; past epidemics in Cuba & Jamaica in association w/ cigar smoking & cassava, resp. Epid: Smoking, excessive ETOH intake, malnourished. Ddx: B_{12} deficiency-related optic neuropathy, dominant optic atrophy, compressive optic neuropathies. Dx: Possible peripapillary hemorrhage in early stages; check B_{12} levels. Rx: IM hydroxycobalamin, multivitamins, smoking, & ETOH cessation. Prog: Visual stability w/ Rx; variable improvement.

Radiation optic neuropathy (J Neuro-ophth 2004;24:243): Def: Radiation-induced dz of ON. P/w: Acute/subacute > chronic visual loss yrs after exposure; (typically 2 yr);

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monocular or binocular; may be sequential visual loss. Epid: Prior radiation exposure of at least 50 Gy. Dx: Exam w/ retrobulbar optic neuropathy; pallor chronically; brain & orbital MRI w/ gado shows enhancement & enlargement of involved region. Ddx: Tumor. Rx: None of proven efficacy; may try hyperbaric oxygen, corticosteroids. Prog: Poor visual outcome; may affect any portion of visual pathway (chiasm, tract, radiations).

Others: Ethambutol, ?amiodarone, ?sildenafil, other organic solvents (toluene).

INFLAMMATORY, INFILTRATIVE & INFECTIOUS OPTIC NEUROPATHIES

Def: ON dysfxn 2/2 inflammation, infxn, or both. Swollen disk = disc edema or swelling (papilledema = disc edema due to ↑ ICP).

P/w: Subacute visual loss, younger pts, in setting of systemic si/sx of underlying dz.

Dx: Si/sx optic neuropathy (↓ acuity, color vision, APD, ON-type field defects). Funduscopy. If+disc swelling: (1) Check BP. (2) Determine if swelling is 2/2 ↑ ICP.

Ddx: Idiopathic demyelinating optic neuritis is often the major alternative dx.

Evaluation for Presumed Inflammatory, Infiltrative or Infectious Optic Neuropathy

Orbital &	Coronal STIR images aid in ONs evaluation evaluate

brain MRI w/ gado	chiasm & CSF space around ONs look for evidence of underlying dz in parenchyma & meninges
Serology	ACE, ANA, Lyme ab, RPR, FTA-ABS, Bartonella IgM/G, VZV IgM/G
CSF	Check opening pressure; routine studies (cell count, protein, glucose, gram stain); VDRL, Bartonella PCR, VZV PCR
Body imaging	Chest CT
Other tests	PPD
Fluorescein angiogram	May confirm presence of pathologic disc swelling (showing disc leakage of dye); may assist delineate extra-disc dz (i.e., retinal dz)

INFLAMMATORY-INFILTRATIVE OPTIC NEUROPATHIES

Sarcoid-associated optic neuropathy (Sem Ophth 2008;23:157): Def: Granulomatous inflammation in ON or chiasm. P/w: Typically subacute, severe monocular visual loss (variable pain); co-existent diabetes insipidus (especially if chiasm involved), HAs (meningitis), facial nerve palsies; often preceded by systemic sarcoidosis (pulmonary, skin); other ocular manifestations are more common (uveitis, retinal vasculitis). Epid: Age 20—40; African descent. Dx: Disc granulomas & swelling (if anterior dz); orbital & brain MRI w/gado (enhancement & enlargement of ON or chiasm, meningeal enhancement, pituitaryhypothalamic involvement); chest CT; serum ACE; ↑ protein & WBC (mild) in CSF; biopsy of skin, lymph nodes, lung, or brain. Ddx: Optic neuritis, optic perineuritis, primary neoplastic or metastatic optic neuropathy. Rx: Initial high-dose corticosteroids, chronic maintenance steroids; Chronic Rx: Consider methotrexate, anti-TNF-α gents, cyclophosphamide. Prog: Typically relapsing-remitting course, vision may be restored w/ Rx.

Lupus-associated optic neuropathy (Adv Ophth 1979;47:13): Def: Likely many mechanisms—vasc. occlusion, inflammation, demyelination of ON. P/w: Subacute or chronic monoc. or binoc. visual loss (variable pain); co-existent spinal cord dz; often preceded by SLE (skin, joint, kidney, serous linings), but may be first sign; rare pseudotumor cerebri-like presentation. Epid: 20-30s, F >> M. Dx: Fundus often wnl; disc pallor if chronic; orbital &

brain MRI w/ gado (variable ON enhancement, WM dz); serum ANA, antiphospholipid syndrome (APS) abs. Rx: Initial corticosteroids, consider other agents (methotrexate, azathioprine, cyclophosphamide, plasmapheresis, IVIg, anticoagulation in APS). Prog: Chronic or relapsing-remitting course; visual improvement may be seen.

Other autoimmune-related optic neuropathies (very rare)

Optic perineuritis—subacute monocular visual loss (variable pain); disc edema & retinal hemorrhages, ON sheath enhancement on MRI. Ddx: Sarcoidosis, TB, syphilis, & Lyme dz. Rx: Treat underlying dz or w/ corticosteroids if idiopathic.

Sjögren-related optic neuropathy—Optic neuritis-like presentation w/ acute or subacute painful monocular visual loss; systemic (xerostomia, arthralgia, myalgias) & ocular (keratoconjunctivitis) signs, variable WM dz on MRI; Rx: Consider corticosteroids.

Behcet dz-related optic neuropathy—↑ ICP w/ papilledema; systemic si/sx of Behcet's (genital & oral ulcers, lymphadenopathy). Rx: Immunomodulatory & acetazolamide.

Autoimmune optic neuropathy—Recurrent, acute painful visual loss.

INFECTIOUS OPTIC NEUROPATHIES

Lyme-related optic neuropathy (J Neuro-ophth 1997; 17:108): Def: ON dysfn 2/Borrelia. Subdivided based on mechanism: (1) Intracranial HTN (papilledema); (2) post- or parainfectious demyelination of anterior ON (papillitis); (3) Direct infxn of ON & retina (neuroretinitis). Role of (2) & (3) in Lyme dz is controversial. Lyme-related information below further based on these subdivisions (1, 2, & 3)

P/w: (1) HA, neck pain, diplopia (esotropia), whooshing in ears, blurry vision, Lyme-dz. Rash. (2) monocular visual loss, pain w/ eye mvmts, recent Lyme-related rash. (3) monocular visual loss, recent Lyme-related rash. Epid: Endemic areas (N.E. USA, N. Europe). (1) Pediatric population; (2),(3): All ages, rare.

Dx: Skin exam. Funduscopy: shows: (1) marked disc swelling & peripapillary splinter hemorrhages; (2) variable, mild disc swelling; (3) disc swelling, subretinal fluid from disc to macula, macular star (leakage of exudates around fovea in star pattern). Lyme serologies. LP: [shows: (1) ↑ ICP, WBC, & TP; in (2) & (3) variable, mildly ↑ WBC & TP. Orbital & brain MRI w/ gado (variable enhancement of anterior ON; variable meningeal enhancement;

enlarged CSF space around ONs w/ ↑ ICP]. DDx: Pseudotumor cerebri, optic neuritis. Rx: IV ceftriaxone. Prog: Typically complete recovery w/ Rx.

Syphilis-related optic neuropathy: Def: Treponema pallidum infxn of ON. P/w: Typically chronic visual loss (tertiary stage); can present acutely in early stages of syphilis similar to AION (acute, painless monocular visual loss); other signs of neurosyphilis if chronic dz (tabes dorsalis, dementia, other cranial neuropathies). Epid: Rare; all ages, but typically adults. Dx: Funduscopy: Acute: disc swelling + splinter hemorrhages; chronic disc pallor; neuroretinitis. Serum FTA-ABS; CSF (↑ WBC & TP, CSF VDRL). Orbital & brain MRI w/ gado (enhancement & enlargement of ON; meningeal thickening & enhancement in chronic dz). DDx: AION, optic neuritis, optic perineuritis, sarcoidosis. Rx: IV penicillin. Prog: Variable improvement in early-stage dz; stability w/ Rx in late stage dz.

Bartonella-related optic neuropathy: Def: ON/retina infxn w/ Bartonella henselae (part of cat scratch dz) P/w: Acute/sub acute monocular visual loss; variable fever, malaise, & lymphadenopathy;± encephalitis, sz. Epid: Kitten scratches. Dx: Funduscopy: disc swelling, subretinal fluid from disc to macula, macular star (exudates around fovea); centrocecal & central scotomas; uveitis & vitritis may coexist. Bartonella serologies;CSF: (variable ↑ WBC & TP, CSF Bartonella antibodies). Ddx: Other causes of neuroretinitis (postviral, Lyme, syphilis, TB, toxoplasmosis, SLE). Rx: Doxycycline; regimen not well-established. Prog: Often-self limited (w/o Rx), resolves over 1-2 mo; typically good visual recovery.

VZV-related optic neuropathy: Def: VZV infxn of ON typically w/ other si/sx VZV reactivation. P/w: Acute or subacute monocular visual loss w/ preceding or concurrent facial (Vl-distribution) or ophthalmic zoster. Epid: Adults. Dx: Funduscopy: Optic disc swelling & peripapillary hemorrhages acutely. VZV serologies; CSF (variable ↑ WBC & TP; CSF VZV antibodies); orbital & brain MRI w/ gado (enhancement & enlargement of ON; variable enhancement of trigeminal nerve). Ddx: AION, optic neuritis, neoplastic optic neuropathy. Rx: IV acyclovir ± corticosteroids. Prog: Variable visual improvement.

Other infectious optic neuropathies (rare/poorly established unless o/w noted)

TB-related optic neuropathy—Usu. in endemic areas (Southeast Asia, India); subacute monocular visual loss w/ variable disc edema & granulomas; often dominated by other CNS signs: (meningoencephalitis, intracranial HTN, other cranial neuropathies).

HIV-related optic neuropathy—In early stage of HIV; opticneuritis-like presentation.

CMV-related optic neuropathy—In AIDS, subacute painless visual loss w/ disc edema; ± hemorrhagic necrotizing retinitis; ±ventriculitis & lumbosacral polyradiculitis.

Toxoplasma gondii, Toxocara species, & Cryptococcus neoformans-related optic neuropathies—Toxo in setting of AIDS/other CNS lesions; Toxocara w/systemic infxn sx, wheezing, abd pain, & HA; Crypto may → ↑↑↑ ICP & papilledema or optic disc granulomas.

Myclopasma pneumoniae, HHV-6, & West Nile virus-related optic neuropathies: Optic neuritis-like presentations; all may be 2/2 parainfectious demyelination.

COMPRESSIVE AND NEOPLASTIC OPTIC NEUROPATHIES

For related dzs of chiasm, see “Chiasmopathies” section. Def: Mass lesions, cause ON dysfn through extrinsic compression or intrinsic growth. P/w: Insidious monocular visual loss w/ optic neuropathy; binocular w/ chiasm compression (or b/l ON lesions).

DDx: Demyelinating, infiltrative (e.g., sarcoidosis), & ischemic optic neuropathies. All may → optic disc swelling & ON enlargement on MRI. Dx: Funduscopy: disc pallor; ±nonglaucomatous disc cupping w/ involved ON. Orbital & brain MRI w/ gado. Consider NF-1 or NF-2 testing (w/ON glioma & meningioma, resp.). Consider metastatic workup.

NEOPLASTIC OPTIC NEUROPATHIES

ON meningioma (Arch Ophthal 2002; 120:1505; Neurosurgery 2002;51:890): Def: Proliferation of arachnoid cap cells of ON sheath; meningiomas from olfactory groove & planum sphenoidale can → optic neuropathy (& frontal & olfactory dysfxn). P/w: Insidious monocular visual loss; transient & gaze-evoked visual sx. Neoplastic compressive optic neuropathies. Epid: F > M, NF-2. DDx: Sarcoidosis, metastasis, optic perineuritis. Dx: Funduscopy w/ disc pallor >> disc swelling, may see optociliary shunt vessels on disc; homogenously enhancing linear mass of ON sheath by MRI; ±intralesional calcifications; small lesions at orbital apex easily missed by MRI (even w/ marked sx). Rx: Observation; radiation considered in progressive dz; resection detrimental to complex meshwork of vessels w/in ON sheath. Complications: Radiation optic neuropathy. Prog: Variable visual prognosis w/o Rx; good results (i.e., stability) reported w/ radiation.

Low-grade ON glioma (Br J Ophthal 1969;53:793): Def: Low-grade proliferation of glial cells in ON, typically pilocytic astrocytoma of ant. visual pathway; posterior gliomas also exist (chiasm, tract, radiations). P/w: Visual

loss (asymptomatic to severe) in 1st decade; may be discovered incidentally in NF-1; children may p/w strabismus from evolving amblyopia; proptosis if intraorbital. Epid: 1/3 w/ NF-1. Ddx: Meningioma & other primary ON—ganglioglioma, astrocytic hamartoma, hemangioma, Melanocytoma. Dx: Other si/sx of NF-1 (iris Lisch nodules, skin lesions). MRI: Minimally enhancing enlargement of ON. Rx: Many advocate no Rx; chemoRx & radiation sometimes considered; resection avoided given intrinsic nature of lesion & high risk of subsequent visual loss. Complications: Radiation optic neuropathy. Prog: Typically stable or very slowly progressive visual loss; very rare evolution into high grade glioma w/ progressive visual loss.

High-grade ON glioma: Def: High-grade proliferation of glial cells in ON or chiasm. P/w: Rapid monocular visual loss (binocular if chiasm); ±orbital si/sx (proptosis, orbital congestion) w/ ant extension & cerebral signs w/ post extension. Epid: Adults; typically w/o NF-l history. Ddx: Optic neuritis, NMO, metastatic optic neuropathy, sarcoidosis. Dx: MRI: Enhancing enlargement of ON; may extend to brain. Rx: Chemo + XRT (per other high-grade glioma); ±resection. Prog: Progressive visual loss; high mortality.

ON metastasis (Arch Ophthal 2000;1 18:217): Def: hematogenous or contiguous spread from orbit, brain, or choroid; typically affects substance of nerve rather than sheath (latter as part of meningeal carcinomatosis). P/w: Monocular slowly progressive visual loss; sometimes acute monocular visual loss; concomitant ocular motor palsies; pain w/ facial numbness; HA; ±known h/o CA. Epid: Usu: paranasal spread from nasopharyngeal CA & lung or breast adenocarcinomas; also colon, kidney, melanoma, esthesioneuroblastoma, lymphoma, leukemia. DDx: Radiation optic neuropathy, AION or optic neuritis (w/ acute presentations). Dx: Funduscopy: Disc swelling when mass is anterior; rarely collections of tumor cells seen anterior to disc; mass may extend into peripapillary choroid; if posterior, fundus nl in acute phase, but w/ pallor chronically; systemic search (exam & imaging) for source of metastasis; rarely FNA of lesion. Rx: XRT, chemotherapy depending upon primary tumor. Complications: Delayed radiation optic neuropathy. Prog: Some stabilize w/ Rx, but continued progression is expected; poor overall prognosis.

Paraneoplastic optic neuropathy (Ann Neurol 2003;54:38): Def: May be a/w anti-CRMP-5 Ab; very rare. P/w: Subacute monocular/binocular visual loss; underlying known systemic cancer (typically lung); often additional concurrent paraneoplastic neurologic syndromes (encephalomyeloneuropathy in anti-CRMP-5 Ab syndrome). Ddx: AION, optic neuritis, other inflammatory or infiltrative optic neuropathies. Dx: Funduscopy:Variable disc swelling & hemorrhage, retinitis, & vitritis (constellation seen in anti-CRMP-

5 syndrome); anti-CRMP-5 Ab; LP; imaging search for systemic cancer. Rx: Steroids, Tx underlying cancer, IVIg, plasmapheresis tried. Prog: Guarded visual & poor global prognosis.

NONNEOPLASTIC COMPRESSIVE OPTIC NEUROPATHIES

Arterial aneurysms: Supraclinoid ICA including ophthalmic aneurysm compressing lateral posterior ON; cavernous sinus ICA aneurysm (when giant) may compress ONs

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from below; AComm or ACA aneurysm may compress from above. P/w: Insidious monocular or binocular visual loss. Epid: Often idiopathic, but genetic & connective disease risk factors. Ddx: Neoplastic compression. Dx: Funduscopy: pallor w/ variable disc cupping; Visual fields: nasal defects w/ supraclinoid ICA aneurysm. CT or MR angiography. Rx: Aneurysm clip or coil; cavernous ICA aneurysm difficult to intervene upon. Complications: CRAO or BRAO from ICA or ophthalmic artery intervention. Prog: Continued visual loss w/o Rx; poor overall visual prognosis.

Other causes: Sinus mucocele, fibrous dysplasia.

TRAUMATIC OPTIC NEUROPATHY

Def: Direct traumatic-optic neuropathy (TON): w/ penetrating orbital trauma; ON directly damaged. Indirect TON: W/ mild-severe trauma to frontal or temporal bone → damages optic canal & ON in canal. Epid: MVA & bicycle accidents most common.

P/w: Acute monocular or binocular visual loss w/ trauma. May be unrecognized if other traumatic body/brain injuries (which is common) or if visual loss is mild & monocular.

Dx: Funduscopy: Disc swelling, hemorrhage or nerve avulsion in direct TON; nl in acute phase of indirect TON; chronic phase of indirect TON shows optic disc pallor. Orbital CT to r/o rare compressive lesion from trauma (hematoma, bony fragment).

Rx: No current evidence for effective Rx. ?Corticosteroids or ON sheath fenestration w/ indirect TON (most do not recommend); surgical evacuation if appropriate (e.g., hematoma). Prog: Usu w/o visual improvement.

PAPILLEDEMA & IDIOPATHIC INTRACRANIAL HTN

Reference: Arch Neurol 1982;39:461.

Def: Papilledema refers specifically to optic disc swelling from ↑ ICP. Disc swelling occurs 2/2 impaired axoplasmic flow; develops over days from onset

of ↑ ICP. Causes of ↑ ICP include: Neoplasia, infxn, immune-mediated inflammation, diffuse central demyelination, cerebral VST, inborn & acquired errors of metabolism & toxins, cranial abnlities, spinal block, & marked systemic HTN. No cause identifiable: dx idiopathic intracranial HTN (IIH) (aka pseudotumor cerebri); involves ↓ CSF absorption.

Epid: ↑ ICP: Any age group, has myriad causes. IIH: Mainly in overweight women aged 20s-30s; also a/w tetracycline exposure & corticosteroid withdrawal; rare familial IIH. P/w: scant visual sx early (e.g., mild blurring); visual loss w/ severe papilledema (when central vision affected); vitamin A toxicity; transient visual obscurations (often w/ bending forward), positional HA (worse from standing to sitting, prolonged supine), horizontal diplopia, whooshing sounds, "pulsatile tinnitus," neck stiffness, n/v. Dx: (1) Funduscopy: Optic disc swelling (begins superiorly & inferiorly) w/ splinter peripapillary hemorrhages (best seen w/ green light), subhyaloid or vitreal hemorrhage (w/ rapid rise of ICP), obscuration of vessels at disc margins (from swollen NFL), loss of optic cup (late), variable cotton wool spots, chorioretinal folds (if severe), & loss of venous pulsations (only implies nl ICP at that moment, as ICP can fluctuate). (2) Visual fields: Enlarged blind spots (2/2 displacement or compression of photoreceptors adjacent to disc); prolonged ↑ ICP → visual field constriction (begins inferonasally; central field affected last); serial visual fields recommended. (3) U/l or b/l abducens deficit/s. (4) Check blood pressure. (5) MRI & MRV brain to r/o mass lesions & venous sinus thrombosis. (6) LP to confirm high ICP.

DDx: Physiologic disc elevation (nasal > temporal), optic disc drusen. Optic disc tilting, optic disc hypoplasia; other causes of optic disc swelling (neoplasia, ischemia, inflammation, HTN).

Rx: (1) ↑ ICP: treat underlying cause. (2) IIH: Acetazolamide long-acting capsules 500 mg PO Bid (up to 2,000 mg/day); warn of common (often transient) SEs to ensure compliance (dysguesia, tingling). Furosemide if acetazolamide (sulfa) allergic or refractory. Severe visual loss or refractory to meds: CSF shunting, ON sheath fenestration. HAs refractory: consider other common primary HA d/o's (e.g., migraine) & Rx. Treat systemic HTN (untreated may increase risk of visual loss). Weight loss, nutrition counseling for IIH. (3) ICP lowering medicines & shunting also considered in non-IIH causes of papilledema when HA & visual loss require Rx; serial LP not routinely recommended.

Prog: (1) IIH: Most improve, can be tapered off meds in 8-12 mo; high ICP may remain despite resolution of si/sx; delayed recurrences w/ visual loss occur (Corbett, 1982). Poorer prognosis w/ initial severe visual loss (loss of central acuity or marked visual field loss); usu. treated more aggressively. (2)

Papilledema takes wks to resolve after ICP → nl. Some do not get full resolution; optic atrophy may ensue w/ blurred disc margins ("secondary atrophy").

CHIASMOPATHIES

Def: dysfxn of optic chiasm, typically from external neoplastic compression, but nonneoplastic compression, intrinsic dz, & rarely, toxins may be culprit.
P/w: Typically nonlocalizing visual complaints such as blurred vision; photophobia; HA; pituitary or hypothalamic dysfxn (e.g., galactorrhea, acromegaly, precocious puberty, diencephalic syndrome); frontal lobe dysfxn.
DDx: Optic neuropathy that produces temporal visual field defects: B_{12} deficiency-related optic neuropathy, hereditary optic atrophy.

Dx: ↓ visual acuity (often asymmetric), dyschromatopsia. Temporal visual field defects (superior or inferior; asymmetric): w/ compression from below or above, defects begin adjacent to vertical midline, not peripherally; even if only monocular temporal defect, still high concern for chiasmopathy. Junctional scotoma or field defect: w/lesion of anterior chiasm, an i/l ON-type defect (central or paracentral scotomas) & c/l superotemporal defect. Optic disc pallor. Check brain & orbital MRI w/ gado. If MRI unrevealing check for B_{12} deficiency & other causes of optic neuropathy.

Specific etiologies:

Pituitary adenoma: Low-grade (hormone secretory or non-fxning). P/w: Slow-onset visual loss (often unnoticed); hyperprolactinemia (galactorrhea, amenorrhea, ↓ libido), ↑ ↑ growth hormone (acromegaly, frontal bossing, thick skin) most common although those w/ visual dysfxn typically large & non-fxning. Dx: Exam: Superotemporal field defects, CN III, IV, VI palsies if cavernous sinus invasion; MRI: Smooth, homogenously non-enhancing sellar mass w/in the normally enhancing pit gland compressing chiasm from below. Rx: Prolactinomas: First Rx medically (dopamine agonist), others monitored w/ exam (visual fields) & MRI; if visual compromise: resection (transphenoidal). Prog: Good if Rx early; can recur—must have serial exams/MRIs.

Pituitary apoplexy: Rapid enlargement of adenoma. P/w: Life-threatening condition w/ acute binocular visual loss & diplopia w/HA or coma; typically postpartum hemorrhage into infarcted & enlarged adenoma. Dx: Severe visual loss w/ ocular motor palsies; panhypopituitarism. Rx: Corticosteroid & thyroid hormone replacement & surgery.

Craniopharyngioma: Low-grade tumor, arises from Rathke cleft. P/w: Slow-

onset visual loss; variable signs of frontal lobe & hypothalamic dysfxn, hydrocephalus; occurs in children & adults (bimodal). Dx: Inferotemporal or superotemporal visual field defects; MRI: Sellar region cystic mass w/ peripheral enhancement that compresses chiasm from above or below. Rx: Surgery, but complication rate >> for pituitary adenoma (endocrine Δs, iatrogenic visual loss). Prog: Visual recovery can occur; recurrences w/ accumulation of cystic fluid or growth of tumor. Must f/u w/ serial exam & MRI.

Meningioma: Typically low-grade tumor from meninges of skull base (tuberculum sellae, diaphragma sellae, & anterior clinoid). P/w: Gradual visual loss, superotemporal visual field defects. Dx: MRI: Homogenously enhancing sellar mass pushing up on chiasm. Rx: Surgical.

Aneurysms: Locations: Supraclinoid & cavernous carotid, ophthalmic, ACA, or AComm. P/w: Carotid lateral compression, nasal or bi-nasal field defects; ocular motor & trigeminal deficits. Dx: CTA, MRA. Rx: Decompression/coiling may → visual improvement. Risk of SAH.

Glioma: Tumor of chiasm/hypothal; more common in NF-1 pts. P/w: Gradual blurred vision; temporal visual field defects, optic pallor; endocrine dysfxn. Rx: MRI: Minimally enhancing enlarged chiasm. Rx: Typically stable. If clinical worsening: ?XRT & chemoRx.

Sarcoidosis: Infiltrative granulomatous lesion; often → meningeal thickening & hypothal involvement. P/w: Visual loss may be acute, subacute, or chronic & w/concomitant or past cranial neuropathies (e.g., facial palsy), uveitis. Dx: MRI shows enhancing enlargement of chiasm w/ thickened & enhancing adjacent meninges; search for systemic sarcoidosis (e.g., chest imaging). Rx: Corticosteroids & other immunomodulatory medicines.

Demyelinating dz: Acute/subacute visual loss as part of NMO, CIS, MS. Dx: Funduscopy: Typically nl acutely, later disc swelling & hyperemia if extends anteriorly; disc atrophy chronically; w/ NMO, concurrent or past episodes of longitudinal transverse myelitis. MRI: Enhancement/enlargement of chiasm. ±spinal MRI, NMO serum Ab, LP. Rx: Acute Rx = IV steroids. If severe visual loss consider IVIG, plasmapheresis, & rituximab for NMO.

Other causes: Post-XRT, postsurgical, ethambutol toxicity, germ cell tumor, hamartoma, epidermoid, dermoid, metastases, lymphocytic adenohypophysitis, lymphoma, histiocytosis, TB meningitis, Rathke cleft cyst, sinus mucocele, vascular malformations, trauma.

CEREBRAL DISORDERS OF VISUAL DYSFXN

Homonymous hemianopia: Homonymous field defect in each eye c/l to lesion. TL lesions → superior defect (pie in sky). PL lesion → inferior defect. Macular sparing w/post lesion. Etiol: PCA or MCA stroke, hemorrhage, trauma, PRES, posterior cortical atrophy, posterior CJD (Heidenhain variant).

Visual neglect: Inattention to visual space (but intact remaining visual pathways), 2/2 nondominant inf. PL dz. Intact visual detection in neglected region (demonstrate by removing competing stimuli, e.g., in dark show bright object in neglected region). ±c/l sensorimotor neglect/deficits. Etiol: MCA stroke, hemorrhage, trauma, tumor, demyelination.

Alexia w/o agraphia: ↓ ability to read (retained ability to write) 2/2 left OL & splenium dz; disconnects left angular gyrus from right occipital lobe. Accompanying right homonymous hemianopia. Etiol: PCA stroke, hemorrhage, demyelination.

Balint syndrome: Variety of difficulties from b/l occiptoparietal dz: Simultagnosia (inability to process entirety of visual scene), ocular apraxia (inability to direct eye mvmts), optic ataxia (impaired motor mvmts when using visual information), concurrent inferior visual field defects. Etiol: Borderzone infarction (MCA-PCA boundary), Alzheimer dz, posterior cortical atrophy, PRES, posterior CJD (Heidenhain variant), PML.

Anton syndrome: Cortical blindness 2/2 b/l OL dz; often denial of deficit w/ confabulation, inf visual field defects. Etiol: Borderzone stroke (MCA-PCA boundary), b/l PCA strokes (basilar embolus), trauma, hemorrhage, PRES, posterior CJD (Heidenhain variant).

Akinetopsia: ↓ motion perception 2/2 b/l OL/TL dz. Etiol: Antidepressants, b/l stroke.

Prosopagnosia & visual object agnosia: ↓ recognition of faces or objects 2/2 b/l OL/TL dz. Accompanying c/l homonymous hemianopia, alexia w/o agraphia. Etiol: PCA stroke, hemorrhage, demyelination, HSV encephalitis, posterior cortical atrophy, Alzheimer’s dz.

Central dyschromatopsia: Impaired ability to visualize color from occipitotem-poral (fusiform & lingual gyrus) dz. Pts typically unaware of deficit. c/l homonymous superior visual field defect. Etiol: PCA stroke, hemorrhage, demyelination.

EFFERENT NEURO-OPHTHALMOLOGY

EFFERENT EXAMINATION OVERVIEW

Examine: Lid position, pupils in light & dark (& quality of constriction & dilation), eye mvmts of each eye independently (ductions) & eyes moving

together (versions), saccades & pursuits, adventitious eye mvmts in primary & eccentric gaze. If strabismus (ocular misalignment) not apparent w/ duction or version, do alternating cover testing while pt fixates on target in primary, right-, left-, & upgaze as well as head tilts; w/ mild left abducens palsy, for example, only sign may be a subtle esotropia on left gaze (by alternate cover testing).

ANATOMY OF THE EFFERENT VISUAL PATHWAY

Supranuclear control: Frontal eye fields (FEF; in premotor cortex) project to c/l paramedian pontine reticular formation (PPRF); PTO jxn also important for cortical eye mvmnt control. Damage to FEF → i/l gaze deviation. Damage to PPRF → c/l gaze deviation.

Brain stem: CN III nucleus (midbrain), CN IV nucleus (midbrain), CN VI nucleus (pons). CN III nucleus: Consists of medial oculomotor component (oculomotor nerve to superior rectus, medial rectus, inferior rectus, inferior oblique, levator palpebrae muscles), & paramedial parasympathetic component (Edinger-Westphal nucleus to iris sphincter & ciliary muscles). Nerve exits ventral midbrain after coursing through red nucleus, substantia nigra, & cerebral peduncle. CN IV nucleus: Consists of medial motor component (trochlear nerve to superior oblique muscle). Nerve fibers cross to c/l side & exit dorsal midbrain. CN VI nucleus: Consists of medial motor component (abducens nerve to lateral rectus muscle). Nerve exits ventral caudal pons. PPRF: Controls horizontal conjugate gaze; internuclear communication through myelinated medial longitudinal fasciculus (MLF). Internuclear ophthalmoplegia (INO) results from MLF dz. Damage to MLF & adjacent PPRF → “one & a half” syndrome (INO + i/l gaze palsy). Vertical conjugate gaze controlled by internuclear communication through rostral interstitial nucleus of MLF (riMLF) in dorsal midbrain.

Dorsal midbrain syndrome includes limitation of upgaze due to injury of riMLF. Subarachnoid space/cisterns: Cranial nerves course anteriorly toward cavernous sinus. Can be affected by basilar meningitis or space-occupying lesions. Cavernous sinus: Dura-lined venous plexus through which runs the ICA, postganglionic sympathetic nerves, CN III, CN IV, CN VI & CN V (V1 & V2 branches). CN VI is free floating, all other nerves are adherent to lateral dura. Lesions affecting cavernous sinus: Meningioma, lymphoma, pituitary adenoma, nasopharyngeal carcinoma, metastatic dz, intracavernous ICA aneurysm, carotid-cavernous fistula (auscultate for orbital bruit), Tolosa Hunt, Wegener’s, other causes of pachymeningitis. Orbital apex: Contains ON & ophthalmic artery in addition to CN III, CN IV, CN VI, & CN V1 (CN V2 exits through foramen rotundum). Lesions affecting orbital apex: Orbital

pseudotumor, thyroid-associated eye dz, meningioma, lymphoma, nasopharyngeal carcinoma, metastatic dz, mucormycosis, aspergillosis, Tolosa-Hunt. Look for conjunctival injection, proptosis, chemosis. Superior orbital fissure: Contains ophthalmic vein + CN III, CN IV, CN VI, & CN V1. Orbit/Tenon capsule: Contains retro-orbital fat, ON, ciliary ganglion (parasympathetic), muscles of ocular mvmt. Oculosympathetic pathway: Originates in hypothalamus, descends through brainstem & cervical cord (intermediolateral cell column) to C8-T2 (ciliospinal center of Budge), synapses & exits cord, ascends near cord to synapse on superior cervical ganglion (near lung apex), then ascends along carotid through cavernous sinus to end organs (Muller muscle, pupil dilator muscle). Damage to this pathway: Partial or complete Horner syndrome. Oculoparasympathetic pathway: Input from retina projects to pretectal nucleus in dorsal midbrain, then projects ipsilaterally (through pretecto-oculomotor tract) & contralateralˆ (through posterior commissure) to Edinger-Westphal nuclei; signal then travels w/both oculomotor nerves to both ciliary ganglia w/in orbit, then innervates iris sphincter muscle (pupillary constriction) & ciliary muscles (accommodation). Underlies consensual response to light as well as lens accommodation for near vision. Damage: Parinaud (aka dorsal midbrain) syndrome, Adie tonic pupil, Argyll Robertson pupils.

OCULOMOTOR NERVE PALSY (CN III PALSY)

Def: ↓ fxn of CN III structures: SR, MR, IR, IO, levator palpebrae, ciliary- & iris constrictor-muscles, 2/2 lesion of oculomotor nucleus/fascicle/nerve. Epid: Ischemic CN III palsy (usu elderly+DM/HTN). P/w: (1) Nerve lesion—diplopia, severe ptosis; ocular/retro-orbital pain w/ ischemic CN III palsy; HA w/ PComm aneurysm & migraine. (2) Fascicle lesion (ventral midbrain)—diplopia; i/l severe ptosis; c/l weakness, ataxia, tremor, bradykinesia. (3) Nuclear lesion (dorsal midbrain)—b/l severe ptosis, diplopia, lethargy.

Exam: (1) Eye down & out (2/2 unopposed LR & SO activity) w/ mydriasis (2/2 unopposed iris dilator muscle); partial lesions w/ variable CN III-innervated muscle or pupillary involvement (2) Mydriasis: w/ compressive CN III palsy (parasympathetic fibers run on nerve exterior); may be absent (“spared pupil”) in ischemic CN III palsy (w/ external blood supply, external pupillary fibers tend to be spared); exceptions occur. (3) Variable CN IV, CN V 1st division, CN V 2nd division, & CN VI involvement w/ cavernous sinus involvement. (4) Variable ON involvement w/ orbital apex dz (in addition to CN IV, CN V 1st division & CN VI). (5) w/ midbrain lesions, c/l weakness, ataxia, tremor, bradykinesia, lethargy

W/u: CTA, MRA or conventional angiogram to evaluate for aneurysm. Consider brain & orbital MRI w/ gado. Consider LP. Consider anti-AChR

Abs & further myasthenia testing.

DDx: (1) MG & thyroid-eye dz. I NO (eg demyelinating lesion). (2) Nerve lesion — aneurysm (PComm most common), ischemic/diabetic CN III palsy, uncal herniation, head trauma, cavernous sinus dz's, GCA (ischemia to nerve), ophthalmoplegic migraine, meningitis, sarcoidosis, schwannoma, meningioma, metastasis. (3) Fascicle lesion - stroke, trauma, demyelination, tumor. (4) Nuclear lesion - hydrocephalus, trauma, pineal tumor.

Prognosis: Ischemic CN III palsy usu resolves w/in 3-6 mos.

TROCHLEAR NERVE PALSY (CN IV PALSY)

Def: ↓ fxn of CN IV-innervated superior oblique. 2/2 lesion of CN IV nucleus, fascicle, or nerve. Epid: Ischemic CN IV palsy—a/w elderly, DM, HTN, and h/o trauma (may be mild). P/w: Nerve lesion: Vertical or oblique diplopia; mild ocular/retro-orbital pain w/ ischemic lesion. Nuclear lesion (dorsal midbrain)—vertical or oblique diplopia; c/l Horner syndrome. Exam: Eye is hypertropic (2/2 unopposed inferior oblique activity)—worst in adducted position; alternating hypertropia w/ b/l CN IV palsies (right hypertropia on left gaze; left hypertropia on right gaze). Head tilt away from lesion (compensating for inability to intort eye). Funduscopy: extorsion can be seen

(fovea in abnlly low position). Variable CN III, CN V 1st division, CN V 2nd division, & CN VI involvement w/ cavernous sinus involvement. Variable ON involvement w/orbital apex dz (in addition to CN III, CN V 1st division & CN VI involvement). W/ midbrain lesions, c/l Horner (ptosis, miosis; see Horner section). W/u: Consider brain & orbital MRI w/ gado. Consider LP. Consider anti-AChR Abs & further myasthenia testing. ?CTA, MRA or conventional angio r/o aneurysm (rare w/ CN IV palsy). Ddx: (1) Skew (hyperopia often resolves in supine; often +other brainstem si/sx). MG. Thyroid-eye dz. (2) Nerve lesion—trauma (may produce b/l lesion), aneurysm (PComm most common), ischemic/DM CN IV palsy, hydrocephalus, cavernous sinus dzs (per above), GCA (ischemia to nerve), ophthalmoplegic migraine, meningitis, sarcoidosis, schwannoma, meningioma, metastasis. (3) Nuclear lesion—trauma, hydrocephalus, pineal tumor. Prognosis: Traumatic & ischemic CN IV palsy usu resolves w/in 3-6 mo.

ABDUCENS NERVE PALSY (CN VI PALSY)

Def: ↓ fxn CN VI-innervated lateral rectus. 2/2 lesion of abducens nucleus, fascicle, or nerve. P/w: (1) Nerve lesion—horizontal diplopia, ↑ at distance (when concomitant CN V 1st division distribution pain or numbness, petrousapexlesion = Gradinego syndrome). (2) Fascicle lesion (pons)—

horizontal diplopia, ↑ at distance, c/l weakness & numbness. (3) Nuclear lesion (pons)—↓ horizontal gaze (concurrent PPRF lesion), weakness & numbness.

Exam: Eye is esotropic (from unopposed medial rectus activity). Variable CN III, CN IV, CN V 1st division, & CN V 2nd division involvement w/ cavernous sinus involvement. Variable ON involvement w/ orbital apex dz (in addition to CN III CN IV, & CN V 1st division involvement). W/ pontine lesions, may see impaired horizontal gaze, weakness, numbness. W/u: Consider CTA, MRA, conventional angio r/o aneurysm (rare w/ CN VI palsy). Brain & orbital MRI w/ gado. ±LP, anti-AChR antibodies & further myasthenia testing. DDx: (1) Myasthenia gravis & thyroid-associated eye dz. (2) Nerve lesion—b/l CN VI lesion suggests clival tumor or ↑ ICP; u/l CN VI lesion suggests ↑ ICP, Gradinego syndrome (nasopharyngeal carcinoma, mastoiditis), trauma, aneurysm, ischemic or diabetic CN VI palsy (uncommon), cavernous sinus dzs (per above), GCA (ischemia to nerve), ophthalmoplegic migraine, meningitis, sarcoidosis, schwannoma, meningioma, metastasis. (3) Nuclear lesion—stroke, hemorrhage, demyelination, tumor. Prognosis: Traumatic & ischemic CN VI palsy usu resolves w/in 3-6 mo.

MULTIPLE OCULAR MOTOR PALSIES

Def: Dysfxn of >2 ocular motor nerves (oculomotor, trochlear, & abducens). Causes: pathology in orbit, cavernous sinus, meninges, subarachnoid space.

P/w: Blurred or double vision. Signs of other cranial neuropathies.

Dx: Brain & orbital MRI. ±LP w/ cytology, systemic search for malignancy, myasthenia & thyroid testing: AChR-Ab, TSH, T4, thyroid-stimulating Ab, anti-thyroid Abs.

Ddx: Thyroid eye dz, orbital pseudotumor, orbital tumor, myasthenia gravis, mitochondrial dz (Kearns-Sayre, chronic progressive external ophthalmoplegia), ophthalmoplegic migraine.

Diseases: Tumor (leptomeningeal carcinomatosis, lymphoma, meningioma, schwannoma, chordoma, chondrosarcoma, pituitary apoplexy), meningitis (TB, syphilis, other bacterial), cavernous sinus thrombosis, cavernous-carotid fistula, cavernous carotid aneurysm, trauma, ophthalmoplegic migraine (CN III >> 6 > 4), botulism, basilar artery stroke, thiamine def, GBS (w/ anti-GQ1b Ab), CIDP,sarcoidosis,Tolosa-Hunt synd, GCA (ischemia to nerves or EOM's).

THYROID-ASSOCIATED EYE DISEASE & ORBITAL PSEUDOTUMOR

Thyroid-associated eye dz (Am J Ophthal 1996;121:284): Def: Immune-mediated inflammation of orbital contents (muscles, connective tissue, lacrimal gland, fat); often (but not always) in association w/ hyperthyroidism. P/w: Subacute b/l proptosis, mild ocular pain, diplopia (esp on upgaze), conjunctival injection (Bartley, 1996); si/sx of hyperthyroidism may precede, coexist, or follow eye dz. Epid: Common orbital d/o of adults; large majority develop hyperthyroidism; ↑ risk w/ women, older pts, smoking, radioactive iodine. Ddx: Orbital tumor, orbital pseudotumor, myasthenia gravis, ocular motor nerve palsies. Dx: Exam: Lid retraction, lid lag, proptosis, periocular swelling; restricted eye mvmts (IR & MR commonly → impaired upgaze & abduction); Imaging: orbital CT/MRI = regular enlargement of EOMs w/ tendon sparing. Rx: Most only supportive care (eye lubrication); corticosteroids, decompressive surgery or radiation w/ severe orbital congestion; cosmetic surgery once quiescent (orbital decompression, lid surgery). Prog: Typically self-limited (1-3 yr), but some w/ progression; occasional visual loss (optic neuropathy) w/ severe or fulminant dz.

Orbital pseudotumor: Immune-mediated inflammation of orbital contents (muscles, connective tissue, lacrimal gland, fat). P/w: Unilateral acute proptosis, orbital pain, diplopia, & periorbital swelling. Epid: Middle-aged adults. Ddx: Thyroid-associated eye dz, orbital tumor, orbital infxn, Wegener granulomatosis, histiocytosis, PAN, sarcoidosis. Dx: Proptosis, lid swelling, chemosis, restrictive eye mvmts; orbital imaging (CT or MRI) shows enlargement of EOMs w/ tendon involvement (all muscles can be involved). Rx: Rapid steroid response, NSAIDs. Prog: Often complete response to; recurrences common; rare visual loss (compressive optic neuropathy, glaucoma, retinopathy) w/ severe dz.

OCULAR MYASTHENIA GRAVIS

Reference: Muscle Nerve 2008;37:141.

Fluctuating, fatigable, & variable weakness of extraocular muscles due to ab-mediated interruption of nl neuromuscular synaptic transmission. Epid: F > M. F: 30-40s, M: 50-60s. P/w: Initial sx ocular (ptosis & diplopia) in >80% myasthenics. Exam: Medial rectus (& superior & lateral recti) most commonly involved, but all extraocular muscles can be involved; may see pattern similar to INO (“pseudo-INO”). Hypometric saccades (pre-edrophonium); hypermetric saccades (postedrophonium). Manual elevation of ptotic lid may result in lowering of c/l lid (due to relaxation of central tone to lid elevators). Sustained upgaze (>30 s) → worse ptosis & worsen medial rectus weakness. Ptosis may improve w/ rest, edrophonium test, or ice pack. Cogan lid twitch—Overshoot of lid on attempted upgaze (from depressed

position). Asymptomatic orbicularis oculi & neck weakness common. Fatigueable arm & leg weakness may be asymptomatic or non-existent in early stages. W/u: (1) Anti-AChR abs (positive in 50%); very low yield of other myasthenia Abs (e.g., anti-MuSK). (2) Consider edrophonium testing (test dose of 2 mg, then 2-8 mg until positive response or total of 10 mg given; consider pre-treating w/ 0.4 mg atropine to avoid side effects; have additional atropine in case of severe side effects (symptomatic bradycardia, hypotension); monitor for improvement of ptosis & impaired eye mvmts). (3) Consider EMG (single fiber EMG, repetitive nerve stimulation). (4) Chest CT r/o thymoma. (5) Check TSH & T4 (common concurrent thyroid dz). Ddx: Thyroid-related eye dz, ocular motor palsies. Rx: Prisms ↓ (diplopia (limited by fluctuation of weakness & variability of strabismus). Consider: Pyridostigmine (limited effectiveness w/ isolated eye sx), corticosteroids, thymectomy (if thymoma & onset <50 yo). Prognosis: 80% → generalized myasthenia.

GAZE ABNORMALITIES

Types of gaze abnlities: (1) Supranuclear gaze abnlity—eye mvmt d/o 2/2 lesion of any structure sending input to ocular motor nuclei (i.e., nuclei of CN III, CN IV, & CN VI); examples—stroke of FEF, hemorrhage near PPRF, convergence insufficiency, divergence insufficiency. (2) Internuclear gaze abnlity—eye mvmt d/o 2/2 lesion of pathways that connect ocular motor nuclei; example—INO from MLF lesion. (3) Nuclear gaze abnlity—eye mvmt d/o 2/2 lesion of ocular motor nuclei.

Types of conjugate eye movements

Saccades: Gaze shifting mechanism to rapidly provide foveal fixation. Cortical areas that generate c/l horizontal saccade: FEFs (posterior middle frontal gyri), supplementary eye fields (supplementary motor regions), & parietal eye fields (posterior parietal cortex).

Horizontal saccades: Descending projections to brainstem: decussation in midbrain to c/l PPRF → CN VI nuclei & CN III nuclei (via MLF).

Vertical saccades: Descending projections to brainstem: riMLF of midbrain → CN III-CN IV nuclei. Additional brainstem regions to facilitate, produce, or maintain saccades: c/l superior colliculus, riMLF, cerebellar flocculus, perihypoglossal complex, & medial vestibular nuclei. Additional brainstem region to inhibit undesired saccades: omnipause neurons of raphe interpositus nucleus.

Smooth pursuit: Gaze shifting mechanism to track & maintain foveal fixation. Generated cortically to produce i/l horizontal pursuit: occipital, temporal, & parietal junction; cortical saccade-generating areas (above) also contribute.

Horizontal pursuit: Descending projections to brainstem (double decussation pathway): posterior limb of i/l internal capsule → dorsal pons → decussation to c/l cerebellar flocculus & posterior vermis → cerebellar outflow via inferior cerebellar peduncle to medial vestibular nucleus → second decussation to abducens nucleus.

Vertical pursuit: Presumed similar pathway, but second decussation to riMLF. Interstitial nucleus of Cajal (inC) of midbrain, & post commisure play additional roles.

Vestibulo-ocular reflex (VOR): Stabilizes gaze, maintains foveal fixation. Head mvmt → semicircular canal signal → pontomedullary vestibular nuclei → MLF → CN III, CN IV, & CN VI nuclei.

Optokinetic nystagmus: Smooth pursuit followed by corrective saccade. Generated in temporal & parietal regions → accessory optic tract system → dorsolateral pontine nuclei → medial vestibular nucleus → nuclei of CN III, CN IV, & CN VI.

EYE MOVEMENT DISORDERS

Horizontal gaze palsy: ↓ Horizontal eye mvmts, may affect any conjugate eye mvmt type; may be supranuclear nuclear gaze palsy. P/w: Depends on location of lesion; ± concurrent weakness, neglect, language disturbance, level in arousal. Etiol: Stroke (hemispheric, pontine, or thalamic); sz (forced c/l horiz gaze); postsz (impaired c/l gaze); pontine mass (cavernous hemangioma, other hemorrhage, glioma); central pontine myelinolysis; thiamine deficiency; congenital ocular motor apraxia; ataxia telangiectasia syndrome; MSA; Gaucher’s dz; mitochondrial dz (Kearns-Sayre, chronic progressive external ophthalmoplegia). W/u: W/ pontine (PPRF) lesion, impaired i/l eye mvmts; i/l hemifacial weakness, & c/l weakness neglect; w/ diffuse pontine lesion, locked-in syndrome (anarthria, quadriplegia, preserved vertical eye mvmts alone); w/ cortical lesions, impaired c/l saccade or i/l pursuit (depending upon cortical location), language disturbance (dominant hemisphere) or neglect (nondominant hemisphere); brain MRI; brain MRA or CTA in selected cases. Prog: Gaze paresis in hemispheric stroke or hemorrhage is often self-limited.

Vertical gaze palsy: ↓ vertical eye mvmts, may affect any conjugate eye mvmt type (listed above); may be supranuclear or nuclear gaze palsy. P/w: HA, n/v, ↓ arousal (w/ hydrocephalus). Etiol: Dorsal midbrain mass (pineal tumor, tectal glioma, third ventricular enlargement—hydrocephalus), midbrain or thalamic stroke, oculogyric crises (med induced), benign gaze deviation of infancy; thiamine deficiency; Whipple’s dz; ataxia telangiectasia syndrome;

MSA; PSP; Niemann-Pick's dz; mitochondrial dz (Kearns-Sayre, chronic progressive external ophthalmoplegia). Dx: Accompanying dorsal midbrain signs—light-near pupillary disassociation, convergence-retraction nystagmus (convergence jerk & inward globe mvmt w/ upward saccade attempt), lid retraction; brain MRI; brain MRA or CTA in selected cases.

INO: Internuclear gaze palsy w/ impaired adduction of one eye 2/2 i/l damage of midbrain or pontine MLF. P/w: Horizontal (or oblique) diplopia; oscillopsia. Epid: Young women (demyelination); elderly (stroke). Etiol: Demyelination (CIS, MS); lacunar stroke. Ddx: Myasthenia (pseudo-INO); thiamine deficiency. Dx: For INO, exotropia; impaired (absent or slowed) i/l saccades, & c/l adducting nystagmus; INO may be unilateral or b/l; concurrent skew deviation; brain MRI; brain MRA or CTA in selected cases. Rx: Consider base-in prisms (for exotropia) if does not resolve. Prog: typically resolves w/ demyelination; often improvement w/ stroke.

One-and-a-half syndrome: Conjugate (supranuclear or nuclear & internuclear) gaze palsy in one direction & INO (impaired adduction) in opposite direction; 2/2 damage of PPRF or abducens nucleus & MLF fibers; lesion in dorsal pons. P/w: Horizontal diplopia. Etiol: Stroke, demyelination, hemorrhage (hypertensive, cavernoma), pontine glioma. Ddx: Myasthenia. Dx: Brain MRI; brain MRA or CTA in selected cases. Rx: Base-in prisms (for exotropia).

Skew deviation: Supranuclear lesion disrupting pathway from utricular & semicircular canal input to MLF & ocular motor nuclei → vertical eye misalignment. P/w: Vertical or torsional diplopia; ± brainstem si/sx (↓ arousal, dysarthria, weakness, ataxia). Etiol: Stroke (elderly), demyelination (young), tumor. Ddx: CN IV palsy, MG. Dx: Hypertropia (w/ medullary lesion, c/l hypertropia; w/ MLF lesion, i/l hypertropia); unlike CN IV palsy, often commitant (same degree of deviation in different directions of gaze) & may abate in supine position; skew deviation w/ ocular torsion & head tilt called ocular tilt reaction; other signs of brainstem dysfxn often present (as above); brain MRI/MRA. Rx: base-up or base-down prisms (for hypertropia) if does not resolve. Prog: May self resolve (stroke or demyelination).

Convergence insufficiency: Supranuc. deficit (location unk) → ↓ convergence. P/w: Horizontal diplopia w/ near tasks (e.g., reading). Epid: Head trauma pts; also w/ other midbrain lesions; decompensated/ "breakdown of" exophoria. Ddx: Myasthenia. Dx: Full ductions on exam. Rx: Base-in prisms (for exotropia); strabismus surgery.

Divergence insufficiency: Supranuclear deficit (uncertain location) → impaired ability to abduct eyes. P/w: Horizontal diplopia at distance. Epid: Elderly pts; concomitant small vessel brain dz. Ddx: b/l CN VI deficits,

myasthenia, ↑ ICP, pontine mass (glioma). Dx: Full ductions on exam; brain MRI. Rx: Base-out prisms (for esotropia); strabismus surgery.

Convergence spasm: Def: Supranuclear deficit that produces forced convergence; typically volitional & psychogenic. P/w: Diplopia, blurred vision. Epid: Personality d/o. DDx: b/l CN VI palsies, TBI, lower brainstem injury. Dx: Miosis & convergence, nl abduction by oculocephalic testing, resolution of miosis when one eye occluded; consider psychiatric evaluation; consider MRI if additional signs. Rx: Reassurance; psychiatric care considered.

NYSTAGMUS AND OTHER INTERRUPTIONS OF FIXATION

Nystagmus: Slow drift of eyes from fixation followed by corrective (fast or slow) mvmt.

Mechanisms: Disrupted fixation due to faulty (1) VOR. (2) Neural integrator (w/in nucleus prepositus hypoglossi, medial vestibular nuclei, inC, & vestibulocerebellumflocculus)—neural mechanisms to sustain eccentric eye positions to counteract elastic orbital forces. (3) Cerebral visual fixation mechanisms.

Presentation: n/v, vertigo, oscillopsia, & blurred vision w/ new, acquired nystagmus; nausea & vomiting prominent w/ peripheral dz. (visual acuity w/o oscillopsia w/ congenital forms of nystagmus. ±Brainstem & cerebellar si/sx (esp w/ acquired central nystagmus).

Treatments: Many agents tried, disappointing results (poorly tolerated, poor efficacy).

ACQUIRED NYSTAGMUS IN PRIMARY GAZE

Nystagmus from peripheral vestibular disease: Quality: Fast phase horizontaltorsional. Triggers: Changes in head position. Other features: Suppressed by fixation, changes in head position (e.g., Dix-Hallpike w/ BPPV), head shaking, hyperventilation, mastoid vibration, Valsalva. Supportive: Preservation of saccades & pursuits, Fatigues, short-lasting, hearing loss. Mechanism: Faulty VOR. Causes: BPPV, Meneire’s dz, vestibular neuritis, labyrinthitis. Rx: Epley maneuver (for BPPV); anticholinergic agents (diphenhydramine, scopolamine), benzodiazepenes, acetazolamide (for Meniere); vestibular rehabilitation.

Nystagmus from central disease—downbeat nystagmus: Quality: Fast-phase down, slow-phase up. Triggers: Downward-lateral gaze & convergence (e.g., reading or walking down stairs). Other features: Not suppressed by fixation.

Supportive: Concurrent horizontal nystagmus, si/sx cerebellar dz (ataxia, impaired pursuit). Mechanism: Faulty neural integrator (special role of flocculus to inhibit unwanted downward eye mvmts; dz leads to upward drift & downbeat nystagmus). Causes: Dz or toxins (lithium, alcohol, various antiepileptic medications) affecting vestibulocerebellum (cerebellar degeneration, demyelination, stroke, or hemorrhage) or craniocervical junction (Chiari malformation, syringomyelia, demyelination, stroke). Rx: benzos, baclofen, anticholinergic agents, memantine, gabapentin.

Nystagmus from central disease—upbeat nystagmus: Quality: Fast phase up. Triggers: +in neutral position & all gaze directions. Other features: Not suppressed by fixation. Supportive: Pursuit & saccadic intrusions. Mechanism: Faulty neural integrator; less well understood (than downbeat), but lesion often w/in medullary hypoglossal nuclei or ventral tegmental tract; can occur from dz of medullar, pons, or midbrain. Causes: Thiamine deficiency, stroke, demyelination, tumor. Rx: As for downbeat nystagmus.

Nystagmus from central disease—(pure) torsional nystagmus: Quality: Fast phase pure torsional (detect by observing conjunctival vessels). Triggers: Present in neutral position. Other features: Not suppressed by fixation. Supportive: Coexistent INO or ocular tilt reaction. Mechanism: Faulty neural integrator; poorly understood; medullary dz. Causes: Stroke, tumor, demyelination, syringomyelia. Rx: As for downbeat nystagmus.

ACQUIRED (& PHYSIOLOGIC) NYSTAGMUS IN ECCENTRIC GAZE

Physiologic (end point) nystagmus: Horiz fast phase in direction of gaze evoked by eccentric gaze in nl individuals. ↑ w/ fatigue; small amplitude. Fixation & pursuit nl. Rx: None.

Gaze-evoked nystagmus: Horiz. fast phase in direction of gaze evoked by eccentric gaze. Large amplitude; fixation & pursuit are impaired. ±Other si/sx of cerebellar & brainstem dysfxn. Mechanism: Faulty neural integrator; dz of horizontal gaze holding structures (nucleus prepositus hypoglossi & medial vestibular nuclei) & vertical gaze holding structures (inC) as well as vestibulocerebellum & paramedian tracts. Causes: Sedatives, ETOH, AEDs, episodic ataxia type 2, cerebellopontine damage. Rx: Not typically necessary.

OTHER TYPES OF NYSTAGMUS AND INTERRUPTIONS OF FIXATION

Pendular nystagmus—To & fro motion (usu in horiz. or vert. plane; may be circular or elliptical); no fast phase; underlying MS or brainstem stroke; Rx:

Memantine or gabapentin.

Periodic alternating nystagmus—Horiz. nystagmus, changes direction q90s w/5-10 min nystagmus-free intervals; shifting null point; usu congenital & benign; may be acquired (brainstem lesion); 2/2 cerebellar nodulus & uvula dz; treat w/ Baclofen, anticonvulsants.

Seesaw nystagmus: Cyclic elevation & intorsion of one eye w/ depression & extorsion of other (cycle then reverses); from dz of parasellar or midbrain region (inC).

Opsoclonus & ocular flutter: Involuntary random conjugate saccades at irregular intervals; concurrent myoclonus, ataxia & higher cognitive Δs; dz of omnipause neurons of pons; may be postinfxn, immune-mediated, or paraneoplastic; search for neuroblastoma in children & other tumors in adults; treat w/ steroids, IVIg, plasmapheresis; remove tumor.

Oculopalatal myoclonus: Pendular nystagmus + palatal tremor; mos after dz of Mollaret triangle (central tegmental tract, RN, dentate nuc); Rx: Memantine, VPA, anticholinergics

FORMS OF INFANTILE NYSTAGMUS

Congenital nystagmus: Usu recognized in first few mos of life. Quality: Horizontal w/ pendular waveform. Triggers: fixation. Maintains horizontal jerk features even in vertical gaze. Often lessens w/ convergence or at null point (preferred head position at which nystagmus amplitude is lowest). Mechanism: May occur in isolation as idiopathic condition or associated w/ congenital ON or retinal abnlities. Causes: Unknown. Rx: Correct any refractive error; prisms or eye muscle surgery to shift null point to primary position.

Latent nystagmus: Benign; p/w oscillopsia during eye examination. Covering one eye produces horizontal fast phase beating away from covered eye. Provocative: Monocular occlusion. Other features: Variable associated congenital esotropia, vertical deviation of occluded eye, & congenital nystagmus; manifest latent nystagmus may develop as an acquired condition w/ monocular visual loss of any cause. Mechanism: unknown. Causes. W/ manifest latent nystagmus, any process that reduces acuity in one eye. Rx: None required

Spasmus nutans: Begins w/ in first year; typically course of 1-2 yr. Quality: pendular, high freq, low amp. Provocative: changing frequency & amplitude w/ varying gaze position. Other features: Head nodding (2-3 Hz) & torticollis. Mechanism: Unknown. Causes: Rarely underlying optic pathway glioma, other midline brain tumor, or underlying alternate cause of visual loss.

Evaluation: Brain MRI, ophthalmologic examination. Rx: None required.

PUPILLARY ABNORMALITIES

PHYSIOLOGIC ANISOCORIA

Most cases of anisocoria are physiologic, 1-2 mm. Dx: Degree of anisocoria similar in light & dark conditions; nl speed of constriction & dilation b/l. Differences in lid position also common (1-2 mm difference), so relatively small pupil w/ relative ptosis ≠ Horner's syndrome.

THE LARGE PUPIL

General: Most cases are physiologic. Impaired parasympathetic input to iris constrictor is main pathologic cause of mydriasis. Other causes: ↑ sympathetic tone or iris pathology.

Presentation: If isolated (e.g., tonic pupil), may c/o blurred vision (from large aperture & impaired lens accommodation) & photophobia. If compressive CN III lesions, may c/o pain, HA, diplopia. Midbrain lesions may p/w ptosis, sleepiness, weakness, sensory loss, & ataxia.

Ddx: (1) Pharmacological (anticholinergic, sympathomimetic)—unintended (albuterol or ipratropium nebulizers, scopolamine) or dilated eye exam, esp if very large (>7 mm). (2) Other ocular causes—local (iris) trauma, infxn inflammation (iritis), acute angle-closure glaucoma (photophobia, redness, pain). (3) Tonic pupil—loss of pupillary ruff, regions of preserved constriction, constricts to near & to dilute pilocarpine; when idiopathic termed Holmes-Adie pupil (full syndrome typically young women w/ loss

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of DTRs); other etiologies—Sjögren's, GCA, VZV, Lyme, syphilis, & paraneoplastic. (4) CN III palsy w/ pupillary involvement—isolated pupil uncommon; expect one or more EOMs (SR/MR/IR/IO) involved & levator palpebrae; causes—compression (PComm aneurysm, tumor, uncal herniation), infiltration (tumor, infxn, inflammation); rarely CN III ischemia (typically spares pupil). (5) Midbrain lesion—hydrocephalus, pineal tumors, demyelination, inflammation, infxn.

Dx: (1) Determine if large or small pupil is pathologic: fails to constrict to light or anisocoria ↑ in light→ larger pupil is pathologic. (2) Pupils >7 mm likely 2/2 meds (e.g., nebulizers). (3) Look for signs of CN III dysfxn: Impaired adduction, elevation, & depression. (4) Look for signs of midbrain dysfxn: B/l ptosis & mydriasis; lethargy; c/l weakness, ataxia, tremor, or bradykinesia. (5) Consider CTA or MRA (for CN III compressive lesions such as PComm aneurysm). (6) Consider brain CT or MRI (for CN III or midbrain

compressive lesions such as uncal herniation). (7) Consider LP (for CN III inflammatory or infiltrative lesions).

THE SMALL PUPIL

General: Most anisocoria is physiologic. Main pathologic cause: ↓ sympathetic input to iris dilator (i.e., Horner syndrome). Other causes: ↑ parasympathetic tone or local pathology ofiris.

Horner syndrome: Subdivided by pathology of three neuron pathways: 1st order (hypothal → C8-T2), 2nd order (C8-T2 → sup cervical ganglion (SCG)), & 3rd order (SCG → iris dilator).

Presentation: Horner syndrome overview—ptosis, miosis, lower eyelid elevation, facial anhidrosis, mild conjunctival injection, blurred vision (↑ accommodation). First order HS—rarely isolated; i/l hemifacial & hemibody anhydrosis; lesions of (1) hypothalamus—↓ arousal, endocrine dysfxn, disrupted sleep; (2) midbrain—c/l CN IV palsy; (3) pons—dysarthria, dysphagia, weakness, numbness; (4) dorsolateral medulla—i/l facial numbness, c/l body numbness, hypophonia, & i/l ataxia (i.e., Wallenberg synd). Second order HS—Horner alone, or w/: i/l hemifacial & hemibody anhydrosis; lesions of cervical cord & brachial plexus → wkness, numbness, pain, bowel/bladder dysfxn. Third order HS—i/l hemifacial anhydrosis (lesion pre-ICA bifurcation = entire hemiface; post-bifurcation = lower hemiface). Lesions of (1) ICA → neck pain, retro-orbital HA, pulsatile tinnitus, CN IX-XII palsies, MCA-ACA stroke; (2) cavernous sinus → CN V 1st/2nd division, CN III/IV/VI palsies; (3) orbit—same as cav sinus but ON involved & CN V 2nd division spared; note—CN III (parasympathetic) palsy +HS may → fixed midposition pupil.

DDx: (1) First order Horner syndrome—(1) hypothalamic—tumors/infxns/inflamm (sarcoid, histiocytosis); (2) midbrain/pons—hemorrhage, trauma, demyelination, tumor; (3) medulla—PICA/vertebral a. stroke, demyelination, tumor. (2) Second order Horner syndrome—apical lung tumor, brachial plexus injury, trauma, syringomyelia, neoplasia (neuroblastoma), transverse myelitis, & cervical cord infarction. (3) Third order Horner syndrome—ICA dissection/thrombosis, cav sinus dz (e.g., inflamm/thrombosis/tumor), orbital dz, cluster HA, neck or intraoral trauma (may be iatrogenic injury through tubes & lines). (4) Argyll Robertson pupil—b/l miosis; reacts to near but not light (syphilis). (5) Chronic tonic pupil—initial large tonic pupil becomes small w/ time. (6) Local iris pathology—inflammatory, trauma, infxn. (7) Systemic & local meds & toxins—noradrenergic blockade or opioid/cholinergic stimulation.

Dx:(1) In Horner syndrome, look for miosis, dilation lag (from light to dark

conditions), mild ptosis (severe ptosis not seen in Horner), lower eyelid elevation, anhidrosis, mild conjunctival injection, pseudoenophthalmos, blurred vision (2/2 ↑ accommodation), ↓ intraocular pressure; w/ congenital Horner, ↓ iris pigment (blue eye). (2) Cocaine test—w/ ↓ dilation, confirms Horner; nl pupil dilates. (3) 1-2 days after cocaine test, consider hydroxyamphetamine test—w/ dilation, Third order neuron is intact & lesion is in first or second order neurons. (4) Apraclonidine testing—dilation in chronic Horner because of iris dilator denervation supersensitivity); no response in nl pupils or early Horner. (5) Consider brain & neck MRI/MRA (w/ fat suppression) & CTA. (6) Consider chest & shoulder imaging.

Neurology Consult Issues

MEDICATION-RELATED NEUROLOGIC COMPLICATIONS

Triad of HTN, tachycardia, hyperthermia often 2° to med or drug-drug interaction.

Differential: Serotonin syndrome (SS), neuroleptic malignant syndrome (NMS), malignant hyperthermia (MH), anticholinergic syndrome (ACS).

	SS	NMS	MH	AC
Offending agent	Increased serotonin	Dopamine antagonist	Volatile anesthesia	An
Sx onset	<12 h	1-3 days	30 min-24 h	<1
Pupils	Mydriasis	Nl	Nl	My
Reflexes	Hyper	Brady	Hypo	Nl
Tone	↑	Rigid	Rigid	Nl
Bowel sounds	↑	Nl↓	↓	Ab decreas
Treatment	Sedation	Sedation	Cooling	Se
	Paralysis	Cooling	Dantrolene	Ph
	Cyproheptadine	Dantrolene		

(*NEJM* 2005; 352:1112.)

SEROTONIN SYNDROME

Introduction: MS Δ, autonomic hyperactivity, NM abnormalities; occurs in 14%-16% of people OD on SSRIs; usually occurs between minutes-hours of ingestion; Sis/sx: range from mild to life-threatening; vital signs: fever, HTN, tachycardia; autonomic hyperactivity: mydriasis, hyperactive bowel sounds,

diaphoresis; MS: mild agitation, agitated delirium; reflexes: hyperreflexia, clonus; motor: rigidity, hypertonicity, myoclonus, shivering.

Offending meds: SSRI: sertraline, fluoxetine, paroxetine, citalopram; antidepressants: trazodone, buspirone, venlafaxine; MAOI: phenelzine; Analgesics: meperidine, fentanyl, tramadol; antiemetics; valproate, sumatriptan, dextramethorphan, linezolid, ritonavir, lithium, LSD, ecstasy, ginseng, St. John's wort.

Dx: Labs: metabolic acidosis, rhabdomyolysis, ↑ serum aminotransferase, ↑ creatinine.

Tx: Remove offending agent; usually resolves w/in 24 h w/ supportive care; fever is 2° to motor activity; so goal is to control this; BZD; Cyprohepatidine (5-HT2A agonist): 12 mg bolus followed by 2 mg q2h (up to 35 mg) until sxs resolve over first 24 h session; followed by 8 mg q6h; olanzapine 10 mg SL; chlorpropamide 50-100 mg IM, intubate if necessary.

NEUROLEPTIC MALIGNANT SYNDROME

Introduction: Idiopathic reaction to dopamine antagonists; occurs in up to 1% of pts taking neuroleptic agents, M > F, young > old, mortality rate up to 10%; Sis/sxs: slow onset, bradykinesia, akinesia, muscular rigidity, hyperthermia, fluctuating consciousness, autonomic instability (hyperthermia, tachycardia, HTN), rhabdomyolysis.

Offending meds: Neuroleptics: Haloperidol, thiothixene, chlorpromazine; atypical antipsychotics: clozapine, resperidone, olanzapine, quetiapine; w/d of levodopa/carbidopa or amantadine; antiemetics: Prochlorperazine; peristaltic agents: metoclopramide; sedative: promethazine.

Proposed mechanism: Dopamine deficiency or dopamine-2 receptor antagonism in the basal ganglia and hypothalamus resulting in altered temp set point.

Diagnosis: Elevated CK, myoglobinuria and leukocytosis.

Tx: Stop offending agents; fluid resuscitation; maintain normothermia w/ antipyretics or other cooling methods; dantrolene; dopamine agonists: bromocriptine (2.5-5 mg orally 3×/day, <30 mg/day), amantadine (100 mg orally 3×/day), levodopa/carbidopa; Bzs (lorazepam 1-2 mg q8h) for catatonia and agitation; Beta-blockers for tachycardia/HTN; DVT prophylaxis.

Resources: http://www.nmsis.org; hotline for medical professionals (1-888-667-8367).

MALIGNANT HYPERTHERMIA

Introduction: AD defect in Ca transport in skeletal muscle → hyper-Ca and

hypermetabolism; incidence: 1 in 20,000 to 50,000; Sis/sxs: Hyperthermia, ↑ conc. end tidal

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P.303

CO_2, hypertonicity, hyperthermia, skin can be mottled with cyanotic areas w/ patches of bright red; muscle contractures; cardiovascular instability; occurs w/in 30 min; mortality <10%; early death from hyper-K, acidosis, hypotension; late death from DIC, renal failure, multiorgan dysfxn.

Off meds: Halothane, succinylcholine, caffeine, vasopressor, atropine, cardiac glycosides, infxn, stress, anoxia.

Safe drugs: Nondepolarizing neuromuscular blockers, nitrous oxide, ketamine, opiates, barbiturates, Bzs, propofol.

Dx: Labs: ↑ Na, Ca, Mg, K, phos, CK, lactate, lactate dehydrogenase; myoglobinuria; testing: muscle biopsy exposed in vitro to halothane or caffeine → contraction (nl response is relaxation); heterogeneity of genetic mutations makes mutational testing challenging.

Tx: Stop offending agent; Na bicarb to treat acidosis; IVF; tx hyper-K; trend labs, watch for DIC; dantrolene (blocks Ca release from SR w/out inhibiting reuptake): IV push dose of 2.5 mg/kg, repeated every 5 min as needed up to 10 mg/kg.

Resources: http://www.mhaus.org; hotline for medical professionals (1-800-MH-HYPER).

ANTICHOLINERGIC SYNDROME

Introduction: Sis/sxs: “Red as a beet” (skin flushed), “hot as a hare” (hyperthermia), “dry as a bone” (dry mucous membranes, no sweating), “blind as a bat” (blurred vision, cycloplegia), “mad as a hatter” (confusion, delirium, hallucinations); ileus, urinary retention.

Offending meds: Atropine, scopolamine, antihistamines, TCAs.

Treatment: Sedation, cooling; Bzs for agitation; watch for QT prolongation; activated charcoal; physostigmine 1-2 mg IV q2min (avoid w/TCAs); complications (bradycardia, heart block, sz); keep atropine at the bedside.

PERIOPERATIVE STROKE RISK

(NEJM 2007:356:706)

Etiology: 45% occur w/in 24 h of surgery (usually 2/2 manipulations of heart/aorta or particulate release from bypass machine, hypoperfusion); remaining occur later (2/2 afib, MI, hypercoag); uncommon causes:

air/fat/paradoxical embolus, dissection. Risk based on surgery complexity: Double/triple valve (9.7%) > aortic repair (8.7%) > single valve (4.8%-8.8%) > CABG + valve (7.4%) > CEA (5.5%-6.1%) > head/neck tumor resection (4.8%) > CABG (2%) > peripheral vascular (0.8%-3%) > gen surg (0.2%).

Risk factors: Preop: age > 70, female; hx of HTN, DM, CRI, tobacco use, COPD, PVD, CAD, CHF, EF < 40%; carotid stenosis; aortic athero; sudden discontinuation of antithrombotic agents preop. Intraop: type/nature of surgery; type of anesthesia; duration of surgery, bypass and aorta cross-clamp. Postop: Heart failure, EF, MI, arrhythmia, dehydration/blood loss, hyperglycemia.

Predicting the Risk of Stroke among Pts Undergoing CABG

Risk Factor	Score	Total Score	Stroke Risk (%)
Age 60-69	1.5	0-1	0.4
Age 70-79	2.5	2	0.6
Age >80	3	3	0.9
Nonelective		4	1.3
Immediate	1.5	5	1.4
W/in 3.5 hours	6	2.0	
Female gender	1.5	7	2.7
Medical history		8	3.4
EF < 40%	1.5	9	4.2
H/o vasc dz	1.5	10	5.9
DM	1.5	11	7.6

Cr >2 or dialysis pt	2	12	<10

(*Ann Thorac Surg* 2003:76: 436.)

Intraoperative monitoring: Jugular bulb venous sats, TCD, optical topography, SSEP, EEG, carotid artery stump pressure, cerebral oximeter.

Prevention: Beta-blockers/statins may be beneficial. CEA: ASA 81-325 mg/day pre-and postop. CABG: ASA 75-325 mg/day preop, D/C 5 days preop, then resume 6 h postop; consider clopidogrel 300 mg po load + 75 mg/day postop.

Perioperative Anticoagulation Management

	Prosthetic Valve	Atrial Fibrillation	Venous Clot	Bridge Anticoag
High risk	Recent stroke/MI; MV; AoV (caged or single leaflet)	Recent stroke/MI; rheum MV dz	clot <3 wks; active cancer; APL ab	Strongly recommended
Moderate risk	AoV bileaflet + >2 risk factors	>2 risk factors	clot <6 mo; prior clot while off warfarin	Consider
Low risk	AoV bileaflet	<2 RF	—	Optional

(*Thromb Res* 2003;108:3.)

Tx: IV tPA is contraindicated after major surgery but catheter-based therapy (e.g., IA thrombolysis, mechanical clot retrieval) generally felt to be appropriate in certain instances, although without clinical trial data.

NEUROMUSCULAR DISORDERS IN THE ICU

Respiratory weakness: Critical illness neuropathy/myopathy, tumor, stroke, sedating meds or muscle relaxants, meningitis, GBS, ALS, C-spine lesion, phrenic nerve injury, MG, Lambert-Eaton Syndrome, botulism, polymyositis, dermatomyositis, muscular dystrophies.

CRITICAL ILLNESS MYOPATHY

Diffuse wkness 2/2 muscle damage in critically ill pts, often in the setting of recent IV glucocorticoid use and triggered by hyperglycemia, hyperthyroidism, or SIRS.

Presentation: Flaccid tetraparesis, facial muscle wkness common, extraocular muscle wkness rare; difficult to wean from ventilator; sensation and DTRs nl.

Workup: ↑ CK; NCS/EMG: nl-low MUPs, broadening of cMAPs, variable fibrillation potential activity, variable recruitment but nl sensory responses; muscle bx: myosin loss.

Tx: Variable recovery over wks to mos; PT/OT; D/C glucocorticoids; intensive glucose control; tx underlying critical illnesses.

CRITICAL ILLNESS NEUROPATHY

Diffuse wkness 2/2 axonal loss in critically ill pts, often in the setting of sepsis, SIRS, or multiorgan failure.

Presentation: Atrophy, axial wkness, ↓ or absent sensation and DTRs, CNs intact, difficulty weaning from ventilator.

Workup: CK nl; NCS/EMG: Low sensorimotor amplitudes, MUPs recorded w/ EMG higher before than after nerve stimulation; muscle bx: Neurogenic atrophy.

Tx: Variable recovery over wks to mos; PT/OT; D/C glucocorticoids; intensive glucose control.

CRITICAL ILLNESS MYOPATHY

Diffuse wkness caused by inadequate nutrition → muscle protein catabolism.

Presentation: Proximal > distal wkness and atrophy.

Workup: Hypoalbuminemia, vitamin def; EMG: Absent fibrillation potentials; muscle bx: Type 2 fiber atrophy.

Tx: Nutrition, vitamin supplementation, PT/OT.

ALCOHOLIC NEUROPATHY

Axonal neuropathy, incl autonomic neuropathy and symmetric polyneuropathy, caused by alcohol neurotoxicity, often w/ vitamin def. Pts are predisposed to compression neuropathies.

Presentation: Distal and symmetric sensory loss (vibration and touch) and/or wkness; paresthesias, dysesthesias, myalgias, ataxic gait; loss of reflexes.

Workup: EtOH consumption hx; blood alcohol level; vitamin levels,

specifically thiamine or erythrocyte transketolase activity.

Tx: Thiamine, nutrition, alcohol cessation counseling; TCAs or gabapentin for symptomatic control of dysesthesias.

ALCOHOLIC MYOPATHY

Acute (w/ binge) or chronic wkness 2/2 skeletal muscle damage from alcohol.

Presentation: Acute: Asymmetric/symmetric wkness w/ myalgia and swelling, occas assoc w/ dysphagia, CHF, cardiac arrhythmias (2/2 electrolyte derangements) and renal failure (2/2 rhabdomyolysis); Chronic: shoulder + hip wkness and atrophy w/ cramps, less commonly pain w/ assoc polyneuropathy.

Workup: Acute: ↑ CK, myoglobinuria; EMG: Fibrillations and myopathic changes; muscle bx: muscle fiber necrosis. Chronic: CK rarely elevated.

Tx: Alcohol cessation counseling; acute: correction of electrolyte derangements, cardiac arrhythmias, and renal failure.

HEPATIC ENCEPHALOPATHY

Etiologies: Hepatotoxic meds, tumor (primary vs. mets), EtOH, primary biliary cirrhosis, infectious hepatitis, cholecystitis, vascular insufficiency.

Precipitating factors: ↓ oxygen delivery: Resp distress, hypoxia, GIB; Infxn: Sepsis, spontaneous bacterial peritonitis; Metabolic dysfxn: Hypo-K, metabolic alkalosis, hypoglycemia; Meds: Sedatives, tranquilizers; Hypovolemia; Other factors: shunting treatment of portal-HTN, sedatives.

Presentation: General: cachexia, ascites, jaundiced, edema. Neurologic: Disturbance of sleep-wake cycles, asterixis, hyperreflexia, bradykinesia, transient decerebrate posturing, occasionally focal deficits (e.g., hemiplegia).

Workup: Mental status exam, consider formal psychometric testing; ↑ LFTs, hyper-NH_3 (postprandial arterial level), hypo-Na, hypo-K; check electrolytes, BUN, glucose and tox screen to exclude other metabolic dysfxn, uremia, hypoglycemia, and intoxications; CT/MRI to eval for cerebral edema and exclude other lesions (e.g., SDH); EEG: global reduction of freq and ↑ in amplitude w/ loss of alpha rhythm; evoked potentials: event-related responses show P300 peak after auditory stimuli; MRS: ↑ glutamine/glutamate:creatine ratio.

Tx: Identify and correct precipitating factors; reduce NH_3 levels: Lactulose 45-90 g/day to have two to three bowel mvmts/day or lactitol to lower NH_3 levels; if no clinical change in 48 h, add neomycin 500 mg tid or 1 g bid (risk

for ototoxicity, nephrotoxicity); protein restriction in pts w/ chronic encephalopathy who are resistant to lactulose tx or worsen w/ protein intake; for fulminant cerebral edema, consider induced hypothermia; placement of intracranial pressure monitors is controversial, carries a sig risk of ICH 2/2 coagulopathy; transplantation.

Selected Pediatric Neurologic Disorders

METAL METABOLIC DISORDERS

Wilson disease: Familial hepatolenticular degeneration.

Defect: Mutation of ATP7b (copper transport ATPase). Locus 13q14.3. Incidence = 1:50,000-100,000. AR inheritance.

Si/sx: Classically p/w movement d/o + hepatic failure. If onset in 2nd decade, neurologic si/sx such as gait or speech disturbance, followed by dysarthria, dystonia, dysdiadochokinesia, faciolinguopharyngeal rigidity, & gait difficulties. Tremor ± chorea, parkinsonism, psychiatric si/sx, cirrhosis, Kayser-Fleischer ring (seen in 100% cases w/ CNS involvement). Variable prognosis. Can have normal lifespan if Rx instituted early.

Dx: (1) Imaging: MRI w/ cerebral atrophy, T2 hypointensity of the globus pallidus & T2 hyperintensity of caudate, putamen, thalamus, dentate nucleus & pons. (2) Labs: Low serum copper & ceruloplasmin, elevated LFTs, high urine copper. (3) Liver biopsy: Elevated copper in liver w/ assay of copper content by spectrometry. (4) Neuroophthalmologic slit-lamp exam showing Kayser-Fleischer rings. (5) DNA testing for mutation analysis.

Rx: D-penicillamine, trientine, zinc acetate, or tetrathiomolybdate. Liver transplant controversial. Screen siblings (Neth J Med 2008;66:348-350).

Hemochromatosis

Defects: (1) Classic Type I: C282Y gene, locus 6p21.3. (2) Class II juvenile: AR hemojuvelin gene, locus 1q21 & hepcidin antimicrobial peptide, locus 19q13. (3) Class III: AR transferrin receptor-2, locus 7q22. (4) Class IV: AD ferroportin, locus 2q32.

Si/sx: Parkinsonism, cerebellar ataxia, dementia, myoclonus, action tremor, cervical dystonia, cirrhosis, primary hepatocellular carcinoma, arthritis, DM, bronze skin pigmentation.

Dx: Normal MRI (may have brain atrophy). High serum iron, transferrin saturation & ferritin. Biopsy: Hepatic iron is the most sensitive index of preclinical disease. Genetic testing.

Rx: Phlebotomy for ferritin >300 mg/L in men; ferritin >200 mg/L in women, regardless of the presence or absence of sx (Hum Mol Genet 2001;10:2181-

2186).

Pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz disease)

Defect: Pantothenate kinase deficiency. PANK2 mutations. Locus 20p13-p12.3.AR.

Si/sx: Onset 7-10 yr w/ dystonia, dysphagia, parkinsonism, choreoathetosis & retinitis pigmentosa; later cognitive & psychiatric sx. Spastic quadriplegia & death w/in 5-10 yr.

Dx: Imaging: T2 hyperintensity w/ surrounding hypointensity in medial globus pallidus ("eye of the tiger sign"). Definitive dx: PANK2 mutations.

Rx: Symptomatic, deep brain stimulation for dystonia (Nature Genet 2001;28:345-349).

PEROXISOMAL DISORDERS

X-linked adrenoleukodystrophy (cerebral form & adult forms)

Defect: Mutation in the ABCD1 gene leading to defect in peroxisomal β-oxidation & very long chain fatty acid (VLCFA) accumulation. Locus Xq28.

Si/sx: (1) Cerebral form: Onset 4-6 yr, 85% present initially w/ neurologic sx. Often begins w/ psychiatric d/o, academic performance decline, ataxia, spasticity, loss of vision, hearing, dementia, sz (late). (2) Adult form: Onset after 20 yr w/ spastic paraplegia & sensory neuropathy + sphincter disturbances & impotence. Both may develop adrenal insufficiency, optic atrophy. Progress to vegetative state & then death by 3 yr after onset.

Dx: (1) Cerebral form: T2 hyperintense posterior periventricular white matter w/peripheral enhancement. Adult form: T2 hyperintensities of lateral spinal cord. (2) High plasma & RBC VLCFA, abnl response to ACTH stimulation test. Low plasma cortisol in advanced cases. (3) Biopsy: Skin for enzyme assay in cultured fibroblasts. (4) Definitive dx: Mutation analysis.

Rx: Corticosteroids replacement, Lorenzo oil (decreases VLCFA), bone marrow transplant ASAP after initial clinical stages + MRI brain findings. AEDs for sz (Nat Clin Pract Neurol 2007;3:140-151; Arch Neurol 2007;64:659-664).

Refsum disease

Defect: AR defect in phytanoyl-CoA hydroxylase or peroxin-7; locus 10pter-p11.2, 6q22-q24.

Si/sx: Insidious onset in 1st-3rd decade w/ night blindness (from retinitis pigmentosa), recurrent or chronic polyneuropathy (often symmetric, distal,

vibration > pain & temp), palpable nerves, cerebellar ataxia, dysmetria, dysarthria, sensorineural hearing loss, cardiomyopathy, ichthyosis, pes cavus. Death may occur from sudden cardiac death.

Dx: (1) MRI w/ symmetrical T2-hyperintensity involving the corticospinal tracts, cerebellar dentate nuclei, & corpus callosum (only seen in infantile form). (2) Labs: ↑ plasma branched-chain FAs (mostly phytanic acid), ↑ CSF protein (1-7 g/L). (3) Biopsy: Skin for enzyme assay in cultured fibroblasts. (4) Mutation analysis.

Rx: Avoid phytanic acid in diet ± plasmapheresis (Hum Mutat 2004;23:209-218).

LYSOSOMAL DISORDERS

Metachromatic leukodystrophy (late infantile, juvenile, & adult form)

Defect: Deficiency of arylsulfatase A (locus 22q13.31-qter) or saposin B. AR inheritance.

Si/sx: Late infantile form: Normal development until age 2. Initially gait disturbances, peripheral neuropathy. Progressive distal to proximal LE weakness w/ loss of DTR, ataxia, dysarthria, spasticity, blindness, mental retardation & dementia. Vegetative state then death in late childhood. Juvenile form: Onset between 4 and 12 yr. Behavioral/psychiatric sx w/ gait disturbances. Progressive truncal, & limbs ataxia, spasticity, mental retardation, sz & dementia. Vegetative state then death w/in 10 yr. Adult form: Onset after age 15 w/ psychiatric/schizophrenic sx. Mental retardation, sz, & slowly progressive dementia follow. May have slow demyelinating peripheral neuropathy. Vegetative state then death w/in 20 yr.

Dx: (1) MRI w/ T2-hyperintense white matter w/ spared U fibers; posterior predominance. (2) Labs: CSF high protein (when weakness +). NCS: Reduced motor conduction velocities (only late in the course of the juvenile/adult form). Urine: High sulfatides. (3) Biopsy: Skin for enzyme assay in cultured fibroblasts. (4) Definitive dx: Low enzyme activity in peripheral leukocytes or cultured fibroblast. Prenatal dx from amniocentesis.

Rx: Bone marrow or umbilical cord blood transplantation in the early clinical stages. AEDs. Antipsychotics for adult form (Ann Neurol 2008;64:583-587; Arch Neurol 2005;62:309-313).

Fabry disease

Defect: Accumulation of glycosphingolipids. Alpha-galactosidase A deficiency. Locus Xq22.

Si/sx: Painful crises in the extremities (acroparesthesias), & abdomen (autonomic dysfunction), hypohidrosis. Depression, suicide, & strokes from atherosclerosis. Diarrhea, renal failure, angiokeratoma, cornea verticillata, cardiomyopathy, hearing loss. May develop stroke or renal or cardiac complications.

Dx: (1) Imaging: MRI T1 hyperintense pulvinar (thalamus). T2 hyperintense periventricular white matter. CTA may reveal vertebrobasilar dolichoectasia or evidence of stroke. ECHO may reveal LVH. (2) Labs: Increased plasma globotriaosylsphingosine. Urinary trihexoside assay & microalbuminuria. (3) Biopsy: Skin for enzyme assay in cultured fibroblasts. (4) Definitive dx: Enzyme assay, molecular screening. Prenatal dx from amniocentesis.

Rx: Enzyme replacement therapy (reverse cardiomyopathy). Experimental ex vivo hematopoietic stem cell gene therapy (Clin Genet 2004;66:158-165; Neurology 2009;72:63-68).

MITOCHONDRIAL & ENERGY METABOLISM DISEASES

MELAS: Mitochondrial encephalopathy w/ lactic acidosis & stroke-like episodes

Defect: Mutation in several mtDNA genes, including MTTL1, MTTQ, MTTH, MTTK, MTTS1, MTND1, MTND5, MTND6, & MTTS2. Maternally inherited.

Si/sx: Onset in childhood or early adulthood w/ sudden partially regressive neurologic attacks resembling strokes. Hemiparesis, hemianopia, cortical blindness, aphasia. Migraine-like headache, sz, mental deterioration. Progressive external ophthalmoplegia (10%), progressive deafness. Commonly short stature.

Prognosis: Variable. Episodes are often transient, but can result in dementia.

Dx: (1) Imaging: Serial alternating cortical, & subcortical areas of destruction of the parieto-occipital lobes & basal ganglia (w/ calcifications) sparing white matter (unique feature). MRI acutely DWI bright; not necessarily corresponding w/ vascular territories. MRI SPECT w/ high lactate peak. (2) Labs: CSF & blood- elevated lactic acid. (3) Muscle biopsy: Ragged red fibers (although clinically, exercise intolerance is rare). (4) Definitive dx: CSF or blood microarray for mitochondrial DNA A3243G mutation (minority has 3271 or 3291).

Rx: Coenzyme Q10 & steroids have shown some beneficial effect (Ann Neurol 2008;63:473-481).

Leigh syndrome: Subacute necrotizing encephalomyelopathy

Defect: Mutations of nuclear- & mitochondrial-DNA encoding genes of the mitochondrial respiratory chain complexes I, II, IV, & V; coenzyme Q & pyruvate dehydrogenase complex deficiency. AR (X-linked), maternal inheritance only if mtDNA.

Si/sx: 75% onset 3-12 m; 25% adults. Developmental delay, FTT, hypotonia, spasticity, chorea, deafness, ataxia, dystonia & peripheral neuropathy. Decompensation episodes w/ lactic acidosis, regression. Hypertrophic cardiomyopathy.

Dx: (1) Imaging: T2 hyperintensities in bilateral brainstem & basal ganglia. (2) Labs: Elevated lactate in CSF & blood mostly postprandial or after glucose challenge. Elevated blood pyruvate. (3) Biopsy: Ragged red fiber in muscle biopsy may be rarely present. (4) Definitive dx: Mutation analysis.

Rx: Carbohydrate restricted diet. High doses of thiamine. CoQ10. $NaHCO_3$ if acidosis. (Pediatr Neurol 2008;39:223-235).

Kearns-Sayre syndrome

Defect: Mutation in several mtDNA genes. Familial & nonfamilial form.

Si/sx: Onset before 20 yo w/ chronic, progressive ophthalmoplegia & pigmentary retinopathy, weakness of facial, pharyngeal, trunk & extremity muscles & deafness, cardiomyopathy, dysphagia, small stature. Progressive course, often die of cardiac cause.

Dx: Imaging: Basal ganglia calcifications. Labs: High plasma lactate & pyruvate. Markedly increased CSF protein. Biopsy: Ragged-red fibers in skeletal muscle. Definitive dx: Mutation analysis.

Rx: Mitochondrial cocktail (vitamins), coenzyme Q10 (J Med Genet 2003;40:858-863).

Leber hereditary optic neuropathy

Defect: 18 allelic variants of mutated mtDNA, though 11778, 3460, & 14484 are present in at least 90% of families. Exclusively maternally inherited.

Si/sx: Acute or subacute central vision loss leading to central scotoma & blindness presenting at mean age of 27-34 yr. Dopa-responsive parkinsonism & myoclonus. Normal life-span.

Dx: Imaging: Normal. Definitive dx: Mutation analysis.

Rx: L-dopa. Mitochondrial cocktail (vitamins), coenzyme Q10 (Neurology 2008;70:762-770).

MERRF: Myoclonic epilepsy w/ ragged red fibers

Defect: Mutation in more than 1 mitochondrial gene: MTTK, MTTL1, MTTH, MTTS1, MTTS2, MTTF. Exclusively maternally inherited.

Si/sx: Onset in early childhood or adulthood w/ myoclonic epilepsy followed by other epilepsy d/o, progressive ataxia mental retardation, exercise intolerance. Pts typically progress to disabling ataxia, & mental retardation.

Dx: Labs: High serum levels of pyruvate or pyruvate & lactate. Biopsy: Skeletal muscle showing ragged-red fibers. Definitive dx: Mutation analysis.

Rx: Mitochondrial cocktail (vit), coenzyme Q10 (Arch Neurol 2004;61:269-272).

Alpers' disease

Defect: Mutation in the nuclear gene encoding mtDNA polymerase gamma (POLG). Locus 15q25. AR inheritance.

Si/sx: Onset in infancy or childhood w/ delayed milestones followed by intractable myoclonic or tonic-clonic epilepsy, psychomotor retardation, & later blindness. Liver failure. Poor prognosis w/ progressive neurologic deterioration.

Dx: MRI w/ T2-hyperintensity of cortical & subcortical white matter & basal ganglia. Definitive dx: Postmortem examination of the brain & liver. Mutation analysis.

Rx: Low carbohydrate diet, although not proven (Arch Neurol 2008;65:121-124).

MNGIE: Mitochondrial neurogastrointestinal encephalopathy

Defect: Mutation in the nuclear gene encoding thymidine phosphorylase. Locus 15q25, 22q13.32-qter. AR inheritance.

Si/sx: Onset between the 20-50 yo w/ ptosis, progressive external ophthalmoplegia, diffuse leukoencephalopathy, peripheral neuropathy, & myopathy, gastrointestinal dysmotility, thin body habitus. Most pts die before 40 yo.

Dx: Imaging: Signs of leukoencephalopathy on brain MRI. Labs: Elevated plasma deoxyuridine, thymidine, uracil, & thymine. Biopsy: Ragged-red fibers in skeletal muscle. Definitive dx: Mutation analysis.

Rx: Mitochondrial cocktail (vit), coenzyme Q10 (Neurologist 2004;10:8-17).

Carnitine palmitoyltransferase II deficiency

Defect: Carnitine palmitoyltransferase IA deficiency. Locus 1p32. AR

inheritance.

Si/sx: Onset in young adulthood w/ recurrent episodes of rhabdomyolysis triggered by prolonged exercise, fasting, or febrile illness. Normal life span.

Dx: (1) Labs: Recurrent myoglobinuria & elevated CK during attacks. Tandem mass spectrometry of serum acylcarnitines (elevated palmitoylcarnitine & oleoylcarnitine w/ normal acylcarnitine. (2) Biopsy: Skin fibroblast for enzyme analysis. (3) Definitive dx: Analysis of cultured skin fibroblasts is available.

Rx: Avoid prolonged exercise & recommend frequent carbohydrate feedings. Bezafibrate restores the capacity for normal fatty acid oxidation in muscle cells in patients w/ a mild form of CPT2 deficiency by stimulating the expression of the mutated gene (N Engl J Med 2009;360:838-840).

Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency

Defect: Deficiency of VLCAD. Locus 17p13. AR inheritance.

Si/sx: Onset in infancy, childhood, or early adulthood w/ episodic lethargy & muscle weakness induced by prolonged exercise or fasting & accompanied by hypoglycemia. Prognosis depends on severity of dz. Better prognosis w/ later onset.

Dx: Labs: Recurrent myoglobinuria & elevated CK during attacks. Elevated VLCFA w/ normal ketones. Biopsy: Muscle shows lipid storage in Type I fibers. Definitive dx: NBS & mutation analysis.

Rx: Frequent small carbohydrate feedings, dietary fat restriction & carnitine supplementation reduce frequency of attacks (Am J Hum Genet 2007;81:1133-1143).

Neurocutaneou

Disorder	Cutaneous Findings	CNS Findings	Associated Findings
Tuberous sclerosis (1/5,000-10,000)	Angiofibroma (adenoma sebaceum); congenital	Cortical tubers, subependymal nodules, SEGA,	Retinal hamartomas, pulm lymphangiomyoma renal angiomyolip

	hypopigmented macules (ash leaf spots 87%); shagreen patch (usu lumbosacral); less common: periungual/subungual fibroma; cafe au lait spots	sz, PDD, MR	
Von Hippel-Lindau (1/36,000)	Vascular, broad, purpuric or even ecchymotic lesions (uncommon)	Cerebellar & spinal heman-gioblastomas in 70% (usually after the 3rd decade but may be found in children); 1/2 develop unilateral or bilateral blindness from subretinal edema, hemorrhage, or retinal detachment	Multisystem tumors: Retinal he giomatosis (˜3rd decade), PCC, rena cysts, islet cell pancreatic tumors
Sturge-Weber (1/50,000)	Nevus flammeus aka port wine stain (angiomatous lesion usually distributed in the region innervated by V1); 5%-8% of newborns born w/ this have risk of Sturge-Weber syndrome; size of lesion does not predict CNS	Due to nonprogressive leptomeningeal & cortical angiomatosis (ipsilateral. to cutaneous lesion) w/ atrophy, calcification, & sclerosis. MR & sz (75%-90%)	Glaucoma (60 due to choroid vas malformation of th eye) ± heman-gion involving the visce

	involvement	Spastic hemiparesis from chronic cerebral hypoxia; vascular headaches	
NF1 1/30,000	2+ of: café au lait macules, 2+ neurofibromas or 1 plexiform neurofibroma, skin-fold freckling, optic glioma, lisch nodules, bony dysplasia, 1° relative w/ NF1	@ risk for peripheral & CNS tumors 15% optic gliomas (3%-5% symptomatic), other low grade astrocytomas, plexiform neurofibromas (25%), malignant peripheral nerve sheath tumors (5%-10% lifetime risk of transformation); LD (65%), ADHD (50%), seizures	HTN, renal ar stenosis, lisch nodu PCC, short stature, macrocephaly, precocious puberty moyamoya
NF2 (1/40,000)	Bilateral vestibular schwannomas, 1° relative w/disease plus unilateral vestibular schwannoma, any 2 of: neurofibroma, meningioma, glioma, schwannoma or cataract	Bilateral vestibular schwannomas a/w hearing loss; tinnitus, vertigo; focal weakness caused by spinal tumor or neuropathy; meningiomas, ependymomas,	Posterior caps lens opacities

		Schwannomas	
Incontinentia pigmenti	Staged skin lesions are erythematous & bullous @ birth; will later crust w/ residual pigmentation; follows lines of Blashko	In >30%; seizures, cerebral ischemia/edema, spasticity, cortical blindness, & developmental delay >10%	Skeletal chan alopecia, hypodont dystrophic nails; cataracts, strabism vitr hem, retinal Δs/detachment
Hypomel-anosis of Ito	Uni/ bilateral hypomelanotic whorled, streaked/reticulated macules on trunk, head, or extremities following the lines of Blashko	MR (60%); epilepsy (50%); autism (10%); ± hemi-megalencephaly. Hypotonia or arthrogryposis	Dysmorphism hemi-hypertrophy; dental; heart; renal
Ataxia telangiectasia (1/80,000-100,000)	Telangiectasias (bulbar conjunctivae, bridge of nose, ears, neck, & antecutibal fossae) first seen @ 3-6 yrs, then granulomas, graying hair, café au lait spots	Slowly progressive cerebellar ataxia, then choreoathetosis (˜85%), oculomotor apraxia, & nystagmus May have dysarthria, ↓ reflexes, hypotonia, muscle weakness cognitive impairment (initially of nl intelligence).	Loss of skin elasticity & subcutaneous fat; recurrent sinopulm infections Children are r likely to develop lymphoma, leuken lymphosarcoma, & Hodgkin disease

AD = autosomal dominant; ADHD = attention deficit hyperactivity disor
disease; htn = hypertension; LD = learning difficulties; MR = mental retardati
disorder; PCC = pheochromocytoma; SEGA = subependymal giant cell astroc

Source: Nowak. The Phakomatoses: Dermatologic Clues to Neurologic A