POCKET NOTEBOOK

# POCKET NEUROLOGY

Second Edition

M. Brandon Westover
Emily Choi DeCroos
Karim Awad
Matt T. Bianchi

Wolters Kluwer

## *Edited by*

**M. Brandon Westover MD, PhD**
*Assistant Professor of Neurology, Harvard Medical School*
*Boston, Massachusetts*

**Emily Choi DeCroos MD**
*Neurohospitalist, Department of Neurology, Erlanger Health System*
*Affiliated Assistant Professor of Medicine, University of Tennessee*
*College of Medicine*
*Chattanooga, Tennessee*

**Karim Awad MD**
*Director, Sleep Medicine, Harvard Vanguard Medical Associates*
*Boston, Massachusetts*

**Matt T. Bianchi MD, PhD**
*Assistant Professor of Neurology, Harvard Medical School*
*Boston, Massachusetts*

## Contributing Authors

**Ayush Batra, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Matthew B. Bevers, MD, PhD**
*Clinical Fellow in Neurology, Harvard Medical School, Boston, Massachusetts*

**Shamik Bhattacharyya, MD, MS**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Matt T. Bianchi, MD, PhD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Alessandro Biffi, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Michael P. Bowley, MD, PhD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Kate T. Brizzi, MD**

*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Adam Chen, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Rene A. Colorado, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Ryan R. Darby, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Mark Etherton, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Taha Gholipour, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Tamara B. Kaplan, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Jennifer A. Kim, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Richard C. Krolewski, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Alice D. Lam, MD, PhD**
*Clinical Fellow in Neurology, Harvard Medical School, Boston, Massachusetts*

**Alexis Lizarraga, MD**
*Clinical Fellow in Neurology, Harvard Medical School, Boston, Massachusetts*

**Marcelo Matiello, MD, MSC**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Sara Mayer, MD**
*Clinical Fellow in Neurology, Harvard Medical School, Boston, Massachusetts*

**Julie J. Miller, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Saad Mir, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Khaled Moussawi, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Ellen B. Penney, MD, PhD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Amanda L. Piquet, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Pooja Raibagkar, MD**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Laura Rosow, MD**
*Clinical Fellow in Neurology, Harvard Medical School, Boston, Massachusetts*

**Joel Salinas, MD, MBA**
*Partners Neurology Residency, Harvard Medical School, Boston, Massachusetts*

**Olga R. Rosenvald Szenberg, MD**
*Partners Neurology Residency, Harvard Medical School, boston, Massachusetts*

**Nancy Wang, MD**
*Partners Neurology Residency, Harvard Medical School, boston, Massachusetts*

**Rodrigo Zepeda, MD**

*Clinical Fellow in Neurology, Harvard Medical School, boston, Massachusetts*

## Reviewers

**Anthony Amato, MD**
*Professor of Neurology, Harvard Medical School, boston, Massachusetts*

**Alireza Atri, MD, PhD**
*Ray Dolby endowed Chair in brain Health Research, Ray Dolby Brain Health Center, California Pacific Medical Center, San Francisco, California*
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Karim Awad, MD**
*Director, Sleep Medicine, Harvard Vanguard Medical Associates, Boston, Massachusetts*

**James Berry, MD, MPH**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Riley M. Bove, MD, MSC**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**David Chad, MD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**David W. Chen, MD, PhD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Tracey Cho, MD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Adam B. Cohen, MD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Merit E. Cudkowicz, MD, MSC**
*Julianne Dorn Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**William S. David, MD, PhD**
*Associate Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Emily Choi DeCroos, MD**
*Neurohospitalist, Department of Neurology, erlanger Health System, Chattanooga, Tennessee*
*Affiliated Assistant Professor of Medicine, University of Tennessee College of Medicine, Memphis, Tennessee*

**Brian L. Edlow, MD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Erik Ensrud, MD**
*Director, Neuromuscular Center, Boston Veterans Affairs Healthcare System, Boston, Massachusetts*

**Steve S. Han, MD, PhD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Graham Huesmann, MD, PhD**
*Carle Foundation Hospital, Research Assistant Professor, University of Illinois*

**Albert Hung, MD, PhD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Vikram Khurana, MD, PhD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Eyal Y. Kimchi, MD, PhD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Joshua P. Klein, MD, PhD**
*Associate Professor of Neurology and Radiology, Harvard Medical School, Boston, Massachusetts*

**Terrance Kummer, MD, PhD**
*Assistant Professor of Neurology, Washington University School of Medicine, St. Louis, Missouri*

**Thabele M. Leslie-Mazwi, MD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Brijesh Mehta, MD**
*Director, Stroke and Neurocritical Care, Memorial Neuroscience Institute, Hollywood, Florida*

**Jesse Mez, MD, MSC**
*Assistant Professor of Neurology, Boston University School of Medicine, Boston, Massachusetts*

**Stephen W. Parker, MD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Mikael L. Rinne, MD, PhD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Eric S. Rosenthal, MD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Mouhsin M. Shafi, MD, PhD**
*Instructor in Neurology, Harvard Medical School, Boston, Massachusetts*

**Nagogopal Venna, MD, MRCP**
*Associate Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

**Brian J. Wainger, MD, PhD**
*Assistant Professor of Neurology and Anesthesia, Critical Care and Pain Medicine, Harvard Medical School, Boston, Massachusetts*

**M. Brandon Westover, MD, PhD**
*Assistant Professor of Neurology, Harvard Medical School, Boston, Massachusetts*

# Preface

Like most neurology residents, we relied heavily on Pocket Medicine during our intern year in internal medicine. Early during neurology residency, we often wished that there was a comparably concise and complete pocket handbook for neurology house officers. This wish ultimately gave birth to the first edition of *Pocket Neurology*. The enthusiastic reception for the first edition, and more importantly, seeing the “yellow book” carried on the wards and in clinics by residents at many different hospitals, has been very gratifying.

This new edition of *Pocket Neurology* provides a thorough updating of all topics, adds additional figures and tables, and comes in both print and electronic forms. As in the first edition, the primary authors for all chapters are neurology residents and fellows, to ensure that the viewpoint remains maximally relevant to neurologists in the trenches, paired with experienced attending neurologists, to ensure that all topics reflect not only the latest data but also the thorough synthesis that comes through long practice and broad exposure to a wide variety of neurological disease.

We have striven to make this book both a practical and a thorough guide to the entire 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. Our authors have written *Pocket Neurology* with the goal that, paired with experience and sound clinical judgment, each chapter should contain all the information needed to handle virtually any new neurology case that residents are likely to encounter in the hospital and clinic, organized in a readily accessible way.

We hope that users will find *Pocket Neurology* a useful companion on their journey toward mastering the art and science of neurology.

# Neurologic Emergencies: Quick Reference

Matthew B. Bevers

Eric S. Rosenthal

## ACUTE ISCHEMIC STROKE

**Stroke:** Due to ischemia 2/2 cerebrovascular occlusion. Typically thrombotic or embolic. P/w variety of neurologic sx incl. wkness, numbness, aphasia, dysarthria, gaze deviation, ataxia, gait instability. Sx usually acute onset, but may fluctuate or "stutter" over several days.

*Risk factors*: Age, HTN, hyperlipidemia, smoking, DM, hypercoagulability, cardiac arrhythmias, e.g., atrial fibrillation, cardiomyopathy, and cardiac thrombus, among many others.

**Initial steps in evaluating acute stroke:** Determine time last seen well. Note: If pt awakens w/sx, time of onset is when last seen normal, not discovery time.

- Evaluate for acute recanalization or decompressive therapies when:
  - Presentation w/in 6 h of onset or any duration for basilar thrombus.
  - Large MCA or large cerebellar infarct (>1/3 cerebellum or encroaching fourth ventricle) w/risk of edema, hydrocephalus, of mass effect.
- Obtain NIH stroke scale (NIHSS) & document vitals & time.
- Determine if meets criteria for IV TPA. See below for indications & contraindications.
- Contact neurointerventionalist or facility w/an interventional service to determine if candidate for IA TPA or mechanical clot retrieval.

### IV TPA

**Indications:** Age ≥18 yr; significant neurologic deficit expected to result in longterm disability; CT brain does not show hemorrhage or well-established new infarct; acute ischemic stroke sx w/time of onset clearly defined as < 4.5 h. (*NEJM* 2008;359:131).

| **Contraindications (0-3 h)** | **Additional contraindications (3-4.5 h)** |
|---|---|
| Hypodensity > 1/3 MCA territory on CT | All 0-3 h contraindications apply |
| Hemorrhage on CT | NIHSS > 25 |
| Stroke, TBI, intracranial procedure < 3 mo | Oral anticoagulant use (regardless of PT/PTT) |
| h/o ICH, brain aneurysm, AVM, tumor | Combination of previous stroke and DM |
| Resolving or minimal deficit | **Cautions for IV tPA** |
| Suspicion of SAH | NIHSS > 22 (most centers still treat) |

| | |
|---|---|
| Trauma or surgery < 15 days | Glucose < 50 or > 400 |
| Active or GI/GU bleeding < 22 days | Known L heart thrombus |
| Recent LP or noncompressible arterial puncture | Pericarditis, endocarditis, high risk for septic emboli |
| INR > 1.7, PT > 15, PTT > 40, Plt < 100, other known bleeding diathesis | Liver or kidney dz causing increased bleeding risk |
| Use of novel oral anticoagulants | Pregnancy |
| SBP > 185, DBP > 110 despite meds | Ophthalmic hemorrhage |
| Sz at onset (if deficits thought to be postictal) | Life expectancy < 1 yr/other severe comorbidity |

**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 ICU or specialized stroke care unit for at least 24 h. Avoid arterial sticks, anticoagulation, and antiplatelet agents for 24 h. During the first 24 h after TPA is given, check BP q15min × 2 h, then q30min × 6 h, and then q1h for 24 h after starting Rx.
- F/u CT brain at 24 h. STAT CT if change in neurologic exam.
- When stabilized: routine workup. (See chapter on *Vascular Neurology*.)



**IA TPA/Mechanical Thrombolysis**

**Pt selection:** Endovascular thrombectomy w/removable stent beneficial in:

- Stroke pts w/anterior occlusion treatable w/in 6 h of onset (MR CLEAN RCT; n = 500; 89% also receiving IV tPA; 17% crossover to nontreatment; median 260 min from stroke onset to groin puncture and 85 min from stroke onset to IV tPA [Berkhemer OA, et al. *NEJM* 2015.]). Ninety-day mRS improved among intervention subjects (32.6% vs. 19.1%) w/o significant difference in mortality or sICH.
- Post-IV tPA stroke pts w/in 4.5 h of ischemic stroke onset w/internal carotid or M1 or M2 occlusion, CT infarct < 70 mL, and > 10 mL salvageable brain tissue on perfusion imaging (EXTEND-IA RCT, n = 70, median 210 min at initiation of endovascular therapy and 145 min from stroke onset to IV tPA; Campbell BCV, et al. *NEJM* 2015.). Both early (>8 point reduction in NIHSS or NIHSS < 1 at day 3; 80% vs. 37%) and delayed (mRS 0-2 at 90 days; 71% vs. 40%) improvement.
- Stroke pts w/proximal anterior circulation occlusion w/in 12 h of symptom onset, excluding those w/large core

infarct or poor collateral circulation on CT/CTA (ESCAPE RCT, n = 316; 75% receiving IV tPA, median 134 min from stroke onset to CT; 51 min from CT to groin puncture; and 110 min from onset to IV tPA; only 15% randomized at >6 h after onset [Goyal M, et al. *NEJM* 2015.]). Improved outcome at 90 days (mRS 0-2 53% intervention vs. 29% control), mortality (10.4% vs. 19.0%), no difference in sICH. Nonsignificant trend towards benefit of intervention at >6 h.

| **Factors Suggesting Likely Benefit from Endovascular Stroke Therapy for Anterior Circulation Stroke** |
|---|
| NIHSS ≥ 8 |
| Time ≤ 6 h for anterior circulation |
| Normal baseline functional status |
| Life expectancy > 12 months |

**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 w/a neurointerventional service. Maintain $O_2$ sat > 92%, manage w/o intubation if possible to speed time to reperfusion. Treat fever w/Tylenol. Keep pt NPO. Avoid Foley, NGT, femoral catheters, a-line, or central venous line unless necessary. Do not give heparin. Do not ↓BP unless MI or BP > 220/120 (or > 185/110 if IV TPA given). 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 24 h ICU observation.

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

## INTRACEREBRAL HEMORRHAGE

**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 hrs or days if the hemorrhage is expanding. Common locations: cerebral lobes, basal ganglia, thalamus, pons, & cerebellum.

**Risk factors or potential underlying causes:** HTN, amyloid angiopathy, aneurysm, vascular malformation, trauma, neoplasm, VST, hemorrhagic conversion of 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 for 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, mass effect/herniation,



cerebellar hemorrhage, depressed mental status. If IVH or hydrocephalus, urgent neurosurgical consult for external ventricular drain or intracranial pressure monitoring.
- *Labs*: CBC, Chem 7, PT-INR, PTT, blood bank sample, d-dimer, fibrinogen, LFTs. If INR > 1.3 or recent heparin or other anticoagulant use, correct coagulopathy STAT.
- Calculate vol. of ICH = (a × b × c)/2, where a = length, b = width, & c = number of cuts on CT brain multiplied by slice thickness in cm. If significant mass effect, consider osmotic agents & hypertonic saline as needed. (See below for management of acute elevation in ICP). Avoid corticosteroids. Consider surgical evacuation in select cases of cerebellar ICH. No e/o benefit from surgical evacuation of basal ganglia, thalamic, & pontine ICH (*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).

**Reversal Agents for Coagulopathy**

| Drug | Reversal Agent |
|---|---|
| Heparin | Protamine 1 mg/100 U of heparin given in last 4 h |
| Lovenox[a] | If <8 h give 1 mg protamine per mg of enoxaparin If >8 h give 0.5 mg proamine per mg of enoxaparin |
| Warfarin | Prothrombin complex concentrate (FEIBA, KCentra; dosing varies)<br>FFP 2-6 U<br>Vitamin K 10 mg × 1 |
| tPA | RIAStap (recombinant fibrinogen) if available Cryoprecipitate |
| Direct Xa inhibitor[b] | Prothrombin complex concentrate |
| Thrombin inhibitor (e.g., dabigatran)[b] | Hemodialysis if feasible |
| Antiplatelet | Consider platelet transfusion for surgery or plt count < 100K |

[a]Protamine for reversal of enoxaparin is recommended by the manufacturer, but efficacy has not been established.

[b]PCC may be effective based on in vitro studies, human trials not available (*Am J Hematol* 2012;87 Suppl 1:S141)

## ACUTE ELEVATION IN INTRACRANIAL PRESSURE (ICP)

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

**Sx:** Headache, altered mental status, somnolence, motor or sensory deficits, speech or swallowing difficulties, szs, 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, hemicraniectomy, or posterior fossa decompression if lesion w/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 7.5% or 23.4% saline, give 30 mL × 1 via central line over 20 min, followed by 15-30 mL q6h via central line if needed. For 3% saline, 40-50 mL/h can go through peripheral IV for up to 12 h and then needs a central line. Contraindications: Na > 160.
  3. Hyperventilation: For goal $pCO_2$ ~ 30 only as bridge to a more definitive therapy.

- If ICP due to tumor or infection: dexamethasone 10 mg IV × 1, then 4 mg q6h.



- For 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, sz, 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, szs, 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]** | **Stains, cx, & Other Tests** |
| Bacterial | High (>18) | High 10-10,000 | PMN predom | High (>50; <45 is 90% sens) | Low (<40) and ratio of CSF: serum <0.3 | GS (sens 50-90%); cx (75% yield), latex agglutination |
| Fungal | High | High (30-300) | Lymph predom | High | Low | Fungal stains & cx, India ink |
| Viral | Nl or mildly high (10-35) | High (25-500) | Lymph predom; PMNs in first 48 h | Nl to high (20-80) | Nl | PCR CSF & serologic studies for specific viruses |
| Tb | High | High (10-500) | Lymph predom | High (10-500) | Low (20-40) | AFB, cx, PCR |

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

From Hauser SL, ed. Meningitis, encephalitis, brain abscess, and empyema. *Harrison's Neurology in Clinical Medicine*. New York: McGraw-Hill; 2006:423-455; Tunkel AR, Scheld WM. Acute bacterial meningitis in adults. *Curr Clin Top Infect Dis* 1996;16:215-239.

## 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/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; add rifampin for specific circumstances[a] | *N. meningitides, S. pneumoniae, L. monocytogenes,* GNR |
| Immunocompromised | Vancomycin + ampicillin + third gen. cephalosporin *N. meningitides, S. pneumoniae, L. monocytogenes,* covering pseudomonas | *H. influenzae,* GNR |
| Post-neurosurgery/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; Bradley WG, Daroff RB, et al., eds. *Bacterial Infections, Neurology in Clinical Practice.* Vol. II, 4th ed. Philadelphia, PA: Elsevier; 2004:1475-1514.)

[a]Add rifampin for *S. pneumoniae* w/intermediate penicillin susceptibility or in locations w/common resistance, in pts undergoing concurrent vancomycin and dexamethasone treatment (dexamethasone may impair CNS penetration of vancomycin), or upon inadequate response to vancomycin after third-generation cephalosporin.

## NEOPLASTIC EPIDURAL SPINAL CORD COMPRESSION

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

**Dx:** HPI, MRI spine w/gadolinium; in pt w/h/o malignancy, obtain imaging of entire spine.

**Rx:** Dexamethasone (controversy exists for traumatic but not for neoplastic cord compression) 100 mg IV then 24 mg po qid × 3 days, followed by taper). 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); prophylaxis against venous thromboembolism.

**STATUS EPILEPTICUS:** See SE section in *Seizures, Epilepsy, and EEG* chapter.

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

**Dx:** Clinical presentation & EEG.

**Rx: See** SE protocol in *Seizures, Epilepsy, and EEG* chapter.

- 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 AED levels: (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 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, abnl movements, 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 (long-term use).

*Valproic acid*: Drowsiness, n/v, GI disturbances, tremor, weight gain, hair loss, fatal hepatotoxicity, pancreatitis, PCOS, Stevens-Johnson/TEN.

*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 mL/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 g/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; max deficit w/in 4 wk of onset. Poorer outcome w/axonal variants, age > 60, bedbound, intubated, rapid onset w/max < 7 days, prior diarrheal illness (*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, wkness of extremities, & resp failure in severe cases. Often fluctuate & are usually worse at night or after exertion. Pts may p/w worsening wkness w/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 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.



## TOXIC/METABOLIC SYNDROMES

Many toxic ingestions or metabolic syndromes can p/w altered mental status (including coma) or other neurologic symptoms, and are important to consider on the differential.

**Workup:** Serum and urine tox screens; specific drug levels if supported by Hx. Thyroid function test, cultures (many syndromes present w/fever).

**Management:** Supportive, incl. intubation if indicated, IV fluids, temperature management.

| Toxic Syndromes Presenting as Neurologic Emergencies |
| --- |

| Syndrome | Presentation | Treatment |
|---|---|---|
| Serotonin syndrome (SSRIs, TCDs, etc.) | Hyperthermia, hypertension, hyperreflexia, tremor, tachycardia | Cyproheptadine, 4-8 mg q4-6h; supportive care |
| Neuroleptic malignant syndrome (haloperidol, other antipsychotics) | Hyperthermia, rigidity, unstable BP, elevated CK | Bromocriptine 5-20 mg tid, dantrolene IV |
| Lithium toxicity | Delirium, ataxia, nystagmus, myoclonus, nephrogenic diabetes insipidus | Fluids, acetazolamide, hemodialysis |
| Organophosphate poisoning | Headache, vomiting, diaphoresis progressing to paralysis, sz | Pralidoxime, atropine |
| Benzodiazepine overdose | Drowsiness, coma, respiratory suppression | Flumazenil |
| Opiate overdose | Unresponsiveness, pinpoint pupils, bradycardia, hypothermia | Naloxone (0.04 mg initially, escalating as needed) |

From Ropper AH, Samuels MA, Klein JP. Disorders of the nervous system caused by drugs, toxins and chemical agents. *Adams and Victor's Principles of Neurology.* New York: McGraw-Hill Education; 2014:1200.

# Lesion Localization in Clinical Neurology

Julie J. Miller

Emily Choi DeCroos

## CEREBRAL HEMISPHERES

### LOBES: KEY FUNCTIONS & LESIONAL DEFICITS

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

**Lesions involving the frontal lobe & clinical manifestations:** *Orbitofrontal synd*: Disinhibition, impulsive behavior. *Frontal convexity synd*: Apathetic, angry/aggressive behavior. There may be associated disturbances in mvmt. *Medial frontal synd*: Mutism, gait disturbances, & bladder incontinence. *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: Somatosensory area in postcentral gyrus.

Attention: Typically nondominant → contralat hemispatial neglect, anosognosia.

**Lesions involving the parietal lobe & clinical manifestations:** *Gerstmann synd*: Lesion in dominant, angular gyrus → acalculia, alexia, finger agnosia, L-R confusion. *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*: Mediated by hippocampus. *Language*: 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 behavior. *Wernicke aphasia*: Receptive language 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 parietooccipital 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, accompanied by R homonymous hemianopia & color naming deficits.

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

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

### 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. *Body of the*

*chiasm synd*: Bitemporal visual field defects (w/or w/o splitting of macula). *Posterior chiasm synd*: Bitemporal 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 → preganglionic 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 through the 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 difficulty 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 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, including 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 sensory info from face & body, respectively, to primary somatosensory cortex. *Medial geniculate*: Relays auditory info from inf colliculus to transverse temporal (Heschl) gyrus. *Lateral geniculate:* Relays visual info from visual pathway to calcarine cortex. *Pulvinar:* Modulate occipitotemporoparietal cortical attention/visual processing. *Reticular:* Relays info between thalamic nuclei.

**Vascular supply of the thalamus:** Tuberothalamic artery: Arises from PComm. Paramedian artery: Branch of basilar or 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/hemisensory painful sensation. *Korsakoff dementia*: Degeneration of dorsomedial & 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 hemisensory loss, hemiparesis, abnormal mvmts, behavior Δs, akinetic mutism, somnolence, changes in mood, apathy, memory disturbances, neglect, deficits in ocular motility, small reactive pupils (diencephalic) visual field deficits, & language difficulty/aphasia.

## CEREBELLUM

Integrates sensory info & sends outputs to the cerebral cortex, brainstem, & spinal cord to coordinate mvmt. Lesions result in ataxia/irreg uncoordinated mvmts. Composed of flocculonodular lobe, vermis, & two hemispheres. Flocculonodular lesions → nystagmus, imbalance; 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, difficulty w/visuospatial ability, flattened affect, inappropriate behavior, dysprosody, agrammatism.

**Cerebellar anatomy:** *Cerebellar cortex*: Three layers: molecular, Purkinje cell, granule cell. *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. *Cerebellar peduncles*: Connect cerebellum to brainstem. *Sup*: Efferent pathway. Deep cerebellar nuclei send efferents in the superior cerebellar peduncles 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. *Inf*: Afferent & efferent. Efferents project to vestibular nuclei & reticular formation & afferent info from vestibular nuclei, spinal cord, & brainstem tegmentum.

**Vascular supply to cerebellum:** Sup cerebellar artery (SCA): sup portion. Anterior inf cerebellar artery (AICA): middle peduncles, middle ant hemispheres. Posterior inf cerebellar artery (PICA): inf portion.

## 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 superioris muscles. *Autonomic:* Efferent pupillary light reflex; lens accommodation.

**Clinical synds & localization points involving the third nerve:**

*INO (internuclear ophthalmoplegia):* Due to medial longitudinal fasciculus (MLF) lesions; 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 & half synd:* MLF + PPRF or MLF + sixth nuclear lesion causing ipsi adduction paresis w/gaze deviation to ipsi side, w/only mvmt contralat abducting nystagmus.

*Horner synd:* Classic triad: ptosis, miosis, anhidrosis. Other possible findings: “Upside down” ptosis from

sympathetic denervation of lower eyelid retractor, heterochromia iridis (diff in eye color b/w two eyes) in congenital lesions, & 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, 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 synd:* CNs II, III, IV, VI, $V_1$, proptosis. *Sup orbital fissure synd:* CNs III, IV, VI, & $V_1$. *Cavernous sinus synd:* CNs 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. *Sensory*: Three divisions: $V_1$: Forehead, cornea, 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. *Sensory*: (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 associated 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 associated w/geniculate neuralgia & herpetic vesicles in eardrum, 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 CNs VI & VII w/retroorbital facial pain due to lesion in petrous apex (may be complication 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 gustatory sweating.

**VIII. Vestibulocochlear nerve:** *Sensory*: Equilibrium & hearing. Composed of vestibular & cochlear nerves.

*Cochlear nerve*: Deficits result in tinnitus, deafness. *Vestibular nerve*: Vertigo, often positional (see table below). Nystagmus: Vertical/horizontal/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** | Usually horizontal, can be torsional or vertical, mixed | Pure horizontal, pure torsional, & pure vertical |
| **Intensity of nystagmus affected by gaze fixation** | Decreased | Unaffected |
| **Fatigability** | Decreases/disappears | Not fatigable |
| **Neurologic si/sx** | Absent | Often present |
| **Latency before onset of nystagmus/vertigo** | Present | Absent |

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

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

**XI. Spinal accessory nerve:** Innervates trapezius & sternocleidomastoid; responsible for shoulder shrug & head turn.

**XII. Hypoglossal nerve:** *Motor*: Tongue mvmt.

## BRAINSTEM



**Brainstem Localization and Associated Lesions**

| Syndrome | Localization and Landmarks | | Clinical Signs |
|---|---|---|---|
| Claude | *Midbrain* | CN III, rubrospinal tract | IIIrd palsy, contralat ataxia |
| Weber | *Midbrain* | CN III, CST | IIIrd palsy, contralat hemiplegia |
| Benedict | *Midbrain* | CN III, rubrospinal & CST | IIIrd palsy, contralat ataxia & hemiplegia |
| Parinaud | *Midbrain* | Vertical gaze center, superior colliculus | Supranuclear paralysis of vertical gaze, impaired convergence, convergence retraction nystagmus, light-near dissoc of pupils, Collier sign or lid retraction, skew deviation |
| Basis pontis | *Pons* | CST | Contralat ataxic hemiparesis, dysarthria-clumsy hand, or pure motor hemiparesis |
| Millard-Gubler | *Pons (ventral)* | Fascicles VI, VII, CST | Ipsi facial palsy, ipsi lateral rectus palsy, contralat hemiplegia |
| Foville | *Pons (tegmentum)* | Fascicles of VI, VII, PPRF,CST | Ipsi facial palsy, gaze palsy to ipsi side, contralat hemiplegia |
| Raymond | *Pons (ventromedial)* | CN VI, CST | Ipsi lateral rectus palsy contralat hemiplegia |
| Marie-Foix | *Pons (lateral)* | CST, spinothalamic, midcerebellar ped | Contralat hemiparesis, contralat pain & temp loss, ipsi ataxia |
| Locked-in | *Pons (bilat, ventral)* | CST, all CN nucl except eyelid & vertical gaze centers | Quadriplegia, aphonia, impaired horizontal eye mvmt (pt awake 2/2 sparing of reticular formation) |
| Wallenberg | *Medulla (lateral)* | Spinal trigeminal, spinothalamic tract, sympathetic tract, nucleus ambiguous, inf cerebellar ped | ↓ face & contralat body pain & temp, Horner synd, ipsi palate deviation, ipsi ataxia, gait instability, n/v/vertigo |
| Medial medullary | *Medulla (medial)* | CN XII, CST, medial lemniscus | Tongue deviation toward the side of the lesion, contralat hemiplegia, ↓ touch & proprioception contralat body |
| Hemiplegia cruciata | *Medulla (lower)* | Crossed CST fiber to arm, uncrossed CST fibers to leg | Crossed motor hemiparesis; paralysis of ipsi arm & contralat leg |

CST, corticospinal tract; CN, cranial nerve; nucl, nucleus; ped, peduncle.

## 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, watershed area of the spinal cord. *Lower* (*thoracolumbosacral*) *region*: Supplied by ant radicular artery of Adamkiewicz.

**Common Spinal Cord Syndromes**

| Syndrome | Presentation | Anatomic Basis |
|---|---|---|
| Transverse myelopathy | *Motor*: LMN wkns at level, UMN wkns below level<br>*Sensory*: Loss of pain, temperature, vibration, proprioception, & touch, two to three segments below level, hyperesthesia/pain at the level<br>*Reflexes*: Hyporeflexia at the level & hyperreflexia below the level | Complete or near-complete transection of the corticospinal, spinothalamic, & dorsal columns |
| Brown-Sequard syndrome | *Motor*: LMN wkns at level, UMN wkns below level<br>*Sensory*: 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<br>*Reflexes*: Ipsi hyporeflexia at the level & hyperreflexia below the level | Ipsi damage to corticospinal, posterior columns, & spinothalamic tracts |
| Anterior cord syndrome | *Motor*: LMN wkns at the level of lesion<br>*Sensory*: Pain & temperature loss below the lesion (intact light touch, vibration, & proprioception)<br>*Reflexes*: Hyporeflexia at the level of lesion | 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 |
| Central cord syndrome | *Motor*: Wkns at the level. May cause a “man in the barrel synd” if at the cervical level<br>*Sensory*: Cape distribution of pain & temperature loss<br>*Reflexes*: Hyporeflexia at the level | Damage of ant 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. Sensory loss from crossing spinothalamic fibers |

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

**MCA:** Wkns & sensory loss of contralat face, arm, & to lesser degree leg, dysarthria, global aphasia & 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 dominant side: Wernicke aphasia. Sup quadrantanopia or homonymous hemianopia. Nondominant lesion: Contralat visual, sensory, & hemispatial neglect. Agitated confusional state may occur w/temporal lobe damage.

**ACA:** Contralat leg wkns & sensory loss, foot/leg > thigh/hip. If both ACAs involved, may have bilat paraparesis. Also abulia, gegenhalten (paratonic rigidity), contralat grasp, & urinary incontinence.

**Anterior choroidal:** Supplies 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). Peduncular hallucinosis: Highly vivid visual hallucinations due to lesions of midbrain/tegmentum. *Postcommunal PCA* (*P2*): Cortical temporal & occipital lobe signs, hemianopia w/macular sparing, palinopsia, metamorphopsia, memory disturbances. Dominant occipital lobe + splenium of the corpus callosum: Alexia w/o agraphia; visual agnosia for faces, objects, mathematical symbols, & colors; anomia. Bilat infarcts: Anton synd, Balint synd.



**SCA:** Ipsilateral upper & lower extremity dysmetria, dysarthria, gait ataxia, & nystagmus, vertigo, n/v. Contralateral loss of pain & temp sensation.

**Basilar artery:** Branches supply pons & sup cerebellum. Small vessel perforators include paramedian, short circumferential, long circumferential. Top of basilar synd: Somnolence/altered mental status, agitation, akinetic mutism, peduncular hallucinations, lid retraction/Collier sign, convergence retraction nystagmus, d/os of ocular mvmt, pseudoabducens palsy, paralysis of vertical gaze, skew deviation, hemianopia.

**AICA:** Supplies lateral pons, middle cerebellar peduncle, ant cerebellar hemispheres, CNs VII & VIII. Stroke may lead to hearing loss & facial palsy together with ipsilateral limb dysmetria, gait ataxia, nausea, vomiting, vertigo, contralat loss of pain/temp sensation.

**Vertebral arteries:** Arise from subclavian arteries proximally, join distally to form basilar. Four segments: V1 (from subclavian artery to C6); V2 (from C6 to C2); V3 (from C2 to atlantooccipital joint); and 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 ipsi 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 above).

**PICA:** Supplies inf & posterior aspects of cerebellar hemispheres & inf vermis. PICA strokes p/w headache & vestibular sx of n/v, vertigo; cognitive & affective changes can occur. If ant lobe is spared, then dysmetria & ataxia may be mild/absent. Cerebellar post lobe edema from PICA infarcts can lead to herniation & brainstem compression. PICA lesions may cause lateral medullary synd (see above).

**Selected small vessel/lacunar syndromes:** *Hemisensory loss & hemiparesis*: Thalamocapsular. *Pure hemisensory loss*: Thalamus. *Pure motor hemiparesis*: Internal capsule, corona radiata, or basis pontis. *Dysarthria-clumsy hand*: Genu of the internal capsule & basis pontis. *Ataxic hemiparesis*: Pons, midbrain, internal

capsule, or parietal white matter.

# Neuroimaging

Alessandro Biffi

Adam B. Cohen

Joshua P. Klein

## TIPS FOR REVIEWING SCANS

Review all images & sequences. Reconstructed images screen for abnl findings, but always review raw data. 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 vs. atrophy, shift of midline structures. Note whether lesion involves gray matter, WM, or both.

## COMPUTED TOMOGRAPHY (CT)

Signal measured in Hounsfield units (HU). From black (hypodense) to white (hyperdense): air -1,000; fat -30-70; water 0; CSF +15; WM 20-30; GM 35-45; acute hemorrhage/thrombus +60-100; bone +1,000. HU values can complement visual inspection in identifying tissues/lesions. CT w/contrast (iodine based) enhances vessels & areas of BBB breakdown (necrosis, infxn, acute demyelination, many tumors). Delayed postcontrast images to assess temporal dynamics of enhancement (e.g., slow flow, vascular malformations). 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 ↓ 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. **CBF** = CBV/MTT.

## MAGNETIC RESONANCE IMAGING (MRI)

Signal from applying magnetic field & measuring relaxation times of hydrogen nuclei.

Gadolinium: MRI paramagnetic contrast, causes “T1 shortening” (hyperintensity). Enhances vessels & areas of BBB breakdown (necrosis, infxn, acute demyelination, many



tumors). Delayed postcontrast images to assess temporal dynamics of enhancement. Lesions that enhance usually neoplastic, pustulent, or bloody.

**MRI sequences:** *T1*: GM darker than WM, CSF dark. *T2*: WM darker than GM, 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); several processes besides acute infarction show restricted diffusion (abscess & hypercellular tumors). *GRE* (gradient echo) & SWI (susceptibility-weighted images): Dark signal corresponds to heavy metals (Fe, Ca, Mn, melanin), including iron-containing blood products; useful for identifying microhemorrhages (hemosiderin). *Diffusion tensor imaging* (*DTI*): Useful for WM tractography, emerging clinical applications. *MR angiography* (*MRA*): Uses timed boluses of gado to enhance arteries. “Time of flight” (TOF) MR angios are noncontrast-based vessel reconstructions of flow void signal, demonstrate flow rather than vessel structure, & can overestimate stenoses. *MR venogram* (*MRV*): Venous study, w/o contrast (TOF). *MR perfusion* (*MRP*): Timed 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 dzs w/↑ cell turnover, Cho is ↑'d. In

neurodegenerative dzs, 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, some metals (Fe, Ca, Mn, melanin), gado, intravascular blood flow | Water/CSF, air, bone, calc, hemosiderin, chronic demyelination, gliosis, intravascular flow void |
| 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, hemosiderin, 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/SWI | | Blood products, 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).
- **Rim enhance:** Fungal or parasitic infxn, abscess, acute demyelinating plaques, granuloma, infarction, lymphoma (in immunocompromised host), radiation necrosis, GBM, subacute ICH. (Mnemonic: "**MAGIC DR**": **M**etastases, **A**bscess, **G**lioma (& lymphoma), **I**nfarction, **C**ontusion, **D**emyelination, **R**esolving hematoma/**R**adiation 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 dz, 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 arterial anatomy, stenosis, & flow (direction & quality). *Carotid Doppler*: Extracranial carotids & verts; *transcranial Doppler*: Intracranial vessels.

**Positron emission tomography (PET):** Indirectly measures metabolism by uptake of a radioactively labeled biologically active compounds, e.g., glucose (tumors & abscesses are hypermetabolic; atrophy & gliosis are hypometabolic). Can be combined w/CT or MRI to improve anatomical localization 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.
- **Hyperacute stroke:** ? Thrombolysis/IA intervention: I-CT (w/CTA).
- **Acute/subacute stroke:** MRI w/DWI & GRE/SWI, w/head/neck MRA.
- **Multiple sclerosis:** MRI brain, cervical +/- thoracic spine, w/DWI & gado.
- **Neoplasm:** MRI brain w/DWI, GRE/SWI, gado.
- **Cranial nerve or brainstem lesion:** MRI brain w/SSFP sequence (FIESTA or CISS): thin cuts through brainstem & detailed views of CNs.
- **Optic nerve lesion:** Brain & orbital MRI w/gado coronal slices through orbits.
- **Aneurysm:** CTA if acutely symptomatic, MRA for surveillance.
- **Dissection:** CTA or MRA w/T1 fat-saturated ("fat-sat") images (to visualize intramural hematoma).
- **Conventional angiogram:** Gold standard for vascular imaging & dissections, residual lumen, vasculitis, vasospasm, moyamoya. Invasive, *risk of stroke* 0.5%-1%.

# NEURORADIOLOGY OF SPECIFIC DISEASES

## HEMORRHAGE

**CT:** Hyperdense (bright) & surrounded by hypodensity (edema, extruded serum).

Note: Hyperacute/chronic subdural hematomas & hygromas can be isodense to CSF.

**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/SWI.

**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 0.5 cm).

**Mnemonic for determining age of intraparenchymal hematoma on MRI:** "**i b**e **i**d**d**y **bid**dy **b**a**b**y **d**oo**d**oo" (or "**i b**leed, **i d**ie, **b**leed **d**ie, **b**leed **b**leed, **d**ie **d**ie").

| Stage (Age) | Hemoglobin | Compartment | T1 | T2 |
|---|---|---|---|---|
| Hyperacute (<24 h) | Oxyhemoglobin | Intracellular | **I**so | **B**right |
| Acute (1-3 days) | Deoxyhemoglobin | Intracellular | **I**so | **D**ark |
| Early subacute (>3 days) | Methemoglobin | Intracellular | **B**right | **D**ark |
| Late subacute (>7 days) | Methemoglobin | Extracellular | **B**right | **B**right |
| Chronic (>14 days) | Hemosiderin | Extracellular | **D**ark | **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, thalamus, pons, & cerebellum. *Cerebral amyloid angiopathy* (*CAA*): Typically lobar. *Mets* that commonly hemorrhage include breast & lung (by incidence) **M**elanoma, **Renal** cell ca, **C**horiocarcinoma, **T**hyroid papillary ca ("**MR/CT"**) (by propensity).



**Venous infarct:** Does not respect arterial territory, extensive edema, hemorrhagic transf.

**Intraventricular:** Typically seen w/SAH & 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 & contracoup effects.

## INFARCTION

**CT:** *Noncontrast:* use high-contrast center/window values (**30/30**) to assess for early infarction: loss of gray-white differentiation, parenchymal hypodensity, sulcal effacement. Hyperdensity w/in a vessel may represent acute thrombus. Soft thrombus appears hypodense compared to calcified atherosclerotic plaque (hyperdense). *CTA:* Vessel cutoff/stenosis; flame-shaped 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 WM 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 that 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/SWI 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 heterogeneous “Popcorn” appearance; GRE/SWI: dark rim (hemosiderin). Angiographically occult if no DVA.

**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 filling 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 on surface of 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 overall similar sensitivity to



CTA (*AJR Am J Roentgenol* 2009;193:1167-1174). Note whether dissection extracranial or intracranial, whether there is intradural extension (risk for SAH). Carotid: Tend to occur near C2-C3 vertebral level, 2-3 cm superior to bifurcation. Vertebral: Tend to occur where artery is nearest bone, at C1 & through transverse foramina.

**CAA:** Lobar ICHs & evidence of prior microhemorrhages in SC WM, T2 hyperintense & GRE/SWI hypointense, superficial siderosis sometimes seen as well.

**Moyamoya:** 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 lobe WM, external capsules, & throughout SC 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 & SC infarction, hemorrhage, & nonspecific WM T2 hyperintensities. Differentiate from reversible cerebral vasoconstriction syndrome & vasospasm via clinical presentation.

**Migraine:** Nonspecific SC T2 hyperintensities, "UBOs" ("unidentified bright objects").

**Transient global amnesia (TGA):** Punctate foci of restricted diffusion w/in limbic & paralimbic structures, reversible.

**Susac syndrome (retinocochleocerebral vasculopathy):** "Punched out" punctate T1 hypointense & T2 hyperintense lesions in the corpus callosum & deep gray nuclei.

## DEMYELINATING & OTHER WHITE MATTER DISEASES

**Multiple sclerosis:** Focal, ovoid WM lesions of PV > SC (perpendicular "Dawson fingers") hemispheric WM, corpus callosum, optic nerves, brainstem (esp medial longitudinal fasciculus), cerebellum (esp middle cerebellar peduncle), optic nerves, spinal cord (<3 spinal segments, incomplete transverse lesion); old lesions T1 dark; acute lesions enhance w/gado (rim or incomplete rim), may restrict diffusion. Rare cortical & deep gray matter lesions.

**ADEM:** Multiple lesions of same age; round, enhancing SC T2 bright lesions in hemispheric WM (& brainstem & cerebellum). More mass effect than typical MS lesions.

**Acute MS or ADEM variants:** *Acute hemorrhagic leukoencephalitis* (*Weston-Hurst dz*): confluent T2 bright WM signal w/mass effect & minimal enhance; hemorrhage on GRE/SWI 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 dz*): Longitudinal cord T2 bright lesion (>3 spinal seg, central, or occupying entire cross section) w/optic nerves & chiasm T2 bright lesions; all lesions expansile w/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 dzs (PML, MS, NMO, ADEM)

Vasculopathies (CADASIL, Fabry dz, Susac syndrome)

Congenital CMV

Brucellosis

Mucopolysaccharidoses, galactosemia, L2 hydroxyglutaric aciduria

Neuroaxonal leukodystrophy w/spheroids, Lowe syndrome

Chromosomal abnormalities, mosaicism

**Confluent**

| | |
|---|---|
| Frontal | Alexander dz; metachromatic leukodystrophy; leukodystrophy w/axonal spheroids |
| Parietooccipital | Krabbe dz; X-linked adrenoleukodystrophy; earlyonset peroxisomal disorder; neonatal hypoglycemia |
| Periventricular predominance | Metachromatic leukodystrophy; Krabbe dz; Sjögren-Larsson syndrome<br>Periventricular leukomalacia<br>HIV encephalopathy<br>Later onset neuronal degenerative disorders, e.g., neuronal ceroid lipofuscinosis<br>Adult polyglucosan body dz<br>Leukoencephalopathy w/brainstem & spinal involvement & lactate elevation |

| | |
|---|---|
| Subcortical predominance | Kearns-Sayre syndrome; Canavan dz; urea cycle defects; L2 hydroxyglutaric aciduria; propionic academia |
| Diffuse cerebral | End stage of all progressive WM dzs<br>Some mitochondrial disorders (MELAS)<br>Vanishing white matter (VWM) dz<br>Others: Megalencephalic leukoencephalopathy w/subcortical cysts (MLC), merosin deficient congenital muscular dystrophy, etc. |
| Cerebellum + middle cerebellar peduncles | Heroin/cocaine toxicity<br>Alexander dz; histiocytosis; premutation Fragile X syndrome; autosomal dominant leukodystrophy<br>Leukoencephalopathy w/brainstem & spinal cord involvement & lactate elevation<br>Early onset maple syrup urine dz; peroxisomal disorders; Cerebrotendinous xanthomatosis (CTX) |
| Brainstem | Peroxisomal disorders; Wilson dz; Alexander dz |
| **Delayed myelination or hypomyelination**<br><br>**T2: hypointensity of WM less marked**<br><br>**T1: hyperintensity of WM less marked** | |
| **No Typical PNS Involvement** | **Typical PNS Involvement** |
| Pelizaeus-Merzbacher dz<br>Galactosemia<br>Early-onset degenerative disorders, e.g., early-onset GM1 & GM2 gangliosidoses, infantile neuronal ceroid lipofuscinosis, Alpers syndrome | Hypomyelination syndromes (e.g., Cockayne) |

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

## OTHER INFLAMMATORY DISEASES

**SLE/APLA:** SC WM (posterior predilection) T2 bright lesions; may be in vascular distribution & ischemic 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); occasional cortical vein thrombosis/infarctions (var hemorrhage).

**Sarcoidosis:** Focal, multifocal, or confluent T2 bright lesions of WM w/var enhancement; also enhancement & 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/SWI) w/extensive asym & confluent ↑ T2 & ↓ T1 signal of SC WM w/minimal enhancement (*Neurology* 2007;68:1411).



**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* & *HTLV-2*: Small, multifocal T2 bright SC WM lesions; in early stages of spinal dz, multifocal enhancing T2 bright thoracic lesions w/var mass effect. *Lyme*: Scant T2 bright PV WM lesions; meningitis, polyradiculitis, & cranial neuritis (w/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; midstages w/PV & putamen & 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 dz*: **(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*) dz: 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*: 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 Enhancement | | |
|---|---|---|
| **Finding** | **Description** | **Etiologies** |
| Pachymeningeal enhance | Dural thickening & enhancement (var nodules)<br>Leptomeningeal sparing | Low ICP<br>Syphilis, TB<br>Sarcoid<br>Wegener granulomatosis<br>GCA<br>Idiopathic<br>Lymphoma & leukemia<br>Metastatic carcinoma<br>Old SAH[a]<br>Superficial siderosis[a] |

| | | |
|---|---|---|
| Diffuse meningeal enhance | Dural enhancement & thickening<br>Leptomeningeal enhancement (follows gyral & sulcal pattern) | Syphilis, TB, other bacteria, viruses<br>Sarcoid<br>Lymphoma & leukemia<br>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 rim enhancement
4. Late capsular (>2 wk): less surrounding edema (T2 bright signal) & increasing capsule (rim enhancement); DWI bright core; concurrent paranasal or mastoid sinus dz on CT

***Bartonella henselae* (cat scratch dz):** 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 (rim or diffuse).

***Borrelia burgdorferi* (Lyme):** See WMD.

***Tropheryma whipplei* (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, & beyond); var hemorrhage (by CT or GRE/SWI), 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, occ 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) w/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 & enhancement; rarer brainstem & cerebellar lesions.

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

**WNV (West Nile virus encephalitis):** variable T2 hyperintense lesions & restricted diffusion.

**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 angioinvasive).

**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 GM nuclei T2 bright, enhancing lesions w/surrounding edema (T2 bright signal); rim enhancement; var hemorrhage (by CT or GRE/SWI).

**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 dz):** 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/in 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., primary brain tumors or metastases. Absence of expansion of subarachnoid space, outward displacement of meningeal vessels, intraparenchymal mass effect or blurring of normal anatomic boundaries.

### Extra-axial tumors

- **Meningioma:** Looks like egg w/dural tail, hyperdense on CT, isointense to GM on T1-weighted MRI, w/homogenously bright enhancement due to high vascularity, T2 hypo- or hyperintense depending on tumor density. Typical locations: parasagittal dura, convexities, sphenoid wings, & olfactory groove. Can encroach & surround 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 remodel/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 posttraumatic 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 dz:** Can involve meninges & subarachnoid space. On MRI, nodular or diffuse pachy-

&/or leptomeningeal thickening & enhancement (*carcinomatous meningitis*). Primary CNS tumor: Think glioma & lymphoma. Metastatic dz: Think melanoma, lung, breast, GI, prostate cancer, hematologic malignancies (leukemia, lymphoma), chloroma (granulocytic sarcoma a/w myelogenous leukemias).

- **Nonneoplastic 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 cerebellopontine 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, microadenoma <10 mm, macroadenoma >10 mm diameter.
- **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 xanthoastrocytoma (PXA):** WHO grade II, most common juvenile supratentorial primary tumor, typically in temporal lobe, often w/clear borders, enhancing w/meningeal attachment.
- **Primitive neuroectodermal tumor (PNET):** Aka medulloblastoma, WHO grade IV, common juvenile infratentorial lesion, M > F, midline vermis lesion that



extends into superior & inferior vela of fourth ventricle. CT hyperdense, heterogeneous enhance; also include ependymoblastoma, medulloepithelioma, neuroblastoma.

- **Ependymoma:** WHO grades I-II depending on site; fourth ventricle > spine, supratentorial.
- **Subependymomas:** 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.
- **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, irregular rim enhancement w/internal necrosis (restricted diffusion), variably elevated 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 & adjacent to septum pellucidum, “bubbly” appearance, heterogeneous 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 hypointense w/marked enhancement & internal restricted diffusion); rim 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 dz:** 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 that 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:** Acute, variable SC WM T2 bright lesions; chronic, sym T1 hyperintense nonenhancing lesions in basal ganglia (manganese deposition).

- **Hypoglycemia:** b/l & sym DWI & FLAIR bright signal of cortex, hippocampus, & basal ganglia; var DWI & FLAIR bright signal of WM incl splenium.
- **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/SWI dark, T1 bright).

**Hereditary metabolic diseases**

- **Wilson dz:** 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.
- **Mucopolysaccharidosis:** 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 dz:** Hippocampal, amygdala, & temporal lobe atrophy, ↓ NAA on MRS. W/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 frontotemporal lobar degeneration (FTLD), which has no abnl PiB signal. $^{18}$F-florbetapir also binds to amyloid, approved for clinical diagnostic use, has longer half life than PiB.
- **Lewy body dementia:** Substantia nigra, posterior cortical, & brainstem atrophy.
- **Parkinson dz:** Atrophy of substantia nigra.
- **Parkinson plus syndromes:**

  Progressive supranuclear palsy (PSP): Midbrain tectum atrophy, abnl periaqueductal signal, ↑ iron in putamen

& red nucl (T2/SWI 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 dz:** 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 & corticospinal myelomalacia (T2 bright w/atrophy).



## VENTRICULOMEGALY & ICP ABNORMALITIES

### Ventriculomegaly

- Hydrocephalus **(obstructive & communicating): Flattened cortical 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 dz; 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 cortical sulci, minimal ↑ PV & periaqueductal T2 signal (transependymal flow).
- **Pseudotumor cerebri:** nl or slightly ↓ ventricles, ↑ T2 signal (CSF) in enlarged optic sheaths, flat pituitary gland/empty sella & posterior sclera, compressed venous sinuses, reverse cupping of optic discs (papilledema).

| 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 mammilopontine distance | >1 cm mammilopontine distance |
| Distended thin corpus callosum—flattened cortical sulci | Nl or atrophic corpus callosum Enlarged cortical sulci |
| Evidence of transependymal flow (acute only) | No evidence of transependymal flow (though can resemble microvascular ischemic dz) |

## 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, beakshaped 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.
- **Septooptic 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, 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/SWI) 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

Mark Etherton

Brijesh Mehta

## 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/negative MRI. Often hard to diagnose, given large differential. Longer TIAs more likely to be from embolus; repeated TIAs w/similar sxs suggest impending vessel occlusion. *Most TIAs should be worked up urgently*, inpt or outpt. Early w/u & Rx 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

- 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

**Stroke Risk**

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

## APPROACH TO TRANSIENT NEUROLOGIC SYMPTOMS

**Top 3:** TIA, sz, migraines. *Others:* Syncope, compressive neuropathy, anxiety, conversion, malingering, prior stroke sx remanifested (metabolic derangement/infxn), amyloid spells.

- **TIA:** *Pts:* Older, M > F, stroke risk factors (HTN, DM). *Sx:* Negative. If multiple modalities (i.e., sensory, motor), all usu occur at once. HA: Sometimes. *Duration:* Brief (~15 min).
- **Szs:** *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. *Thrombotic:* Full main deficit sometimes preceded by warning signs (either TIAs or minor symptoms) or stuttering course (progressive neurologic worsening over

several hours).



| Main Subtypes | |
|---|---|
| Large artery atherosclerosis (~18%) | • Most common sites: carotid bifurcation, vertebrals at origin or at the vertebrobasilar junction, MCA at stem/bifurcation<br>• Rare for plaques to occur beyond first branching point<br>• Risk factors: HTN, DM, dyslipidemia, smoking |
| Cardioembolic (~21%) | • Afib, MI, CHF, prosthetic valves, rheumatic heart dz<br>• Most often lodge in MCA (especially superior division) or PCA territory<br>• Small embolus → cortical/penetrating arteries; large → main branches |
| Small vessel (lacune) (24%) | • Due to atherosclerosis → thrombosis of small penetrating vessels<br>• >20 synds, 5 classic: pure motor, dysarthria/clumsy hand, ataxic hemiparesis, pure sensory & mixed sensorimotor<br>• Often a/w HTN |

### Other causes

**Vasculitis:** Due to autoimmune dz, 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, 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/long-standing HTN; multiple subcortical infarctions → dementia. MR: Extensive white matter changes. Rx: Alzheimer meds not found to be helpful (*Lancet Neurol* 2008;7:310).

**CADASIL (*c*erebral *a*utosomal *d*ominant *a*rteriopathy w/*s*ubcortical *i*nfarcts & *l*eukoencephalopathy):** 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. Noncontrast 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 glycoprotein).

**Imaging:** *CTA*: For endovascular intervention/medical therapy (e.g., dissection, atherosclerosis, vasculitis), comparable to U/S for ICA stenosis. *MRI/MRA*: Measure infarct volume on DWI to assist w/pt selection for intra-arterial thrombectomy in pts w/large-vessel occlusions; Se 95% w/in first few hours of stroke. Final infarct volume predictor of outcome. *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 (↑ 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 ischemic strokes

**Thrombolysis:** IV rt-PA if <3 h from last seen well (dose: 0.9 mg/kg, 10% as bolus). NNT for improvement: 3; number needed to harm: 30. 3-4.5 h rt-PA window in select pts, ECASS-3 showed benefit. Favorable outcome 52.4% w/rt-PA vs. 45% w/placebo (*NEJM* 2008;359:1317). 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: symptomatic ICH 6% rt-PA vs. 0.6% placebo. ↑ risk w/↑ NIHSS: score ≥ 20 → 17% risk <10 → 3% risk (*Stroke* 1997;28:2109). 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 large infarction, mass effect or ICH on CT, MAP >130, NIHSS >15.

**Endovascular Rx:** 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 (nonsignificant) ↓ 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). SPARCL trial (*NEJM* 2006;355:549) 2.2% absolute risk reduction recurrent stroke w/atorvastatin 80 mg. *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) or known stenoses. 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).

**Hemicraniectomy:** potentially useful for malignant MCA infarcts. STATE criteria (Score GCS <8, Time <48 h since LSW, Age <60 yo, Territory infarct >150 $cm^3$ or >50% MCA territory infarct, Expectations life expectancy) to guide OR decision. Age <60 hemicraniectomy vs. medical management mRS ≤3 43% vs. 21% & survival 78% vs. 29% (*Lancet Neurol* 2007;6:215). Less benefit if age >60 (*NEJM* 2014;370:12), *no pts w/mRS 0-2*, hemicraniectomy vs. medical management mRS 3 7% vs. 3%, mRS 4-5 60% vs. 28%.

**SSRI:** *FLAME Trial* (*Lancet* 2011;10:123) fluoxetine 20 mg daily vs. placebo for motor recovery at 90 days. Fluoxetine ↑'d Fugl-Meyer motor scale; fluoxetine 34 vs. placebo 24.3 points.

### 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: Hyperglycemia*: Goal BG 80-140, Rx w/ISS or insulin drip. 1/3 stroke pts affected, a/w poor outcomes, hemorrhagic conversion, & infarct progression. *SHINE Trial* in progress: IV insulin w/BG 80-130 vs. insulin sliding scale w/BG <180. *Hypoglycemia*: 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 vs. rt-PA w/in 3 h. Two parts: Part 1: No diff in neuro improvement at 24 h vs. placebo. Part 2: Favorable outcome vs. 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 vs. rt-PA w/in 6 h, sl. larger rt-PA dose. Overall no difference at 3 mo in rt-PA vs. 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 in previous trials, heparin was given too late & that early Rx is 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 Syst Database Rev* 2008;CD000024) and prevents nine ischemic stroke per 1,000 pts but causes an equal amount of ICH. **(4)** HAEST: 449 pts, LMWH vs. 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%-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 infarctions → symptomatic ICH. Rx: Depends on extent. *Szs*: risk ~10%, ↑ w/cortical strokes, no need for prophylactic AED, most commonly partial sz (±secondary generalization). *Movement disorders:* ~3%, hyper or hypokinetic, commonly w/basal ganglia or thalamic infarcts.

## 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 and then dropping ASA & switching med to bid).

**Clopidogrel:** Used if pt allergic to ASA, conflicting evidence. *CAPRIE* (*Lancet* 1996;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 vs. 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 vs. 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). *CHANCE Trial* (*NEJM* 2013;369:11): 3-wk DAPT in Chinese pts w/minor stroke/TIA, clopidogrel + ASA vs. ASA, reduced risk (HR 0.68), no difference in bleeding.

## 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):** No evidence CAS better than CEA. *CREST Trial* (*NEJM* 2010;363:11): CAS vs. CEA, 4-yr rate of stroke or death 6.4% CAS vs. 4.7% CEA. CAS → ↑ risk periprocedural stroke (w/in 30 days) 4.1% vs. 2.3%; stroke risk after similar to CEA (2.0% vs. 2.4%) ↑ risk MI w/CEA (1.1% vs. 2.3%). Current guidelines: CAS for high-risk surgical pts w/stenosis > 70% & sx. CAS may be appropriate for surgical high-risk pts.

**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-post acetazolamide images taken (MR or CT), Rx dilates vessels & ↑s CBF, vessels already max dilated will show little/no ↑ blood flow. OEF PET *scan*: Shows $O_2$ 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 severely flow limiting → consider anticoag to ↓ progression. ~10% strokes & TIAs 2/2 intracranial stenosis (50%-99% stenotic).

*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.

*SAMMPRIS Trial* (*NEJM* 2011;365:11): pts w/TIA or stroke & severe intracranial stenosis on max medical therapy (ASA 325 mg, clopidogrel 75 mg, & LDL <70) +/- intracranial stenting. 30-day stroke or death risk 5.8% medical management vs. 14.7% stenting.

**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).

*New agents: ARISTOTLE Trial (NEJM* 2011;365:981): RCT warfarin vs. apixaban. Latter had ↓'d composite risk of ischemic or hemorrhagic stroke or systemic embolism.



Apixaban 1.27% vs. warfarin 1.6%. Major hemorrhage: apixaban 2.13% vs. warfarin 3.09%. ICH: apixaban 0.24% vs. warfarin 0.47%.

*ROCKET-AF Trial* (*NEJM* 2011;365:883): warfarin vs. rivaroxaban. Rivaroxaban noninferior for stroke or systemic embolism prevention: rivaroxaban 1.7% vs. warfarin 2.2%. Major bleeding: rivaroxaban 5.6% vs. warfarin 5.4%. ICH decreased: rivaroxaban 0.5% vs. warfarin 0.7%.

*RE-LY Trial (NEJM* 2009;361:1139): warfarin vs. dabigatran. High-dose dabigatran superior for preventing stroke or systemic embolism: dabigatran 1.11% vs. warfarin 1.69%. Rate of major bleeding unchanged. ICH: 0.10% dabigatran 150 mg vs. warfarin 0.38%.

*Left atrial appendage closure: PROTECT AF Trial* (*Circulation* 2013;127:720) Watchman device endovascular occlusion LAA. Watchman device 3.0% vs. warfarin 4.3%, noninferior in preventing stroke, systemic embolism, or CV death. LARIAT device: left atrial appendage ligation percutaneously, studies ongoing.

**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: *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*: RCT comparing ASA 325 mg vs. warfarin in pts w/LVEF <35%; warfarin ↓'d risk ischemic stroke (HR 0.52) but offset by rate of major bleeding *(NEJM* 2012;366:1859). 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 w/mixed results. *RESPECT Trial* (*NEJM* 2013;368:12): intention-to-treat cohort HR w/closure 0.49 but not significant; however, as-treated cohort HR 0.27, significant.

*PC Trial* (*NEJM* 2013;368:1083*)* also trends to benefit w/closure, however not significant.

**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 Rx. 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 vs. warfarin (except for antiphospholipid Ab syndrome → warfarin).

**Antiphospholipid antibody syndrome:** Acquired; can be a/w autoimmune dz (e.g., lupus) or malignancy. 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:** HgbA1c 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 <70 mg/dL. *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 mg 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) ↑'s 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 dz, homocysteinemia, 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/neurointervention: Considered if pt w/sxs despite adequate anticoag.

*Neurointervent*ion: Stenting, vessel occlusion by endovascular coiling or surgical ligation, & bypass procedures.



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

## INTRACEREBRAL HEMORRHAGE

**Intro:** 10%-15% of first ever strokes are ICH (35% mortality at 30 days → 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, aneurysm, 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)** Infratentorial: Yes = 1, No = 0. *30-day mortality*: (5+, 4, 3, 2, 1, 0) → (100%, 97%, 72%, 26%, 13%, 0%).

**FUNC score** (*Stroke* 2008;39:2304)**:** Predicts likelihood functional independence at 90 days. Based on ICH volume, age, location, GCS, & cognitive impairment. Score <4 no chance of functional independence vs. 80% of

pts w/score >11 achieve functional independence.

**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 dz. |
| ***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/graywhite junction on gradient echo. |
| • *Rx*: Avoid anticoag; antiplts only 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 affects mortality/morbidity, consider in large cortical ICH.

*Surgery*: *Supratentorial ICH*: *STICH Trial* (*Lancet* 2005;365;387) → 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). *STICH II Trial* (*Lancet* 2013;382:397) looked at this subgroup, no diff outcomes w/early surgery vs. conservative mgt. *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.

*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.

*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 mo 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 dz. 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/baroreceptor 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).

## VENOUS SINUS THROMBOSIS

**Intro:** Annual incidence 3-4 cases/million. Higher freq in pts <40 yr, thrombophilia, or pregnant women.

**Path:** Usu thrombosis of cerebral veins/sinuses causes ↑'d venular pressure directly or via ↓'d CSF absorption

→ ischemic injury or parenchymal hemorrhage.

**Si/sx:** Thunderclap or subacute HA (90%), focal neuro deficits (44%), or sz (30%-40%) (*Circulation* 2012;125:1704).

**Dx:** D-dimer ˜10%-20% false-neg rate (*Stroke 2005;36:1716*). AHA/ASA 2011 guidelines rec MRV & T2WI.

**Rx:** Heparin → warfarin anticoagulation for 3-6 mo if provoked or 6-12 mo in unprovoked even w/ICH. Randomized control trial heparin vs. placebo showed 80% vs. 10% complete recovery (*Lancet* 1991;338:597). Fibrinolysis may be considered in severe cases but ↑ risk of hemorrhage; 17% w/ICH in one study (*Cerebrovasc Dis* 2003;15:159). Endovascular thrombectomy emergently if radiographic evidence of elevated intracranial pressure (tight sulci, cisterns) secondary to venous outflow obstruction & vasogenic edema; procedure a/w risk for venous rupture & hemorrhage, used as salvage therapy when conservative medical management w/anticoagulation ineffective. Caution w/use of hyperosmolar therapy such as mannitol (osmotic diuretic) for Rx of cerebral edema due to risk of volume depletion & propagation of venous thrombosis.

## 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 vs. craniotomy. Observation for small hematoma (<10 mm thickness, no herniation shift <5 mm), repeat CT in 6-8 h, then serially. Role for 1-wk course phenytoin or Keppra for sz ppx in traumatic SDH/SAH.

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

# Neurocritical Care

Ayush Batra

Terrance Kummer

Brian L. Edlow

## COMA & DISORDERS OF CONSCIOUSNESS

**Coma:** A state of unarousable unresponsiveness, duration typically <2-4 wk; rare cases longer, up to 12 mo (*Funct Neurol* 2014;29:201).

**Vegetative state (VS):** Unawareness of self or environment, but preserved 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, but descriptions of late recovery of responsiveness in pts w/TBI & nontraumatic brain injuries have undermined concept of permanence (*Neurology* 2010;75:239).

**Minimally conscious state (MCS):** Severely impaired consciousness w/minimal but definite behavioral evidence of awareness.

**NOTE**: Neuro exam a/w ˜40% misdiagnosis rate of VS compared to formal assessment w/Coma Recovery Scale-Revised—more sensitive for MCS (*BMC Neurol* 2009;9:35).

**Behavioral Features of Disorders of Consciousness** (*Neurol Clin* 2011;29:773)

| Behavior | Coma | Vegetative State | MCS |
|---|---|---|---|
| Eye opening | None | Spontaneous | Spontaneous |
| Spontaneous mvmt | None | Reflexive/patterned | Automatic/object manipulation |
| Pain response | Posturing/none | Posturing/withdrawal | Localization |
| Visual response | None | None/startle | Recognition/pursuit |
| Commands | None | None | Inconsistent |
| Verbalization | None | Unintelligible vocalization | Intelligible words |
| Communication | None | None | Nonfxnl |

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

**Catatonia:** Unresponsiveness due to psych disorder w/disturbance of motor behavior but maintained consciousness. Stuporous & hyperexcitable forms exist; stuporous form may resemble coma. Behavioral

disturbances: mutism, posturing, waxy flexibility, & catalepsy.

**Coma Scales:** GCS most common scale used.

| Glasgow Coma Scale (GCS) | | |
|---|---|---|
| **Eye Opening** | **Motor** | **Verbal** |
| **E4:** spontaneous | **M6:** follows commands | **V5:** oriented |
| **E3:** to voice | **M5:** localizes to pain | **V4:** confused |
| **E2:** to pain | **M4:** withdraws to pain | **V3:** inappropriate words |
| **E1:** none | **M3:** decorticate flexion | **V2:** incomprehensible sounds |
| | **M2:** decerebrate extension | **V1:** no response |
| | **M1:** no response | |



FOUR score validated for lower GCS, better for TBI & intubated pts

| **FOUR Score** (*Ann Neurol* 2005;58:585) | | | |
|---|---|---|---|
| **Eye Response** | **Motor Response** | **Brainstem Reflexes** | **Respiration** |
| **E4**: eyes open/tracking | **M4**: follows commands | **B4**: pupils & corneals intact | **R4**: regular |
| **E3**: eyes open, no tracking | **M3**: localizes to pain | **B3**: one pupil dilated/fixed | **R3**: Cheyne-Stokes |
| **E2**: eyes closed, opens to voice | **M2**: flexor to pain | **B2**: pupil or corneals absent | **R2**: irregular breathing |
| **E1**: eyes closed, opens to pain | **M1**: extensor to pain | **B1**: pupil & corneals absent | **R1**: intubated, overbreathing |
| **E0**: eyes closed w/pain | **M0**: absent; myoclonic status | **B0**: pupil, corneals, & cough absent | **R0**: intubated, breathing at set rate or apneic |

## Pathophysiology, ddx, & clinical manifestations

Neuroanatomic localization: Dysfxn of brainstem reticular activating system, thalamic relay nuclei, and/or b/l diffuse

dysfxn of cerebral hemispheres. In coma of unknown etiology, subsequently determined causes: diffuse and/or metabolic brain dysfxn > supratentorial lesion > infratentorial lesion > psychiatric “coma” (conversion Rxn, depression, catatonic stupor).

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

*Structural* (compressive/destructive): *Hemispheres* (EDH, SDH, SAH, ICH, stroke, HIE, tumor, abscess, meningitis, encephalitis, vasculitis, leukoencephalopathy, prion dz, PML), *diencephalon* (BG 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*: Hypoxia, ischemia, hypoglycemia, & vitamin cofactor 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, acids, psychotropic drugs, medication overdose), sepsis, hypo- or hypernatremia, acidosis/alkalosis, hypo-/hyper-Mg, hypo-/hyper-Ca, hypophos, temp dysreg (hypothermia or heat stroke), sz or postictal state, & diffuse axonal injury.

### Initial management/evaluation of coma & impaired consciousness

CABs (circulation, airway, breathng), 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, TFTs, adrenal function tests, UA/UCx, Bld Cxs, head CT, and/or brain MRI; consider LP & EEG. Other tests based on clinical suspicion.

**Natural history & prognosis of coma, VS, & MCS:** Prognosis varies depending on cause. Post-TBI better outcomes than postanoxia. Prolonged coma rare; most progress to VS w/in 1 mo. Both VS & MCS can be permanent or transitional states. Likelihood of improvement ↓'s over time for both. VS life expectancy typically 2-5 yr; rarely >10 yr. MCS pts have better chance of fxnl recovery than VS; MCS from TBI more likely to improve than MCS from other etiologies (*J Head Trauma Rehabil* 1997;12:36).

**Neuroimaging in disorders of consciousness:** MRI can help predict which early post-TBI VS pts (6-8 wk) will recover: corpus callosum & dorsolateral brainstem injuries predict nonrecovery (*Lancet* 1998;351:1763). FDG-PET of VS shows ↓ global cerebral metabolism to 30%-50% of nl (*J Neurosurg Anesthesiol* 1999;11:17); FDG-PET of MCS shows high diagnostic se (93%) (*Lancet* 2014;384:514). EEG background rhythm & presence of sleep architecture may have diagnostic utility in VS & MCS (*Ann Neurol* 2014;76:869), but not validated as a prognostic tool. Functional MRI has demonstrated willful modulation of brain activity in some VS & MCS pts (*NEJM* 2010;362:579).

**Therapies in disorders of consciousness:** Amantadine improves rate of fxnl recovery over 4-wk period in pts w/TBI VS & MCS (*NEJM* 2012;366:819). ˜5% of VS & MCS pts respond to zolpidem (*Am J Phys Med Rehabil* 2014;93:101). Experimental approaches: Thalamic DBS has improved responsiveness in 1 pt w/MCS (*Nature* 2007;448:522) & transcranial direct current stimulation of L-dorsolateral prefrontal cortex showed improvement in MCS pt CRS-R scores (*Neurology* 2014;82:1112).



## HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE) 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 & ↑ duration of CPR → ↓ outcome (*Crit Care Med* 1995;23:18).

### Neurological prognosis for coma after cardiac arrest

Goal of bedside exam & ancillary testing: predict poor vs. favorable neuro outcome. Strong predictors of *poor* prognosis are known. However, fever prevention (therapeutic hypothermia or targeted temperature management) alters the specificity of most prognostic indicators; thus, prognostication is more challenging in patients treated w/therapeutic hypothermia. Emerging evidence may eventually allow prediction of *favorable* prognosis. No single datum in isolation is entirely reliable. Concordant findings from multiple modalities (e.g., exam, EEG, SSEP, etc.) allow more reliable predictions and more informed medical decision making.

***Suggested workup (note timing)*:** Statistical value of tests in table below.

**Neuro exam:** Predictors of poor outcome: Absent pupillary, corneal, oculocephalic reflexes 1-3 days postarrest/postrewarming; diffuse myoclonus. Early eye opening & spont eye mvmts not predictive of good outcome; more predictive after 3 days. Single sz & intermittent focal myoclonus do NOT predict poor outcome (*Neurology* 2006;66:62).

**EEG:** Starting during hypothermia. Purpose: (1) monitor for szs; (2) prognosis. Duration: continue ≥24 h after completion of rewarming (findings can evolve). Persistent voltage suppression, burst suppression, epileptiform activity predict poor prognosis (*Resuscitation* 2014;85:1580). Alpha coma NOT invariably a/w poor outcome (*Neurology* 1988;38:773). Postanoxic status epilepticus NOT invariably a/w poor outcome (*Neurology* 2009;72:744).

**SSEP:** Wait ≥48 h after completion of rewarming to do somatosensory evoked potentials. Less reliable if done too early. B/l absence of N20 w/median nerve stim predicts poor outcome. Insufficient data for prognostic value of BAERs & VEPs alone.

**Serum markers:** Consider 48-72 h after rewarming. Neuron-specific enolase (NSE) > 33 µg/L at days 1-3 a/w poor outcome. Serum astroglial S-100B more predictive than NSE at 24 h after return of spontaneous circulation (ROSC) (*Resuscitation* 2011;82:26).

**CT:** Consider 48 h postrewarming if coma continues & prognosis remains unclear.

**MRI:** Consider at 72 h postrewarming if coma continues & prognosis remains unclear. Absence of DWI/ADC lesions a/w better outcome (*Mayo Clin Proc* 2007;82:828). ↓ whole-brain median ADC may predict poor outcome (*Radiology* 2009;252:173). Typical DWI/ADC abnls: cortical ribbon, watershed infarct, thalamus, BG. Findings follow characteristic temporal & spatial patterns involving BG & cerebellum followed by cortical & WM changes in early/late/subacute periods (*Neurocrit Care* 2011;14:61-67).

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



**False-Positive Rates of Univariate Predictors of Poor Neurological Outcome[a] after Cardiac Arrest, with and without Therapeutic Hypothermia (TH)**

| Predictor | Day | FPR: No TH | FPR: TH |
|---|---|---|---|
| Non-VF cardiac arrest | | | 15 (6-30)%[2] |
| ROSC >25 min | | | 24 (13-40)%[2] |
| Low-voltage[c] EEG—early on | 1 | | 47 (35-60)%[3] |

| | | | |
|---|---|---|---|
| Low-voltage[c] EEG—upon rewarming | 1[b] | | 5 (2-14)%[3] |
| Discontinuous EEG (burst suppression) | 1[b] | | 7 (2-23)%[3] |
| Epileptiform activity on first EEG[c] | 1-3 | | 9 (2-21)%[2] |
| Unreactive EEG background | 1-3[b] | | 7 (1-18)%[2] |
| Early myoclonus | 1[b] | 0 (0-8.8)%[1] | 3 (0-11)%[2] |
| Bilaterally absent N20 on SSEP | 1-3[b] | 0.7 (0-3.7)%[1] | 0 (0-8)%[2] |
| Serum neuron-specific enolase (NSE) > 33 µg/L | 1-3[b] | 0 (0-3)%[1] | 11 (4-27)% |
| Absent or extensor-only motor response to pain | 3[b] | 0 (0-3)%[1] | 24 (14-39)%[2] |
| ≥1 brainstem reflexes absent (pupillary, oculocephalic, corneal) | 3[b] | 0 (0-3)%[1] | 4 (1-15)%[2] |
| CT diffuse hypodensity + GCS ≤8 | 1-3[b] | 0 (0-48)%[4] | 0 (0-27)%[4] |
| MRI: Any diffusion restriction | 1-3[b] | 54 (26-80)%[d],[5] | 54 (26-80)%[5] |

[a]Poor neurological outcome = death, unconsciousness, or severe disability at >1 mo.

[b]Assessed after rewarming and discontinuation of sedation.

[c]"Epileptiform activity" = epileptiform discharges of any kind (e.g., spikes, lateralized periodic discharges (PLEDs), or generalized epileptiform discharges (GPEDs)) or electrographic seizures; "*low voltage*" = <10 µv (but not meeting criteria for electrocerebral silence).

[d]Patients who did and did not undergo TH were analyzed as one group.

1. *Neurology* 2006;67:203; 2. *Ann Neurol* 2010;67:301; 3. *Crit Care Med* 2010;38:1838; 4. *Stroke* 2011;42:985; 5. *Neurocrit Care* 2012;2:240.

## THERAPEUTIC HYPOTHERMIA (TH) 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:** 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, in-hospital arrest → TH for these types may be applied at discretion of clinician (*Circulation*

2003;108:118). Hyperthermia is detrimental—odds ratio for unfavorable outcome >2 for each 1°C ↑ in temp after arrest (*Arch Int Med* 2001;161:2007). More recent literature on out-of-hospital cardiac arrest w/coma—hypothermia targeted temp 33°C showed no benefit over 36°C (*NEJM* 2014;369:2197).

**Basic principles & approach to therapeutic hypothermia:** Initiate cooling rapidly. Multiple cooling methods may be required to meet temp goal of 33°C-36°C (91°F-96°F). Total cooling period 24 h begins when cooling is initiated, NOT when target temp reached. Shivering generates heat & contributes to neuronal injury by increasing cerebral metabolism → sedation & paralysis may be necessary.

**Preparation for hypothermia:** Lab eval: CMP, CBC, PT/PTT, fibrinogen, D-dimer. Place a-line for BP monitoring. Monitor core temp: bladder temp probe, or pulm artery temp probe if oliguric (bladder temp probe requires urine in bladder).

**Inclusion criteria:** Not following commands w/in 6 h of cardiac arrest.

**Multivariate Prediction of Outcome in Postanoxic Coma—Pts Treated with Hypothermia** (*Ann Neurol* 2010;67:301-307)

Prognostic value of a combination of at least two of the following negative findings (measured after rewarming after therapeutic hypothermia, between 36 and 72 h post cardiac arrest)

—B/l absent SSEP—Unreactive EEG background

—Early myoclonus—Incomplete recovery of brainstem reflexes

| **Prediction:** | **In-Hospital Mortality** | **Poor 3-6 mo Outcome** |
|---|---|---|
| Sensitivity (95% CI) | 79 (67-88)% | 62 (51-72)% |
| False-positive rate (95% CI) | 0 (0-8)% | 0 (0-14)% |
| PPV (95% CI) | 100 (93-100)% | 100 (93-100)% |
| NPV (95% CI) | 76 (63-86)% | 44 (31-58)% |

Based on outcomes in 111 comatose survivors of cardiac arrest treated w/TH.

**Relative exclusion criteria (hypothermia may carry ↑ risk):** Hemodynamic instability requiring high-dose pressors. Major head trauma → rule out ICH by head CT prior to TH if suspicion for head trauma. 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 NOT a contraindication to hypothermia.

## TRAUMATIC BRAIN INJURY

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

**Epidemiology & risk factors:** ~2.5 million cases per year in the United States; 280,000 hospital admissions;

50,000 deaths; >80,000 w/long-term disabilities. High risk: 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.

**Pathophysiology:** Primary injury occurs from impact, secondary injury after impact (may exceed primary injury). *Primary injury*: Blunt forces: direct injury to tissue → coup contusion, skull fx, EDH, SDH, arterial dissection. Translational acceleration: Brain moves relative to cranium → contrecoup contusion, SDH. Rotational acceleration: Brain rotates relative to cranium → concussion, DAI, SAH, IVH. *Secondary injury*: Diffuse or perilesional, over hours to days. Contusion/hematoma expansion, excitotoxicity, altered mitochondrial metabolism, free radical & Ca-mediated injury, BBB disruption from mechanical injury & inflammatory cytokine release, cortical spreading depolarizations, alterations in gene expression w/increased production of proapoptotic factors.

## Management of mild TBI/concussion

**Concussion definition:** Clinical synd of biomechanically induced brain dysfunction, typically affecting memory & orientation; may involve loss of consciousness, commonly overlapped w/"mild traumatic brain injury" (*AAN Guidelines 2012*).

**Mechanism of LOC:** Not fully understood. May be due to transient dysfxn w/in reticular activating system & due to impact of rotational forces on midbrain & diencephalon (*NEJM* 2007;356:166). <10% of pts dx w/concussion experience LOC.

**Acute symptoms:** Inattention, HA, dizziness, confusion, amnesia (anterograde > retrograde), n/v, photophobia/phonophobia, & concussive convulsion. *Rx:* No AED required for concussive convulsion in absence of SAH or structural damage & no known increased risk of epilepsy. 0.5%-1.0% require neurosurgical intervention (*J Neurosurg* 2004;100:25-34; *JAMA* 2005;294:1519).

**Chronic symptoms:** Recurrent HA, light-headedness, poor attention & concentration, memory deficits, fatigue, depression, emotional lability, & sleep disturbances → duration of posttraumatic amnesia correlates w/duration of LOC & severity of head injury.

**Guidelines for return to play w/sports-related concussion:** Process of graduated exertion to assess symptom return; clinical judgment used to assess appropriate time frame at each step below (*Neurology* 2013;80:2250-2257).

| Steps of Graduated Exertion Process | |
|---|---|
| **Step** | **Notes** |
| 1. Light aerobic exercise | Stationary bike |
| 2. Sport-specific aerobic exercise | Add mvmt & balance |
| 3. Noncontact training drills | Add cognition & agility |
| 4. Contact training drills | After med clearance |
| 5. Return to play | Full game play |

If lowered threshold for injury suspected, strongly rec retirement from contact sports.

## 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 posttrauma, 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.

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).

Current studies suggest MRI better than CT for predicting 3-mo outcomes after concussion (*Ann Neurol* 2013;73:224).

**Postconcussion syndrome:** Presence of HA, dizziness, or nausea at TBI may → long-term sequelae (*JNNP* 2002;73:727). Duration of sx varies & may last up to 1 yr. Dx: ICD-10: Sx onset ≤ 4 wk after concussion & sx in ≥3 of 8: (1) HA, (2) dizziness, (3) fatigue, (4) insomnia, (5) irritability, (6) concentration difficulties, (7) memory trouble, (8) low tolerance for stress & EtOH.

## Initial management of moderate/severe TBI

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



**CABs:** Secure airway & ensure adequate O2; hypoxia ($SpO_2$ <90%) at admission a/w worse outcome (*J Neurotrauma* 2007;24:287). If hypotensive (SBP <90), resuscitate aggressively w/crystalloids; worse outcomes w/albumin (*NEJM* 2007;357:874); r/o internal hemorrhage & spinal cord trauma. 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% (*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/post auricular region; typically >12 h to appear → temporal bone fx. **(3)** *CSF rhinorrhea*: Test watery nose discharge for glucose (mucus has none) &/or β-2 transferrin → cribriform plate injury. **(4)** *CSF otorrhea, hemotympanum* → temporal bone fx. **(5)** *CN palsies*: I (anosmia from cribriform plate injury), III, IV, VI (diplopia, strabismus from orbital fx, cav. sinus injury, or stretching/compression of nerve against skull base), VII, VIII (facial palsy, hearing loss from fx of petrous temporal bone). **(6)** *Carotid-cavernous fistula*: Pulsating exophthalmos, retroorbital bruit → occurs in 8% of 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 to r/o traumatic arterial dissection (a/w ~17% traumatic C-spine injuries) or pseudoaneurysms (especially in pts w/penetrating head injury).

- *Head CTV*: Evaluate for injury to adjacent venous sinus if displaced skull fx.
- *MRI*: More sensitive than CT for DAI; request gradient echo or susceptibilityweighted sequence for microhemorrhage detection. Advanced MRI techniques such as DTI (*Anesthesiology* 2012;117:1300), resting state fxnl MRI (*J Neurosci* 2011;31:13442), & MR spectroscopy (*J Neurotrauma* 2006;23:674-685) may enhance detection of prognostically significant DAI & disruption of neural networks, but these techniques have not been validated for clinical use. Arterial spin labeling (ASL) perfusion MRI can detect acute & subacute changes in regional CBF (*J Neurotrauma* 2010;27:1399).
- *SPECT/PET*: Consider if persistent neurologic/psychiatric symptoms in absence of findings on CT/MRI & excellent negative predictive value (*PLOS One* 2014:9:e91088).



## Radiologic findings

1. *Coup/contrecoup contusions*: Incidence: 25%-35% of severe TBI pts, 5%-10% of moderate TBI pts. Anatomic localization: Superficial gray matter, especially in orbitofrontal, 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, a/w large size of initial lesion, presence of SDH or EDH, age, & coagulopathy (*J Neurosurg* 2002;96:109; *Neurosurgery* 2007;61:222). Expansion typically occurs w/in 6-9 h after trauma (*J Neurotrauma* 2008;25:629) → consider early repeat CT w/in 6 h 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 → punctate 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 IVH 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 (*Radiology* 1994;191:1).
5. *Subarachnoid hemorrhage*: Typically superficial cortical, less commonly in basal cisterns; unlike benign SAH in mild TBI, SAH in severe TBI a/w poor prognosis → likely b/c 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 (i.e., “gliding contusion”) 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 an extra-axial hematoma (*Neurological & Neurosurgical Intensive Care*. Philadelphia, PA: Lippincott; 2004).
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 vessels.

## ICU Management of Severe TBI

### Intracranial pressure

*Indications for ICP monitoring*: Abnormal CT or NL CT w/age >40, motor posturing, or hypotension. Controversy in benefit: Care focused on goal ICP <20 mm Hg w/monitoring was not shown to be superior vs. care w/o monitoring in this study, though numerous limitations (*NEJM* 2012;367:2471).

*Impact of ICP on outcome*: ↑ ICP occurs in up to 77% of severe TBI pts; presence & duration of elevated ICP correlate w/worse outcome (*J Neurotrauma* 2007;24:S1; *Neurocrit Care* 2013;18:26-32).

*Tx of ↑ ICP*: See Increased Intracranial Pressure section.

*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).

*Hypothermia*: Cooling to 33°C for 48 h starting 8 h after TBI not effective in improving outcomes (*NEJM* 2001;344:556). Cooling showed no benefit for severe TBI compared to strict fever control & hemodynamic monitoring (*J Neurotrauma* 2014).

### 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 60-70, unless clearly defined territory of cerebral hypoperfusion, in which case higher CPP may be warranted (Brain Trauma Foundation Guidelines, *J Neurotrauma* 2007).

CPP elevation w/pressors may only improve pericontusional CBF in pts w/baseline hypoperfusion of pericontusional tissue vs. paradoxical decrease in CBF in pts w/normal pericontusional 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 hypocapnia a/w worse outcome (*J Neurosurg* 1991;75:731).

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

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

**Medical therapies**

*Antiepileptic 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 szs on continuous EEG monitoring (*J Neurosurg* 1999;91:750). AEDs indicated for prevention of early posttraumatic szs (<7 days) (*NEJM* 1990;323:497).

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

No evidence that prophylactic AEDs prevent late posttraumatic szs, but may be a role for longer term 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).

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

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

*Sodium management*: Avoid hyponatremia; therapeutic hypernatremia may be indicated for focal and/or diffuse edema causing mass effect.

*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*. New York, NY: Thieme; 2005).

Enteral preferable to peripheral nutrition.

**Surgical therapies**

Early decompressive bifrontotemporoparietal decompressive craniectomy for severe TBI w/refractory ICP showed ↓ ICP interventions, ↓ ICU LOS, but worse outcome on extended Glasgow Outcome Scale at 6 mo (*NEJM* 2011;365:2040).

Decision for decompressive craniectomy remains controversial, & threshold level of ICP used by clinicians. RESCUEicp ongoing evaluating med management vs. decompressive craniectomy + med management.

**Prognosis:** ˜30% mortality in severe TBI; 16% severe neurologic deficits; & 3% VS. 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). DAI a/w high rate of coma & poor outcome, but DTI studies indicate that microstructural reorganization & restoration of axonal integrity may occur in chronic

phase of TBI (*Brain* 2008;131:559). Comprehensive neurorehabilitation improves fxnl outcomes, w/85% of recovery occurring w/in first 6 mo (*Lancet Neurol* 2008;7:728).

# CRANIECTOMY

**Indications:** Reverse mass effect & brain tissue shifts, ↓ ICP, & improve CPP. Craniectomy ↓ ICP by 15% & opening dura lowers ICP by 70%. Considered for cerebral mass lesions, primary ICH, aneurysmal SAH w/associated parenchymal ICH, 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; often concurrent evacuation of brain hematoma.

## 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. ~70%-80% mortality rate due to temporal lobe herniation w/brainstem compression (*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 & brainstem compression by upward transtentorial or tonsillar herniation.

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

*Rx:* **(1)** Med: mannitol, hypertonic saline, & hyperventilation (for acute herniation syndromes). **(2)** Surgery: suboccipital craniectomy w/possible resection of infarcted cerebellum & ventriculostomy. Maintain ventriculostomy postop until no continued mass effect/edema. Suboccipital craniectomy is lifesaving if med Rx unable to prevent progression of swelling or clinical deterioration. Should be performed prior to clinical decompensation; do not wait for med 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 med comorbidities, stable clinical condition, remote onset of hemorrhage, & bleed in dominant hemisphere.

*STICH 2 trial*: International Surgical Trial in Intracerebral Hemorrhage (*Lancet* 2013;382:397). Pts randomized to med mgmt vs. early surgical evac <12 h, showed no statistically significant difference in rate of death/disability at 6 mo, & small survival advantage for surgical evac in pts w/superficial ICH w/o IVH.

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

*Prognosis:* Clinical predictors of poor outcome: Advanced age & lower GCS. Radiologic prognostic factors: hematoma thickness, midline shift, volume, contusions, SAH, or IVH (*Neurosurgery* 1996;39:708-713).

*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. If burr hole performed for chronic SDH, use of subdural drains reduces 6-mo mortality (*Lancet* 2009;374:1067).

*Indications for surgery:* Acute SDH & GCS ≤8 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 for surgery:* Hematoma volume >30 $cm^3$, regardless of GCS score. Midline shift >10 mm. Acute hematoma, GCS ≤8 w/pupillary abnormalities. Early signs of herniation. ↑ ICP.

**Postoperative care: (1)** Swallowing precautions, crystalloid fluids. **(2)** Prevention of ↑ ICP. **(3)** Airway management: Risk of airway collapse due to prolonged recovery of consciousness, especially in cases of brain retraction during surgery. **(4)** Refractory n/v 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 ET tube: Dexmedetomidine, an α-2 adrenergic agonist, ↓s anxiety w/o causing resp depression; approved for use only for first 2 postoperative days.

**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 & Neurosurgery.* New Jersey: Humana; 2004):

*Depressed level of consciousness*: Prevent aspiration, promote optimal gas exchange, start w/controlled modes, as ventilator 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 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 (E.g., Cheyne-Stokes respirations in bihemispheric lesions, metabolic encephalopathies, or pontine lesions; hypoventilation, apnea, or Ondine curse in lateral medullary lesions; apneustic or ataxic respirations in pontine lesions; hyperventilation in pontomesencephalic lesions.)

*Neuromuscular ventilatory failure*: **(1)** *Acute polyneuropathy*: Autonomic instability → ↓ BP w/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); use controlled mode overnight to avoid hypercapnic at night when have ↓ level of consciousness. Respiratory muscle strength recovers next → use PS mode.



## INCREASED INTRACRANIAL PRESSURE

**Definitions:** ICP >20-25 cm $H_2O$ for >5 min.

## CEREBRAL DYNAMICS

**Monro-Kellie doctrine (simplified):** Incompressible brain (~1,300 mL), CSF (~65 mL), and blood (~110 mL) encased in relatively noncompliant skull & 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** CPP goal 60-70 mm Hg (ideal target debated); <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)<br> |
| **CBF ∝ $PCO_2$** when $PCO_2$ 20-80 mm Hg | Hypercarbia → ↑ CBF = ↓ CVR (vasodilation) → ↑ ICP<br>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 wave or "plateau" wave (see figure)** | **Arrhythmic; amp 50-100 mm Hg; last 5-20 min**<br>"Mirror" reductions in CPP (figure below).<br>Always a/w intracranial pathology, sometimes w/signs of herniation.<br>May be due to vasodilatory cascade. |
| **B waves** | **Rhythmic; q30s-2 min; amp 5-20 mm Hg; last 1-5 min.**<br>May be due to vasomotor instability at limits of autoregulation. |
| **C waves** | **Rhythmic; q4-8 min; amp—20 mm Hg.**<br>Occur normally ?due to interaction of cardiac/resp cycles. |

| Etiologies of Acute Elevations in Intracranial Pressure | |
|---|---|
| **Cytotoxic edema (↑ intracellular fluid)** | Ischemic stroke, anoxic injury, cerebral contusion, fulminant hepatic failure, lead intoxication, & Reye syndrome |
| **Vasogenic edema (↑ extracellular fluid)** | Hypertensive encephalopathy, PRES, tumor, abscess, cyst, encephalitis, high-altitude sickness, & eclampsia |
| **Transependymal edema (hydrocephalus)** | Blockade of CSF outflow pathway (tumor, IVH, etc.), blockade of 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, Trendelenburg, 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 a/w ↑ ICP, often via multiple mechanisms (see TBI section).



## CLINICAL MANIFESTATIONS OF ELEVATED INTRACRANIAL PRESSURE

| Clinical Manifestations | |
|---|---|
| **HA ± N/V** | Esp when supine; worse w/cough, Valsalva/BM |
| **↓ MS** | Correlates w/degree of midline shift |
| **Reflex HTN** | Sometimes a/w bradycardia, irregular respirations (*Cushing triad*), indicating herniation imminent or occurring |
| **Visual Sx** | Visual obscurations<br>Diplopia w/CN IV palsy (false localizing sign) Upgaze paralysis w/dorsal midbrain dysfxn Papilledema can take days to develop |
| **Herniation syndromes**<br> <br> | **A. Uncal** (lat transtentorial): Ipsi CN III palsy ("blown" pupil) + c/l hemiplegia/posturing (Kernohan notch phenomenon) temporal lobe mass → medial temporal lobe under tentorium cerebelli<br>**B. Central transtentorial:** Coma + b/l small pupils → decorticate → decerebrate posturing + rostral → caudal loss brainstem reflexes diffuse cerebral edema → ↓ displacement diencephalon<br>**C. Subfalcine:** Coma + c/l weakness → posturing esp leg ± ACA stroke frontal/parietal mass → cingulate gyrus under falx<br>**D. Cerebellar** (↑ or ↓): Cerebellar Si/Sx + medullary dysfxn → coma + b/l posturing |

## EVALUATION FOR ELEVATED ICP

**Emergent noncontrast CT:** Cerebral edema, effacement of basal cisterns, hydrocephalus, mass effect, midline shift, SAH. 60% of pts w/TBI & 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 & underlying lesions. Do not delay CT for MRI. MRI typically unsafe since prolonged supine position → ↑ ICP.

## ICP MONITORING

Invasive technique. Risks: infxn > hemorrhage/neurological injury. Indications for ICP monitoring typically w/following dx: ICH, SAH, hydrocephalus, malignant ischemic stroke, CNS infxns, hepatic encephalopathy, TBI w/**(1)** suspicion or risk of developing ↑ICP **(2)** GCS ≤8 or intubated/sedated/paralyzed.

| ICP Monitoring Devices (See Figure above) | |
|---|---|
| **Intraventricular catheters (A)** | "Gold standard" device<br>Allows tx of ↑ ICP via CSF removal<br>Can be rezeroed to minimize baseline drift; inexpensive<br>High risk infxn (ventriculitis; see below); low risk ICH (1.4%)<br>Abx PPx (Naf/Vanc) often given while in place, equal efficacy c/w to abx impregnated catheters (*JNNP* 2010;81:1064-1067)<br>Vent compression → difficult placement<br>Bedside transducer at level of foramen of Monro (ext aud meatus) |
| **Intraparenchymal pressure transducers (B)** | Catheter or fiberoptic transducer inserted into brain tissue Very low infxn rate (1%). Easily placed<br>Can be advanced → ventricle for CSF removal (catheter only)<br>Can also measure brain T, compliance<br>Baseline drift significant after 4-5 days; expensive |
| **Subdural transducer (C)** | Non-fluid-coupled transducer inserted into subdural space<br>Easily placed. Baseline drift significant after 4-5 days & less accurate than above |

| | |
|---|---|
| **Subarachnoid bolts (D)** | Hollow screw inserted via burr hole in communication w/SA space. Low infxn risk<br>Prone to error (screw displacement, clogging, underestimate ICP)<br>Largely replaced by above devices |
| **Brain tissue oxygen monitors (B)** | Intraparenchymal brain tissue monitoring probes allowing for real-time oxygen tension measurement; capable of monitoring temp as well Invasive w/risk of infxn/tissue injury |
| **Microdialysis catheters (A, B)** | Catheters placed in tissue/region of interest allow for continuous sampling of electrolytes, endogenous molecules, drug concentration/metabolites<br>Invasive technique w/risk of tissue injury & infxn<br>Low temporal/spatial resolution for data acquired |

**Ventriculitis related to intraventricular catheters:** Incidence 2%-27%; rises rapidly after 5 days (*Curr Oper Crit Care* 2012;16:117). Neuro ICU insertion, previous insertion, drainage CSF, steroids *not* a/w ↑ infxn. Abx-coated catheter may ↓ infxn rate (9.4% → 1.3% *J Neurosurg* 2003;98:725). **Lumbar access not recommended** for monitoring/CSF drainage: risk of herniation. Noninvasive monitoring far less reliable & qualitative. **TCD US**: ↓ CPP → ↑ diastolic velocity & pulsatility; estimates ICP w/in 10-15 mm Hg; can miss mild-mod ↑ ICP. **Tympanic membrane displacement:** unreliable & rarely used. ON ultrasound to measure optic nerve sheath diameter accurate in identifying ICP >20 mm Hg (*Neurocrit Care* 2011;15:506-515). **Invasive adjuncts** to ICP monitoring: jugular venous $O_2$ sat ($SjvO_2$), brain tissue $O_2$ ($PbtO_2$, brain pH & temp, CBF, cerebral microdialysis (combined, called "*multimodal" monitoring*).

## MANAGEMENT OF INCREASED ICP

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

| General Prophylactic Measures | |
|---|---|
| **Avoid hypercarbia & anoxia** | May ↑ CBF & CBV. Paralyze for intubation to reduce risk of straining/coughing. |
| **Avoid prophylactic hyperventilation** | Unsustained effect & may contribute to cerebral ischemia. |
| **Avoid hyponatremia** | Risk osmotic edema; use **isotonic fluids** (NS). |
| **Maintain normoglycemia** | Hypoglycemia a/w poor outcome. |
| **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 & ↑ CBV → ↑ ICP. Impaired autoregulation: ↓ MAP → ↓ CPP. |
| **Sedation/analgesia** | Agitation & pain can increase $CMRO_2$ → ↑ CBF & CBV. |

| | |
|---|---|
| **Head of bed to 30°** | Facilitates venous drainage & ↓ 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** | High PEEP (>5-10 mm Hg) can impair venous return & possibly increase ICP. |
| **Early sz PPx for TBI** indications less clear for other dz processes | Sz → ↑ $CMRO_2$ & 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 q12h alternative. |

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



| Acute Interventions | | |
|---|---|---|
| **Intervention** | **Rationale** | **Adverse Effects** |
| **Hyperventilation** | ↓ CBF & CBV Target $PCO_2$ 30 mm Hg No longer used routinely | Risk cerebral ischemia Effects limited to 3-4 h Rebound vasodilation |
| **Osmotherapy** (see below) | Osmotic & vasoconstrictive effects ↓ edema & CBV | See below |
| **Resection of mass/craniotomy/craniectomy** | ↓ mass effect See *Craniotomy* | Surgical morbidity |
| **CSF drainage** | ↓ CSF volume | Infxn, ICH |
| **Pressors** | Adjunct optimization of CPP (↑ MAP → ↑ CPP)<br>Fluids first then NE → dopa/PE<br>For CPP >110, ↓ MAP w/labetolol or nicardipine | May cause ↓ local CBF<br>No controlled studies<br>Use should not be prolonged |
| **Propofol** | ↓ $CMRO_2$ & CBF Short half-life | Hypotension, propofol infusion synd, & hypertriglyceridemia |
| **Barbiturates** | ↓ $CMRO_2$ & CBF<br>Phenobarbital load 5-20 mg/kg & then 1-4 mg/kg/h | Hypotension, multiorgan dysfxn, & long half-life<br>Rarely used |

| | | |
|---|---|---|
| **Hypothermia** See *Cooling* | ↓ $CMRO_2$ & CBF | Infxn, usually requires heavy sedation & MV |
| **Steroids** | ↓ vasogenic edema a/w tumor (only indication)<br>Dexamethasone 10 mg load; 4 mg q6h initial maintenance | Hyperglycemia, infxn, stress ulcers, & critical illness myopathy<br>No benefit beyond neoplasms |
| **Neuromuscular blockade** | Avoids ↑ ICP due to Valsalva | Loss of neuro exam, requires MV, & ↑ critical illness myopathy |

**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 & CVP monitoring. Overall I/O goal even to slight positive w/isotonic crystalloid/colloid/blood; CVP >4. Hypertonic saline (1.5%-3%) can be used as maintenance (no adequate studies). Mannitol & hypertonic saline considered equivalent agents; no clear data on superiority. Glycerol/sorbitol rarely used in United States.



| Hyperosmolar Agents | |
|---|---|
| **20% mannitol**<br>1,100 mOsm/L | **1-5 min:** Reflex vasoconstriction (↑ plasma V → ↑ CBF → ↑ CVR → ↓ ICP); requires intact autoregulation. **15-30 min:** Osmotic effects. **Other:** Improves blood rheology (decreases viscosity), ↓ CSF formation, & free radical scavenging. Dosedependent 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. Check osmolar gap q6h & 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**<br>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; repeat q6h. Titrate to Na 150-160, serum osm 310-320 (directly measure each q6h). Administer 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. Better choice than mannitol in hypovolemic, hypotensive pts or w/renal failure. |
| **3% hypertonic saline**<br>1,026 | Used for maintenance eunatremic/correction hyponatremia in place of water restriction (hypovolemia → ↓ CPP). Delivered as continuous ggt. Can be given via peripheral IV. |

mOsm/L

**Treatment protocol:** Multiple approaches used, some simultaneously or w/intent to temporize for more definitive measures.

| Treatment Options | |
|---|---|
| **Surgical decompression** | Removal of lesion, craniectomy, or CSF drainage |
| **Sedation** | To a motionless, quiet state (RASS 0 or -1) |
| **Osmotherapy** | Mannitol followed by 23.4% saline if necessary<br>Correct hyponatremia w/3% saline if 23.4% saline not used |
| **CSF drainage** | EVD; simultaneous ICP monitoring |
| **CPP optimization** | Pressors if CPP <60-70; MAP reduction if CPP >110 |
| **Hyperventilation** | Target $pCO_2$ 30 mm Hg (25-30 in severe refractory cases) |
| **Barbiturates** | Goal coma w/preserved pupil reactivity; cont. EEG helpful |
| **Hypothermia** | Goal core temp 33-36°C; aim for control of ICP, not temp target |

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

## BRAIN DEATH

**Definition of brain death:** Irreversible cessation of all spontaneous & reflexive brain functions. Brain death is clinically determined by coma, absence of brainstem reflexes, & apnea. Ancillary testing not necessary in adults but may be used for determination of brain death when clinical testing is limited or questionable.

**Preparation for brain death assessment:** Notify local organ bank.

1. Involve pt's nurse &, if appropriate, religious officials and/or med ethics services discussing w/family prior to brain death assessment.
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 stim).
- 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 stim 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 >5 min delay. Facial motor responses: No corneal reflex to touch w/cotton swab. No facial grimace to deep pressure on nail beds, supraorbital ridge, or temporomandibular joint. Pharyngeal & tracheal reflexes: No gag w/stim 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). Preoxygenate 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 over 2 μV at sensitivity of 2 μV & filter settings of 0.1 or 0.3 s & 70 Hz for ≥30 min.<br>EEG interpretation must be confirmed by attending neurologist. |
| 4-vessel angiogram | No contrast filling of cerebral vessels in anterior or posterior circulation.<br>Delayed filling sup sagittal sinus may occur 2/2 ext carotid circulation.<br>Filling of ICAs should stop at petrous segment where ICA → intracranial. |
| SPECT w/Tech 99 | No uptake of isotope in brain.<br>Uptake in meninges & skull may occur 2/2 perfusion from ext carotids. |
| TCDs | Do measurements in b/l intracranial cerebral vasculature & extracranial vasculature (CCAs, ICAs, cervical portions of vertebral arteries).<br>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.<br>TCDs must be performed 2×, 30 min apart. |
| SSEPs | Absent N20 response, however not reliable in catastrophic CNS lesions. |

**Documentation of brain death in medical record:** Date & time of death, etiology & irreversibility of neurologic injury, neurologic examination findings (including absence of all brainstem reflexes), details of apnea test → time of test initiation, preapnea & postapnea pH & $PCO_2$, use of ancillary testing, reason for indication, & interpreting physician's name & results of repeat neurologic examinations, if performed.

# Interventional Neurology

Saad Mir

Brijesh Mehta

## 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 (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)** Use closure device (Perclose or MynxGrip) vs. manual groin compression (if pediatric pt or pt w/significant atherosclerotic dz in femoral artery). **(2)** Serial neurologic exams. **(3)** STAT head CT for any exam change. **(4)** BP monitoring; goal based on procedure performed. **(5)** Keep pt legs straight for 6 h if using manual groin compression, 2 h post closure device. **(6)** Continue anticoagulation (heparin drip) × 12-24 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)** 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)** Nonperfused areas.

**TICI score:** (TICI: "thrombolysis in cerebral ischemia," *Stroke* 2003;34:e109-e137). TICI 0: complete occlusion. TICI 1: minimal perfusion past occlusion. TICI 2a: partial recanalization w/<66% perfusion of vascular territory. TICI 2b: complete recanalization but perfusion is slow. TICI 3: complete recanalization w/normal perfusion.

### Endovascular therapies

**IA thrombolysis:** a/w ↑ recanalization rates for ICA, M1/M2, BA occlusions. Total IA dose = ˜1/3 IV dose (b/c given locally). Advantages: can be used in postsurgical pts & sx onset ≤6-12 h (PROACTII, MRCLEAN, ESCAPE).

**IV** + **IA thrombolysis**: Multimodal Rx shown to result in better recanalization.



**IA thrombectomy or thromboaspiration:** Achieved most commonly w/stentrievers (Solitaire FR, Trevo XP) or Penumbra 5Max ACE aspiration catheter. Offers possibility of faster recanalization, ↑ recanalization rates, ↓ total thrombolytic dose (SWIFT, TREVO-2, ADAPT FAST).

**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, **(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): Inclusion criteria: *Sx duration* <6 h a*ngiographic occlusion* (*TICI* 0 *or* 1) of M1 or M2 MCA. *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. Median NIHSS: 17. ***Outcomes:*** *Recanalization* (*TIMI* 2-3): IA 66% vs. control 18% p ≤ 0.001. 90-day *mRS* <2: IA 40%, control 25%, OR 2. *Mortality*: r-pro-UK 25% & control 27%. *Complications*: 9%, neurologic, anaphylaxis, bleeding. *sICH*: IA 10.9%, 3.1% control, p = 0.06. ***Caveats*:** ↑ sICH rate c/w trials of IV thrombolysis (2/2 ↑ baseline stroke severity).

**"IMSIII":** IAT (thrombolysis ± thrombectomy) + IV thrombolysis vs. IV thrombolysis (*NEJM* 2013;368:893-903): Inclusion criteria: NIHSS >10 and/or radiographic vessel occlusion, sx duration <3 h, IV tPA administration. IAT w/in 5-7 h. Median NIHSS: 17. Rx groups: IV tPA + IAT (IA tPA +/- thrombectomy) vs. IV tPA (control).

***Outcomes***: Recanalization (TICI 2 + 3): IAT 86% vs. control 61%. 90-day mRS of ≤2: IAT 40.8% vs. control 38.7, not statistically significant. sICH: 6.9% IAT vs. 5.9% control p = 0.8. Procedural complications: 16.1%. ***Caveats***: minimal use of newer, superior clot retrievers, no large-vessel occlusion required so 25% in Rx arm did not get IAT, trend toward better mRS w/↑ recanalization.

**"SYNTHESIS":** IAT (thrombolysis ± thrombectomy) vs. IV thrombolysis (*NEJM* 2013;368:904-913.). Inclusion

criteria: NIHSS >6 & sx duration ≤4.5 h, IAT w/in 6 h. Median NIHSS: 13. Rx arms: IAT (IA tPA +/- thrombectomy) vs. IV tPA (control). ***Outcomes***: no recanalization data. 90-day mRS of ≤1: IAT 30.4% IAT vs. control 34.8%, not statistically significant. sICH: 6% in both groups. ***Caveats***: no recanalization data, liberal NIHSS, no large-vessel occlusion requirement, no IV tPA in treatment group.

**"MRRESCUE":** IA thrombectomy vs. standard care (*NEJM* 2013;368:914-923). Inclusion criteria: sx duration ≤8 h, +/- IV tPA, vessel occlusion, CT/MRI stratified by positive/negative penumbra pattern. Median NIHSS 17. Rx arms: IA thrombectomy vs. standard care. ***Outcomes***: Recanalization: 67% IAT. 90-day mRS: 3.9 in both groups. sICH: 9% IAT vs. 6% control, p = 0.24. ***Caveats***: up to 8 h after symptom onset, only two devices used, trend of better mRS w/↑ reperfusion/recanalization.

**"MRCLEAN":** IAT (thrombolysis ± thrombectomy) + IV thrombolysis vs. IV thrombolysis (*NEJM* 2015;372:11-20). Inclusion criteria: sx duration ≤6 h, large-vessel ant. circ occlusion, NIHSS >2. Rx groups: IV tPA + IAT (IA tPA +/- thrombectomy) vs. IV tPA (control). ***Outcomes***: 90-day mRS favored IAT, OR 1.67. TICI 2b/3 58.7% in IAT. 13% of IAT required cervical stenting & 9% had new vascular distribution strokes. ***Caveats***: 16% in IAT arm received no rx, low recanalization %.

**"ESCAPE":** IAT (thrombolysis ± thrombectomy) + IV thrombolysis vs. IV thrombolysis (publication pending). Inclusion criteria: sx duration ≤12 h, large-vessel ant. circ occlusion, NIHSS >5. Exclusion: large core infarct or poor collateralization in >50% of MCA distribution. ***Outcomes***: being published 2015 but preliminary data are positive.

**Guidelines: (1)** Initiation of IAT w/in 6 h (MRCLEAN) to 12 h (ESCAPE) of sx onset for anterior circulation & up to 48 h for posterior circulation strokes. **(2)** No e/o ICH. **(3)** Large-vessel occlusion (ICA, ACA, MCA, PCA, VA, BA). **(4)** NIHSS >5. **(5)** Infarct size <33% of MCA territory on head CT (*Stroke* 2005;36:66). **(6)** MR DWI volume <70 mL (*Stroke* 2009;40:2046). **(7)** Coagulopathy (INR >1.7, PTT >45 s, plts <100 K) not a contraindication for mechanical thrombectomy (*Stroke* 2009;40:516).

**Future:** RCTs that emphasize rapid reperfusion w/the use of newer stent retrievers while reducing time to IAT w/prehospital & inhospital process improvement (*JAHA* 2014;3:e000963). Two RCTs (SWIFT PRIME & THERAPY) on hold given benefit of MRCLEAN.

**Abbreviations:** PROACT, Prolyse in Acute Cerebral Thromboembolism; IMS, Interventional Mgmt of Stroke; SYNTHESIS, Intra-arterial vs. Systemic Thrombolysis for Acute Ischemic Stroke; MRRESCUE, Mechanical Retrieval & Recanalization of



Stroke Clots Using Embolectomy; MRCLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; ESCAPE, Endovascular Treatment for Small Core & Proximal Occlusion Ischemic Stroke; IA, intra-arterial; IAT, intra-arterial therapy; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; VA, vertebral artery; BA, basilar artery; SAH, subarachnoid hemorrhage; & sICH, symptomatic intracerebral hemorrhage.

## 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

**"SAMMPRIS":** Intracranial stenting + aggressive medical therapy vs. aggressive medical therapy (*NEJM* 2011;365:993-1003). Inclusion criteria: TIA or minor stroke w/in 30 days from >70% intracranial stenosis. Outcomes: Composite of stroke & death; stopped early because of ↑ stroke risk in stenting group (14.7% vs. 5.8%, p = 0.002) where 30% of strokes were sICH. Caveats: Rx group required stent placement possibly

increasing complication rates.

**Guidelines:** Per FDA, Wingspan stenting for intracranial atherosclerosis is approved for (1) age 22-80 yo, (2) ≥2 strokes from 70% to 99% stenosis despite max medical mgmt, (3) stroke >7 days ago, and (4) mRS ≤3. It is not approved for TIAs or recent stroke in <7 days.



## CAROTID ARTERY STENOSIS

See chapter *Vascular Neurology* for medical Rx options. CAS, carotid artery stenting.

**Clinical considerations for neurointervention:** 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 weeks 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 CAS. **(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, & small guidewire 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, and 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 meta-analyses, commonly from fibromuscular dysplasia; may not be amenable to emergency surgical correction.

### Clinical trials

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

***"EVA-3S"*** (*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"*** (*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).

***"CREST trial"*** (*Stroke* 2010;41:31): Randomized 2,502 pts w/either symptomatic (>50%) or asymptomatic (>70%) carotid stenosis. Composite of periprocedural CVA, MI, death, or ipsilateral CVA ≤4 yr 7.2% CAS vs. 6.8% CEA, $p = 0.5$. Higher periprocedural stroke in CAS (4.1% vs. 2.3%, $p < 0.01$) & higher periprocedural MI in CEA (2.3% vs. 1.1%, $p < 0.03$). Improved outcomes in CEA if >70 yo vs. <70 yo in CAS.

**Guidelines:** CAS should be considered for symptomatic severe stenosis (>70%) in pts considered high cardiovascular risk for CEA or have difficult surgical access, radiation-induced stenosis, or restenosis after CEA. Interventionalists should have CAS periprocedural morbidity/mortality rates <4%-6% (*Stroke* 2006;37:577);

insurance will not provide reimbursement for CAS in pt who are not deemed high surgical risk.

## CEREBRAL ANEURYSMS

**Epidemiology:** ~3% of adults (incidence ↑ w/higher resolution imaging) 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 Δs, 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 and not seen on noninvasive vessel imaging.

**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:** 0.05%-0.5% risk rupture/year (*NEJM* 1998;339:1725).

**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 <10 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.

**ISUIA: International Study of Unruptured Intracranial Aneurysms (*NEJM* 1998;339:1725)**

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

**Rx guidelines:** based on RCT data of death/poor outcome, coiling preferred over clipping for asymptomatic aneurysms >10 mm, symptomatic aneurysms of all sizes, & aneurysms of all sizes in pts w/hx of aneurysm rupture.

**New device guidelines:** Pipeline Embolization Device diverts flow from aneurysm, causing stagnation & volume reduction. It is FDA approved for pts >22 yo w/large or giant wide-necked aneurysms in the petrous to superior hypophyseal segments of the ICA (PUFS, COCOA).



**Follow-up: (1)** Newly dx'd aneurysms reimage at 6 mo. **(2)** Known aneurysms: q1yr CTA or MRA for 2 yr, then q2-5yr if stable. See below for imaging after clipping/coiling.

**Ruptured aneurysms**

**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:** 24-72 h, HH grade <3: Goal is prevention of rebleeding by managing vasospasm w/*"Triple H"* (HTN, hypervolemia, hemodilution) (*Neurology* 2000;55:1656). Mortality rate up to 8%.

**Aneurysm repair: w/in 24-72 h after rupture.** Clipping more challenging due to cerebral edema, clot around aneurysm, risk of ischemia (*J Neurosurg* 1995;83:394).

**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.

**Rx guidelines:** coiling superior to surgical clipping if aneurysm is amenable to coiling

**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

**Epid:** Incidence: 0.1%; accounts for 1%-2% strokes, 9% of SAH. 90% supratentorial.

**Pathophys:** 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 esp. post-Rx for assessing ↓ in nidal vol. *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.

*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*: [0-3, 3-6, >6] cm → [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)** G*ender*: Females may pose increased surgical risk. **(4)** *Lifetime risk* (%) of hemorrhage calculator: 105—pt age in yr (*Neurosurgery* 2000;46:1024).

**Unruptured AVMs**

**"ARUBA":** Interventional Rx of unruptured AVM vs. medical therapy (*Lancet* 2014;383:614-621). Inclusion criteria: unruptured AVM amenable to intervention (NSG, embolization, XRT, or combo). Outcome: composite of stroke or death. Study stopped w/in 33 mo due interim analysis showing ↑ stroke risk w/intervention group (30.7% vs. 10.1%, OR = 0.33).

**AVM-associated aneurysms:** *Feeding artery aneurysms*: if <7 mm, consider clipping or coiling. *Intranidal* (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).

**Rxs guidelines: Tx all ruptured AVMs. (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;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).



# SPINE DISEASES

## VERTEBRAL FRACTURES

**Etiology: (1)** *Trauma:* flexion-compression fx, axial-compression fx, rotational fx. **(2)** *Osteoporotic fracture*: occurs 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 cord damage. Bone scan: detects more lesions (in CA setting).

**Vertebroplasty:** Consider after 6 wk of conservative management. *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) (*Am J Neuroradiol* 2007;28:555). First randomized prospective long-term study comparing vertebroplasty vs. optimal medical mgt. Day 1: vertebroplasty → ↓ pain. Week 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 (>2 yr) & subgroups of pts that benefit from vertebroplasty over placebo.

**Kyphoplasty:** Consider after 6 wk of 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 in which bone cement is inserted. *Indications:* painful osteoporotic or osteolytic fractures; not used for metastatic lesions. *Contraindications*: similar to vertebroplasty. *Benefits:* ↓ pain (usually w/in 2 wk); restores vertebral body height; improves 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 the neck, shoulders, arms; arm weakness. *Thoracic*: pain radiating into the chest. *Lumbar*: pain in the 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:* chronic discogenic back pain; prospective clinical trials 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; ↓ need for analgesics; does not preclude further surgery. *Complications:* infection; bleeding; nerve damage; worsened pain; recurrence of herniation.

# Seizures, Epilepsy, and Eeg

Alice D. Lam

Rodrigo Zepeda

M. Brandon Westover

Mouhsin M. Shafi

## DEFINITIONS

**Epileptic sz:** Sudden transient si/sx 2/2 abnl, excess, or synchronous neuronal activity.

**Electrographic sz:** An EEG pattern like that seen during an epileptic sz (+/- si/sx).

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

**Unprovoked sz:** Occurs w/o acute illness, 2/2 persistent brain abnormality/dz.

**Acute symptomatic sz:** Synonymous w/"provoked" sz.

**Aura:** First part of sz, often the only part remembered by pt; a focal sz that sometimes progresses to focal dyscognitive or secondarily generalized sz.

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

**Psychogenic nonepileptic spell (PNES):** Si/sx resemble szs but w/o EEG correlate.

**Nonepileptic sz (NES):** Synonym for PNES.

**Epilepsy:** ≥2 unprovoked szs ≥24 h apart, or a tendency toward recurrent unprovoked szs.

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

**Status epilepticus (SE):** Continuous sz lasting >5 min or >1 sz w/o full return to baseline.

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

## DIFFERENTIAL DIAGNOSIS OF SEIZURES

(Adapted from https://www.epilepsydiagnosis.org/epilepsy-imitators.html)

**Syncope (including "convulsive syncope," see below):** Vasovagal, orthostatic, long QT/cardiogenic, breath-holding spells.

**Transient ischemic attack:** Usually presents w/(-) sxs, but can have (+) sxs (e.g., jerking, rigidity, hallucinations, visual illusions). Limb-shaking TIA a/w preocclusive carotid disease. Todd paralysis (transient weakness after sz) can mimic TIA/stroke.

**Transient global amnesia:** *Dx:* Acute-onset anterograde amnesia; no Δ consciousness/loss of self-awareness; cog. impairment ltd to amnesia; no recent TBI or sz; sx duration <24 h; & no other neuro sx other than dizziness, vertigo, HA. *Workup:* MRI may show punctate DWI bright lesion in the hippocampus, usu 24-48 h after sx onset. If atypical presentation or signif vascular risk factors consider stroke w/u. *Etiology/prognosis*: Etiology unknown (theories: venous congestion, hippocampal TIA). *Prognosis*: Usu benign, not recurrent.

**Migraine related:** Migraine w/visual aura, ΔMS with basilar migraine, familial hemiplegic migraine, benign paroxysmal torticollis, benign paroxysmal vertigo, & cyclical vomiting.

**Sleep related:** REM sleep disorders, parasomnias, hypnagogic jerks, sleep-related movement disorders, periodic

leg movements, narcolepsy-cataplexy.

**Paroxysmal movement disorders:** Paroxysmal kinesigenic or nonkinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, episodic ataxia, tics, hyperekplexia.

**Psychiatric:** PNES, panic attack, dissociative state, hallucinations (psych d/o), factitious d/o.

**Miscellaneous:** Spinal myoclonus, ↑ ICP, benign myoclonus of infancy, Sandifer synd (GERD + spasmodic torticollis & dystonia in infancy), spasmus nutans.

## APPROACH TO THE PATIENT WITH TRANSIENT LOSS OF CONSCIOUSNESS

**HPI:** Hx key for dx. (*J Neurol* 2009;256:155-167). These features suggest but not definitive for dx. Abbreviations: **OS**, orthostatic; **VV**, vasovagal; **CG**, cardiogenic; **HV**, hypovolemic.

**Prior to spell:** *Posture*: Δposture → *syncope(OS)*; prolonged standing → *syncope(VV)*. *Activity*: micturition, defecation, coughing → *syncope(VV)*, exercise → *syncope(any)*. *Trigger*: meal, fear, pain, heat, neck shaving → *syncope(VV)*; dehydration (poor intake, vomit/diarrhea), hemorrhage → *syncope(HV);* arm exercise → *subclavian steal*; sleep deprivation, no trigger → *sz*; stress → *PNES*. *Others:* sweating pallor, light-headed, blurred vision → *syncope(any)*; shaking before LOC, aura (epigastric, smell, taste, déjà vu) → *sz.*

**During spell:** *Fall*: flaccid → *syncope(any)*, stiff → *sz*. *Movements:* symmetric, synchronous, focal, prior or at onset of LOC → *sz*; nonrhythmic, multifocal, small amplitude, <15 s, always after LOC → *syncope(any). Eyes*: gaze deviation → *sz*; open → *sz*



*& syncope(any)*; closed → *PNES*. *Tongue biting*: lateral → *sz* (40% of GTCs); tip of tongue → *syncope(any,* in 2%-6%). *Skin:* cyanotic → *sz*; pale → *syncope(any)*. *Others*: head turn to one side → *sz*; mouth frothing → *sz*; incontinence → *sz or syncope(any)*; preserved awareness → *PNES*.

**After spell**: *Consciousness*: prompt recovery (<1 min) → *syncope*, psychogenic; postictal confusion (minute to hours) → *sz*. *Others*: HA, muscle ache → *sz*; Todd paralysis → *sz*; emotional lability → *psychogenic*.

**PMH:** Anemia, cardiac dz, Parkinson, MSA, POTS, neuropathy → *syncope(any)*; CNS lesion, EtOH abuse, epilepsy → *sz*; Florid psychiatric hx, panpositive ROS → *PNES*.

**Exam: (1) VS** ✓ orthostasis: supine to standing → >20 mm Hg ↓ SBP, >10 mm Hg ↓ DBP, or >10-20 bpm ↑ HR. **(2) HEENT**: E/o head trauma, tongue laceration. **(3) CV**: murmurs, rhythm, HF (↑ JVP, S3, displ PMI), carotid bruits. **(4) Neuro:** mental status, focal deficits.

**Initial workup:** EKG, CBC, chem7, serum & urine tox screen; young women ✓pregnancy.

**If HPI suggests syncope (and initial w/u neg), consider (1)** echo: r/o structural heart dz; **(2)** exercise stress test: esp w/exertional syncope; **(3)** tilt table (provokes vasovagal syncope): (+) in 50% w/recurrent unexplained syncope; Se 26%-80%, Sp >90%; **(4)** Holter or loop monitor; **(5)** referral to cardiology.

**If HPI suggestive of sz:** Imaging (CT/MRI brain), EEG, sz w/u (see below).

**If HPI suggestive of psychogenic nonepileptic szs,** see below.

**Treatment of syncope: (1) HV:** rehydrate acutely, encourage regular fluid intake. **(2) OS (autonomic dysfxn):** advise to rise slowly, use compressive stockings, increase fluids, & ↑ Na diet. If conservative measures fail, consider midodrine, fludrocortisone, anticholinesterases. **(3) VV:** identify & avoid triggers. No proven benefit w/β-blockers (*Circulation* 2006;113;1164). **(4) CG:** depends on etiology, consider ref to cardiology & adjustment of vasoactive meds.

## PSEUDOSEIZURES (PSYCHOGENIC NONEPILEPTIC SZS, PNES, OR NES)

**Def:** Spells resembling epileptic szs but w/o EEG correlate. Psych origin; usu somatoform (conversion >

somatization> > factitious, malingering). *~30% PNES pts also have epileptic szs*.

**HPI suggestive of PNES:** Multiple nl EEGs, no response to AEDs, strange triggers (stress, pain, specific mvmts, sounds, lights), occur only around others (e.g., doctor's office), florid ROS, vague somatic sxs, inappropriate lack of concern ("*la belle indifference*"), inducibility by suggestion, h/o sexual trauma, fibromyalgia, chronic pain, fatigue, depression, anxiety.

**Semiology suggestive of PNES vs. seizure:** See table.

**Dx:** Difficult by hx/exam alone. Provocation (suggestion, hyperventilation, photic stim, saline injection), useful, but ? ethical. **Gold std: video EEG showing nl EEG during stereotyped event** (though EEG can be falsely nl w/deep or midline sz). EEG helps distinguish epileptic vs. NES in pts w/both. May need to capture multiple events before definitive dx of PNES.

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

**Prognosis:** Generally poor, but better outcomes assoc w/young onset, early dx, less dramatic features, no other somatoform c/o; hypomotor features (vs. thrashing). *In kids w/PNES*: *Suspect ongoing sexual abuse, mood d/o* (*Epilepsia* 2012;53(10):1679-1689).



**Signs: PNES vs. Seizure**

| **PNES** | | | **Seizure** | | |
|---|---|---|---|---|---|
| | **Se** | **Sp** | | **Se** | **Sp** |
| Preserved awareness | 56% | 93% | Eyes open/widen | 100% | 84% |
| Eye flutter | 50% | >95% | Abrupt onset | 94% | 55% |
| Others alleviate/intensify | 55% | >95% | Postictal confusion/sleep | 81% | 70% |
| Postictal whispering | 58% | 83% | Eyes fixed | 57% | 92% |
| Stuttering course | 42% | >95% | Clenched mouth | 9% | 92% |
| Forced eye closure | 33% | >95% | Hand automatisms | 26% | >95% |
| Pelvic thrusting | 8% | >95% | Ictal scream | 22% | >95% |
| Arched back | 8% | >95% | Grasping | 9% | >95% |
| Head side to side | 25% | 87% | Postictal nose wiping | 23% | >95% |
| Ictal crying | 8% | 91% | Postictal aphasia | 9% | >95% |
| Turn onto belly | <5% | 87% | Postictal snoring | 35% | >95% |

| | | | | | |
|---|---|---|---|---|---|
| Ictal whispering | 58% | 78% | Abrupt offset | 75% | 70% |
| Immediate return to b/l | 64% | 55% | Onset in single limb | 57% | 67% |
| Nonsynchronous mvmt | 17% | 78% | Eyes rolled back | 52% | 67% |
| Seizure >2 min | 67% | 48% | Aura | 50% | 17% |

Se, sensitivity; Sp, specificity; b/l, baseline; mvmt, movements.

Adapted from *Ann Neurol* 2011;69:997.

## EVALUATION OF PATIENTS WITH SEIZURE

**Clinical eval: HPI:** Provoked vs. unprovoked? (see table below). Preceding illness/fever, trauma; aura, ictal/postictal si/sx (confusion, depression, aphasia, exhaustion, sleep, fear, HA, amnesia, nausea, pain, perceptual distortions, psychosis, thirst, wkns).

**PMH/ROS: Epilepsy risk factors:** FHx sz, early hx (prenatal, birth, perinatal), febrile sz, delay in developmental milestones, birthmarks/congenital anomalies, prior szs, stroke, head trauma, CNS infxns. **Sz hx**: Semiology (best directly from witness), diurnal variation, relation to menses, myoclonic jerks, photosensitivity, injuries during sz, # of ED visits for sz in past yr, prior AEDs & why d/c'd. **Triggers**: AED noncompliance, sleep deprivation, EtOH use, stress, flashing lights, fever, menses. **Prior studies:** EEG, CT, MRI, PET, SPECT.

**Exam: Gen:** Skin exam for neurocutaneous d/os (e.g., café au lait, ash leaf macules), body asymmetry, head circumference. **Neuro:** Focal abnlities (suggestive of underlying cause).

**Tests: Standard w/u: (1)** *Labs*: CBC, chem7, LFTs, Stox, Utox, AED levels, UA, CXR. **(2)** *Imaging*: CT if urgent (if concern for acute stroke, ICH, large mass). MRI ± gado preferable (structural abnls: tumor, stroke, infxn, AVM), w/coronal T2 (assess hippocampus). **(3)** EEG (see below). **Consider further w/u:** LP if suspected meningitis/encephalitis, SAH, all HIV+ pts.

**Prediction of seizure recurrence:** Incidence of 2nd sz in adults ~40%-50% w/in 2 yr (*Neurology* 1991;41:965; *Neurology* 1993;43:478; *Lancet* 2005;365:2007). Yield of EEG ↑ w/in 24 h of sz, **51%** vs. **34%** when done later (*Lancet* 1998;352:1007). If 1st EEG nl, sleep-deprived EEG can ↑ likelihood of finding epileptiform abnlities. Multicenter Epilepsy & Single Sz (**MESS**) study: *Neuro exam, imaging, & EEG all nl* → "*low" risk* (30%) of recurrence w/in 5 yr; 1 of above abnl = mod risk (50)%; 2 abnl = high risk (70%) (*Lancet Neurol* 2006;5:317). **AEDs:** After 1 unprovoked definite sz: if nl neuro exam, nl imaging, & nl EEG → OK to defer tx; if abnl exam, imaging, EEG or ≥2 szs → start AED.

| Etiology of Provoked Seizures | |
|---|---|
| **Primary neurologic d/os**<br>*Acute/subacute neurologic insult*: Head trauma, meningitis/encephalitis, brain abscess, stroke, SAH, HIV encephalopathy, cerebral anoxia, hypertensive encephalopathy/PRES, eclampsia, neurosurgery<br>*Structural abnlities*: Mass lesions, vascular malformations | **Systemic d/os**<br>*Metabolic*: Hypoglycemia, hyperglycemia, hyperosmolar state, hyponatremia, hypocalcemia, hypomagnesemia, uremia, hepatic encephalopathy, porphyria, hyperthyroidism<br>*Drugs*: Overdose, withdrawal (EtOH, |

| | |
|---|---|
| | sedatives); others (see below)<br>*Sleep* deprivation<br>*Hyperthermia/High fever*: In children |
| **Drugs that Commonly Cause Seizures or ↓ Sz Threshold** | |
| Analgesics (meperidine, tramadol)<br>Anesthetics: local (bupivacaine, lidocaine, procaine, etidocaine) & general (enflurane, sevoflurane)<br>Antibiotics (FQs, TMP/SMX, penicillins)<br>Anticholinesterases (organophosphates, physostigmine)<br>Antidepressants (Bupropion/Wellbutrin)<br>Antihistamines<br>Antipsychotics (phenothiazines, butyrophenones, clozapine)<br>? Beta-blockers (propranolol, oxprenolol) | Chemotherapy drugs (etoposide, ifosfamide, cisplatinum)<br>Cyclosporine, FK506<br>Hypoglycemic medications<br>Isoniazid<br>Methylxanthines (theophylline, aminophylline)<br>Narcotics (fentanyl, meperidine, pentazocine, propoxyphene, tramadol)<br>Phencyclidine, stimulants (amphetamines, cocaine, ephedrine, ecstasy, phenylpropanolamine, terbutaline |

## EPILEPSY SAFETY COUNSELING

**(1) How to keep a pt safe during a sz**: (1) Stay calm. (2) Time the sz. (3) Turn pt on side to prevent choking. (4) Loosen tight clothing & place something soft under the head. (5) Don't put anything in pt's mouth. (6) Don't restrain pt. (7) Call 911 if sz lasts



>5 min or pt has >1 sz w/o return to baseline. (8) Stay w/pt until awake/alert, or until medical personnel arrive. **(2) General safety**: Szs can result in signif bodily harm & death. Common sense: Don't swim/bathe alone; avoid heights & tall ladders; avoid power tools, heavy machinery, welding equipment; avoid high-risk sports (e.g., scuba diving, hang gliding, motor sports, boxing, downhill skiing, long-distance swimming, hockey). **(3) Driving:** Pts w/epilepsy account for 0.02%-0.04% of all reported motor vehicle accidents (in comparison, 7% of motor vehicle accidents are EtOH related). Laws for resuming driving vary by state. State-specific regulations: http://www.epilepsy.com/driving-laws. Some make allowances for purely nocturnal szs & pts w/consistent pattern of prolonged aura (*Epilepsia* 1994;35:662-705). **(4) AED compliance, side effects, drug interactions**. Refer to AED section for specific AEDs. Pts taking enzyme-inducing AEDs should take *Ca 1,200 mg qd* + *VitD 2,000 IU qd* & receive routine osteoporosis screening. **(5) Depression screen**: W/controlled epilepsy, prevalence = 10%-30%; w/refractory epilepsy = 30%-50%; & gen'l pop'n = 5%-17%. Lifetime prevalence of suicidal ideation in epilepsy (4.6%-30%) 2× c/w gen'l pop'n (1%-7%). **(6) Women's issues:** See also *Pregnancy Neurology* chapter. Discuss contraception, family planning, pregnancy. All women of childbearing age should take *folic acid (0.4-0.8 mg qd),* prior to conception & during pregnancy (*Wyllie's Treatment of Epilepsy.* 5th ed., Chapters 93-95).

## STATUS EPILEPTICUS (SE)

**Practical def:** Sz >5 min or >1 sz w/o return to baseline b/w szs (failure of spontaneous sz termination). Focal or generalized, convulsive (CSE) or nonconvulsive (NCSE).

**Related Dxs: (1)** Sz clusters: Return to baseline b/w szs (less urgent than SE, but ↑ risk of SE). *If at home w/sz clusters or prolonged sz,* Rx w/rectal diazepam gel (Diastat) 0.2 mg/kg, OR SL lorazepam 1 mg, OR nasal midazolam 0.1-0.2 mg/kg; call EMS. **(2)** NES: May be difficult to distinguish; clues favoring szs: hypoxemia, ↑ CPK, acidosis.

**Etiologies of SE (most to least common): Adults:** ↓ AED levels, stroke, remote TBI/congenital malf., EtOH w/d, anoxic injury, metabolic disturbance, drug intox'n, CNS infxn, brain neoplasm, idiopathic, acute TBI. **Kids:** Febrile

szs, remote TBI/congenital malf., ↓ AED levels, acute TBI, stroke, drug intox'n, anoxic injury, metabolic disturbance, CNS infxn, idiopathic.

## GENERALIZED CONVULSIVE STATUS EPILEPTICUS (GCSE)

Generalized convulsions, most often tonic-clonic but can also be myoclonic, tonic, or clonic. As GCSE progresses, motor activity ↓ amplitude & later ceases; 48% pts w/GCSE → nonconvulsive szs (NCS) w/in 24 h; 14% have NCSE. If LOC fails to improve by 20-30 min after convulsions → high probability for NCSE; obtain urgent EEG to confirm & manage.

**Epidemiology:** Incidence in the United States 20-40/100 k. Bimodal distribution across the life span, most common in kids <1 yo & adults >60 yo. 50% of pts w/GCSE have acute neurologic injury, & >50% never had a prior sz. 15% pts w/epilepsy have at least one episode of SE.

**Physiologic complications:** *Neurologic injury*: Glutamate-mediated excitotoxic injury. Szs create ↑ metabolic demand, requiring ↑ cerebral blood flow. Failure of cerebral autoregulation leads to ↑ cerebral edema, ↑ ICP, ↓ cerebral perfusion. *Systemic disturbances*: Hypoxia, hypercapnia, aspiration PNA, pulmonary edema, HoTN, cardiac arrhythmia, cardiac injury, rhabdomyolysis, ATN, hyperthermia, metabolic disturbances (glucose,



K, Na, phos, pH). **EEG:** Five stages: (1) Discrete szs. (2) Merging of discrete szs. (3) Continuous ictal discharges. (4) Continuous ictal activity punctuated by flat periods. (5) Periodic epileptiform discharges. **Imaging:** Brain MRI superior to head CT. Transient MRI Δs include DWI Δs or ↑ FLAIR in hippocampus, neocortex, corpus callosum, posterior thalamus. **Treatment:** Early tx a/w better outcomes. *EEG NOT required for dx of GCSE, should NOT delay tx.* Use pre-established time-based algorithm (e.g., table below). **Prognosis:** M&M vary w/age, etiology, duration. Mortality predictors: Older age (mortality in kids ~3%; adults <60 yo ~26%; >60 yo ~39%; >80 yo ~50%); longer duration (mortality in SE lasting <1 h ~3%, >1 h ~32%); etiology (highest mortality: anoxic brain injury). Twenty to fifty percent of survivors have significant functional disability. Status Epilepticus Severity Score (STESS; see table) somewhat predicts survival.

**Status Epilepticus Severity Score** (*Neurology* 2006;66:1736; *J Neurol* 2008;255(10):1561-1566)

| | **Features** (determined prior to treatment initiation) | **Score** |
|---|---|---|
| Level of consciousness | Alert or somnolent/confused<br>Stuporous or comatose | 0<br>1 |
| Worst seizure type | Simple partial, complex partial, or absence<br>Generalized convulsive<br>Nonconvulsive status epilepticus in coma | 0<br>1<br>2 |
| Age | <65 yr<br>≥65 yr | 0<br>2 |
| Hx of previous seizures | Yes<br>No or unknown | 0<br>1 |
| Total | | 0-6 |

Scores of 0-2 have favorable prognosis (97% survive; of survivors, 81% return to clinical baseline). Scores

≥3 do not accurately predict mortality & should not be used to justify withdrawal of care.

## TREATMENT PROTOCOL FOR GCSE

Adapted from: *Neurocrit Care* 2012;17(1):3–23; *Eur J Neurol* 2010;17:348–355; *Brain* 2011;134:2802–2818; Continuum *Lifelong Learning Neurol* 2013;19(3):767–794.



## NONCONVULSIVE STATUS EPILEPTICUS (NCSE) (AKA ELECTROGRAPHIC SE, ESE)

Def: SE w/o evident convulsions, often p/w AMS (confusion to coma) w/absent/minor motor si/sx. Can be primary or follow GCSE. P/w: Agitation, amnesia, aphasia, catatonia, confusion, echolalia, laughter, lethargy, perseveration, personality Δ, psychosis, singing, automatisms, eye blinking/deviation, face/finger twitching, nystagmus, tremulousness.

**Epidemiology:** In pts w/unexplained altered consciousness, 18% had nonconvulsive szs (NCS), 10% in NCSE,

~75% of szs in the critically ill are NCS. In pts with unexplained coma & no prior szs, 8% were in NCSE. In neuro-ICU pts, electrographic szs found in 27%-34%. Risk factors: Critically ill, ICH, CNS infxn, epilepsy, severe AMS, oculomotor abnls, periodic discharges, or suppression burst on EEG (*Clin Neurophysiol* 2007;188:1661).

**How long to monitor on EEG:** Risk stratified based on presence of epileptiform discharges (ED), incl spikes, sharps, periodic discharges, triphasic waves. Pts w/ED: probability of sz w/in 72 h is <10% & <5% if sz-free >7 & 16 h, resp. Pts w/o ED: probability of sz w/in 72 h <10% & <5% if sz-free for 15 min & 2 h, resp (*Clin Neurophysiol* 2014;126:463).

## Diagnosis

1. *NCSE by strict electrographic criteria*: requires EEG (see table below for criteria)
2. *NCSE by electroclinical criteria*: EEG shows a rhythmic/periodic pattern that does not meet criteria as below but clearly correlates with si/sx.
3. *NCSE by electroradiologic criteria*: EEG shows a rhythmic/periodic pattern that does not meet criteria as below but clearly correlates with brain imaging (MRI, PET) findings.

**Treatment:** No strong evidence to guide tx; decision must be made on case-by-case basis, weighing potential benefits of aggressive tx (e.g., intubation, high dose anesthetics) vs. potential risks. *Benefits*: Rapid termination of szs, prevention of sz-induced secondary brain injury. *Risks*: Side effects of anesthetics (e.g., hypotension, propofol infusion syndrome), prolonged mechanical ventilation & ICU course, with attendant risks of infection.

**Prognosis:** Status Epilepticus Severity Score (STESS, see table) predicts survival. NCSE in coma portends poorer prognosis. NCSE after GCSE has 2× mortality c/w GCSE alone.

Criteria for Nonconvulsive Seizure

EEG pattern = nonconvulsive sz, if duration >10 s & ≥1, primary criteria met. *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 Hz + 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), morphology, or location (gradual spread into or out of a region involving >1 electrodes). Amplitude evolution alone is insufficient.

*Secondary criterion*

1. Positive response to trial of rapidly acting AED, e.g., benzo. (see next table).

*J Clin Neurophys* 2005;22(2):79-91.

Benzodiazepine Trial for Dx of NCSE (*Clin Neurophys* 2007;118(8):1660-1670)

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 ictal EEG pattern resolves & EITHER improvement in clinical state OR appearance of previously absent nl EEG patterns (e.g., posterior "alpha" rhythm). *Test is equivocal if* EEG improves but pt does not.



## NEW-ONSET REFRACTORY STATUS EPILEPTICUS (NORSE)

Pts (often young, healthy) p/w refractory SE a/w cryptogenic encephalitis-like illness. Related dxs in kids: idiopathic hemiconvulsion-hemiplegia & epilepsy syndrome (**IHHES**), febrile infection-related epilepsy syndrome (**FIRES**). **Natural hx:** Prodrome: Low-grade fever, flulike illness, mild resp, or GI infxn. *Early phase:* Discrete szs, encephalopathy, focal deficits. *Fulminant phase:* Refractory szs & SE, up to 30% mortality. *Remission:* SE controlled. *Chronic:* Often poor functional outcome, w/refractory epilepsy, cognitive impairment, brain atrophy. **Etiology:** Unk/varies; causes incl unidentified infxn, parainfxn, inflammatory, autoimmune. **Workup:** Identify treatable dzs (infxn, autoimmune, paraneoplastic). MRI of the brain (acute brain injury, limbic encephalitis, encephalomyelitis), CSF (r/o infxn, send auto-Abs), EEG to guide tx of SE/nonconvulsive szs. **Tx:** Tx underlying cause if found (infxn, abx/antivirals; paraneoplastic, find/tx tumor; autoimmune, immune therapy). For szs/SE: Follow SE protocol above (*Ann Acad Med Singapore* 2005;34:417-20; *Epilepsia* 2010;51(7):1323-1328).

## CLASSIFICATION: SEIZURE TYPES & EPILEPSY ETIOLOGIES

**General principles:** Prognosis & optimal tx depend on characterization of sz type & epilepsy syndrome. Appropriate level of detail in characterization varies w/clinical situation.

**2010 ILAE classification of clinical seizures & epilepsy** (*Epilepsia* 2010;51:676): **Generalized sz**: Sz that rapidly engages bilateral networks.

**Focal sz**: Sz that originates w/in networks limited to one hemisphere; described by clinical features (see tables below) & whether consciousness is impaired (focal dyscognitive sz). Terms ***complex partial*** & ***simple partial*** no longer in the ILAE classification, though still widely used in clinical practice.

**Unknown sz:** Cannot clearly be categorized as generalized or focal (e.g., epileptic spasms).

**Epilepsy Etiologies** (not exhaustive; see *Epilepsia* 2001;42:796-803)

***Genetic*: Chromosomal**: Angelman, Down, isolated lissencephaly sequence, Klinefelter, Miller-Dieker, Pallister-Killian, Ring 14, Ring 20, trisomy 12p, Wolf-Hirschhorn, X-linked lissencephaly, 15q13.3 microdeletion, 18q-syndrome, Inv-dup 15, Del 1p36. **Gene mutations:** ARX, CACNA1A, CACNB4, CHRNA2, CHRNA4, CHRNB2, LGI1, MECP2, SCN1A, SCN2A. **Others:** Aicardi synd, acrocallosal synd

***Structural:* Cortical malformations:** bilateral perisylvian synd., cobblestone, cortical dysplasia (focal or multifocal), focal heterotopia, hemimegalencephaly, lissencephaly, microdysgenesis, microcephaly, megalencephalies, periventricular nodular heterotopia, polymicrogyria, schizencephalies, subcortical band heterotopia. **Neurocutaneous d/os:** Tuberous sclerosis complex, neurofibromatosis, hypomelanosis of Ito,

epidermal nevus synd., Sturge-Weber synd. **Pre-/perinatal insults (anoxia/ischemia/infxn):** Porencephaly, periventricular leukomalacia, cerebral calcifications, & other lesions 2/2 Toxo. **Tumors:** DNET, gangliocytoma, ganglioglioma, astrocytomas, hypothalamic hamartoma (esp w/gelastic szs). **Vascular:** AVMs, cavernous angiomas, ICH, stroke. ***Metabolic:*** Nonketotic hyperglycinemia, D-glyceric acidemia, propionic acidemia, sulfite-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]. ***Immune:*** Anti-AMPA receptor, anti-GAD65, anti-GABA-B receptor, anti-NDMA, anti-VGKA (LGI1, CASPR2), anti-TPO, celiac dz (epilepsy w/occipital calcifications & celiac dz). ***Infectious:*** Bacterial meningitis, cerebral malaria, cysticercosis, HIV, TB, toxoplasmosis, viral encephalitis (HSV, VZV, HH6, WNV). ***Misc:*** Alzheimer dz, head injury, alcohol & drug abuse, Huntington dz, PEHO synd.



**Classification of Seizures**

| Seizure Type | | | Clinical Features | Typical EEG |
|---|---|---|---|---|
| GENERALIZED | Convulsive | Tonic-clonic | Sudden LOC, ictal cry, tonic phase, clonic phase (rhythmic jerking of arms, neck, face) Dur: 1-2 min; LOC+, PC+ | Low-voltage rhythmicity → high-amp spikes → rhythmic artifact |
| | | Clonic | Gen'd repetitive contractions of same muscle groups w/o preceding tonic phase Dur: 1-2 min; LOC+, PC+ | Gen'd high-amp spikes w/rhythmic delta |
| | Tonic | | Sustained posture of limbs, often a/w AMS & falling to ground; often arise from sleep Dur: 5-20 s; LOC+, PC± | Paroxysmal low-amp fast activity (PFA) |
| | Atonic | | Sudden loss of tone (aka drop attacks) Dur: 5-10 s; LOC±, PC± | Variable |
| | Absence | Typical | Staring; impaired consciousness; eyelid fluttering; if >10 s, often + eye blinking; lip smacking Dur: 5-10 s; LOC+, PC- | Gen'd 3 Hz spike & wave |
| | | Atypical | Staring, clonus, subtle myoclonus, atonic, confusion Dur: 15-45 s, LOC+, PC+ | Gen'd <2.5 Hz spike & wave |
| | | Myoclonic | Staring, impaired consciousness, marked rhythmic myoclonic jerks | Gen'd 3 Hz spike & wave |

| | | | | |
|---|---|---|---|---|
| | | | of arms, arms raised upwards Dur: 5-60 s; LOC+, PC+ | |
| | | Eyelid myoclonia | Sudden rhythmic fast eyelid jerks, upward gaze deviation, head ext, awareness retained Dur: <6 s; LOC-, PC- | Gen'd 3-6 Hz polyspike & wave; triggered by eye closure & photic stimulation |
| | Myoclonic | Myoclonic | Generalized rapid jerks of limbs, consciousness usually intact Dur: <1-2 s; LOC+, PC- | Gen'd polyspike & wave |
| | | Atonic | Myoclonic sz followed by atonic sz Dur: 5-10 s; LOC±, PC± | |
| | | Tonic | Myoclonic sz followed by tonic sz Dur: 5-20 s; LOC+, PC± | |
| Focal | | | Depends on localization, may have motor, sensory, experiential, dyscognitive or autonomic components (table 2) Dur: Variable, LOC±, PC± | Variable |
| UNKNOWN | Epileptic spasms | | Sudden flexion, extension or mix of proximal truncal muscles, typically in series Dur: 1-2 s; LOC-, PC- | Gen'd high-amp slow wave then lowamp fast activity or attenuation |

PC, postictal confusion; LOC, loss of consciousness; Dur, duration. Adapted from the ILAE Commission on Classification & Terminology, epilepsydx.org & *Epilepsia* 2010;51:676.



**Descriptive Terminology for Focal Seizures**

| Feature | Subtype | Examples |
|---|---|---|
| Aura | Sensory | Somatosensory, visual, auditory, olfactory, gustatory, epigastric, cephalic |
| | Experiential | Affective, mnemonic (déjà vu, jamais vu), hallucinatory, illusory |
| Motor | Elementary | Convulsive, myoclonic, tonic, versive, dystonic, spasm |
| | Complex | Hypermotor: Pelvic thrusting, thrashing, jumping, rocking, pedaling |

| | | |
|---|---|---|
| | | Negative motor: Hypomotor (↓ movement), atonic, negative myoclonic (brief interruptions in muscle tone) |
| | | Automatisms: Oroalimentary (lip smacking, chewing), manual/pedal, gestural (fumbling, exploratory mvmts), gelastic, vocal (single or repetitive sounds, not words), verbal (words), dacrystic (crying), ambulatory (wandering, walking), mimetic, diphasic, dyspraxic |
| | Epilepsia partialis continua | |
| | Focal sz → bilateral convulsion (previously "*secondary generalized sz*") | |
| Dyscognitive | Altered perception, attention, executive fxn (prev. "*complex partial*") | |
| Autonomic | Cardiovascular (tachycardia, arrhythmia, asystole), GI (nausea, hunger, urge to defecate), vasomotor, thermoregulatory, sweating, goose bumps, pupillary changes, lacrimation, sexual sensation | |
| Somatotopy | Laterality | Left hemisphere vs. right hemisphere. See table below. |
| | Localization | Lobe, gyrus, mesial vs. lateral. See table below. |

Adapted from the ILAE Commission on Classification & Terminology epilepsydiagnosis.org. *Epilepsia* 2010;51:676.

**Lateralizing & Localizing Ictal Features**

| | **Laterality** | **Localization**[a] |
|---|---|---|
| **Ictal feature** | | |
| Eye deviation | Contralateral in frontal sz<br>Contralateral or ipsilateral in occipital sz | Frontal, occipital |
| Early unforced head turn | Ipsilateral | Temporal |
| Late forced head turn | Contralateral | Frontal or focal sz → gen of any origin |
| Focal clonus | Contralateral | Frontal |
| Dystonic limb | Contralateral | Temporal (→basal ganglia) |
| Tonic limb | Contralateral | Frontal |

| | | |
|---|---|---|
| Motionless limb | Contralateral | Temporal, frontal |
| Asymmetric tonic, fencing posture | Contralateral | Frontal, supp. motor cortex |
| Figure 4 sign | Contralateral to ext. limb | Supp. motor cortex, prefrontal gyrus, or focal sz → gen of any origin |
| Oroalimentary automatisms | | Temporal |
| Limb automatisms | Ipsilateral | Temporal |
| Hyperkinetic automatisms | — | Frontal |
| Pedaling, bicycling | — | Frontal |
| Speech arrest | Dominant hemisphere | Temporal, frontal |
| **Postictal features** | | |
| Todd paralysis | Contralateral | Frontal, parietal > temporal |
| Nose wiping | Ipsilateral | Temporal |
| Aphasia | Dominant hemisphere | Language areas |
| Confusion | — | Temporal > frontal |

[a]At the time when the sign appears.

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



**Typical Features of Focal Seizures by Region of Onset**

**Temporal lobe**
*Mesial TL*: Aura (e.g., epigastric, psychic, affective, olfactory), impaired consciousness, fixed stare, early oroalimentary automatisms, limb automatisms (bilateral or ipsilateral to focus), dystonic posturing, postictal confusion, & amnesia
*Lateral TL*: Aura, e.g., hallucinations (auditory,

**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

| | |
|---|---|
| complex perceptual or experiential); language dysfxn; late oroalimentary automatisms; late manifestations ≈ mesial TL | |
| **Occipital lobe**<br>Elementary visual hallucinations, esp in contralateral hemifield; blindness; sensation of eye mvmt; eye deviation (contralateral or ipsilateral); forced blinking; variable spread to PL (sensory sx), TL/OL (formed visual hallucinations), mesial TL | **Parietal lobe**<br>Somatosensory auras; receptive 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.

## EPILEPSY SYNDROMES (PEDIATRIC EPILEPSY)

Epilepsy syndromes present in pediatric population, though many survive into adulthood.

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

**Epilepsy syndromes are defined by:** Age at onset, sz type, 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 hx, developmental prognosis, & epilepsy outcome. Syndrome identification has implications for management, prognosis, research, genetics.

## NEONATAL/INFANTILE

**Self-limited neonatal seizures: Formerly benign neonatal convulsions or 5th day fits** (*Epilepsia* 2002;43(S3):2-10). *Prev*: Rare, <1% of pediatric epilepsy. *Onset*: Days 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 suggest mild developmental deficits in 50% cases, ↑ risk epilepsy later. Cause: Hypotheses include Zn def., rotavirus. ↓ Freq in recent years, no case series reported since the 1990s.

**Self-limited familial neonatal epilepsy: Benign neonatal familial convulsions** (*Ann Neurol* 1991;29:469-473). *Prev*: Unknown; rare. *Onset*: Days 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, KCNQ2, & KCNQ3 w/incomplete penetrance. Later childhood epilepsy 11%-16%.

**Early myoclonic encephalopathy: EME** (*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, ketogenic diet (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.

**Early infantile epileptic encephalopathy: EIEE (Ohtahara)** (*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, 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.

**Epilepsy of infancy with migrating focal seizures: EIMFS (formerly *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 (weeks to months). **(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.

**Genetic epilepsy w/febrile seizures plus: GEFS+** (*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.

**Infantile spasms: IS (West)** (*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 (jackknife) 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/electrodecrement 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, tetrahydrobiopterin def, Menkes), & mitochondrial (NARP mutation). Poor prognosis, rarely good outcome w/cryptogenic etiology ˜5%.

**Myoclonic epilepsy in infancy: MEI (formerly *benign* [BMEI])** (*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.

**Severe myoclonic epilepsy of infancy: SMEI (Dravet)** (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-&-wave complexes, focal & multifocal spikes. Massive myoclonias = bursts of irregular spike & 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.

**Self-limited familial & nonfamilial infantile epilepsy** (*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.

## CHILDHOOD

**Childhood absence epilepsy: CAE (formerly pyknolepsy, 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 lifelong (cognitive & learning)

disabilities, 15% develop JME, may affect long-term psychosocial outcome.

**Childhood epilepsy with centrotemporal spikes: CECTS (formerly *benign*, i.e., BECTS or rolandic epilepsy or 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 CECTS a/w language & developmental delay. Genetic etiology suspected. EEG pattern fxns as biomarker, is inherited aut dom w/age-related penetrance.

**Childhood occipital epilepsy (early-onset)/Panayiotopoulos** (*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 include migraine, GI (gastritis, cyclic vomiting, abdominal migraine), syncope, sleep d/o. Cardiac arrest described but is rare.

**Childhood occipital epilepsy (late onset)/Gastaut** (*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 welldefined 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%.

**Epilepsy w/myoclonic absences (formerly Tassinari):** Ictal 3 Hz myoclonus w/arms “ratcheting” upward. Usually a/w MR. AED resistant (*Epilepsia* 2002;43(S3):27).

**Epilepsy w/myoclonic-astatic seizures: EMAS (formerly myoclonic-astatic epilepsy or Doose)** (*J Clin Neurophysiol* 2003;20:449). *Prev*: Uncommon, 1%-5%. *Onset*: 7 mo-6 yr. *Sz types*: Primarily generalized myoclonic, astatic, or myoclonicastatic 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, MEI, 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.

**Epileptic encephalopathy with continuous spike & wave during sleep: CSWS (formerly ESES)** (*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. CSWS 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%.

**Landau-Kleffner syndrome: LKS (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 CSWS; apparently generalized szs may in fact be focal onset. *Prognosis*: Acquired epileptic auditory agnosia, fewer szs than CSWS (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) CECTS, or iatrogenic aggravation (CBZ), an epileptic encephalopathy can occur. **(3)** Rare secondary LKS (e.g., tumor).

**Lennox-Gastaut syndrome: LGS** (*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 polyspike & 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.

**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 is helpful. Natural course w/slowly progressive hemiparesis, hemianopia, MR, cortical atrophy. Steroids, immunoglobulins, plasmapheresis: Only temporary relief. *Early hemispherectomy unequivocally improves outcome*.

## ADOLESCENT/ADULT

**Autosomal dominant epilepsy w/auditory features & familial mesial temporal lobe epilepsy: ADEAF (formerly ADLTE) & FMTLE** (*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*

*epilepsy w/auditory features* **(ADEAF)**: 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.

**Epilepsy w/GTCs only:** Broadly defined—includes random & nocturnal GTCs. Typically no absences & myoclonic szs (*Epilepsia* 2008;49:2050-2062).

**Juvenile absence epilepsy: JAE** (*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, lifelong 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 aggravates JAE.

**Juvenile myoclonic epilepsy: JME (formerly impulsive petit mal or 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, EtOH, photosensitivity, stress). Genetics: See ref. Absences can appear during childhood → myoclonic jerks & GTCs in midteens. Lifelong; milder in 3rd-4th decade but w/drawal of AEDs → recurrence. 70% control w/VPA. Avoid PHT, CBZ: aggravation.

## VARIABLE AGE

**Autosomal dominant nocturnal frontal lobe epilepsy: ADNFLE** (*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.

**Mesial temporal sclerosis: MTS** (*Curr Opin Neurol* 2004;17:161). *Prev*: Uncommon (1%-5%). *Prev*: Childhood-adolescence. *Onset*: CPS 1-2 min; oral, hand, verbal automatisms w/semipurposeful 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.

**Progressive myoclonic epilepsies** (*Lancet Neurol* 2005;4:239-248). *Prev*: Rare <1%. *Prognosis*: Poor, progressive neurological decline, dementia, cerebellar ataxia. *Rx (for all):* VPA (except MERRF), PB, LEV, BZD, ZNS. *Avoid (↑ myoclonus):* PHT, CBZ, GBP, VBG, TGB. *Use w/caution:* LTG. **Unverricht-Lundborg dz** *onset*: 6-15. *Sz type*: Myoclonic, tonic-clonic, absence. *EEG*: Generalized (poly)spike & wave with photosensitivity, slow background (late). **Lafora dz** *onset*: 12-17. Sz type: Myoclonic, occipital w/transient blindness, atypical absences, atonic, focal dyscognitive. *EEG*: Generalized (poly)spike & wave, occipital sharp slow waves, photosensitivity.

**MERRF** *onset*: Any age. *Sz type*: Myoclonic, tonic-clonic. *EEG*: Generalized spike & wave at 2-5 Hz. *Avoid VPA.* **Neuronal ceroid lipofuscinosis** *onset*: Variable. *Sz type*: Myoclonic, tonic-clonic, atypical absence, atonic. *EEG*: Generalized spike & wave, slow background (early), photosensitive. **Sialidosis** *onset*: Variable. *Sz type*: Massive myoclonus, tonic-clonic. *EEG:* Low-voltage 10-20 Hz vertex-positive spikes. **Dentatorubropallidoluysian atrophy** *onset*: 15-40 (anticipation). *Sz type*: Myoclonic, tonic-clonic. *EEG*: Generalized spike & wave, photosensitive.

## ANTIEPILEPTIC DRUGS (AEDs)

**When to start an AED:** If provoked sz (medication induced, electrolyte abnls, intox, w/drawal), tx underlying cause. Reserve AEDs for pts w/>1 idiopathic sz, underlying brain structural abnl, abnl EEG, focal exam (incl. postictal Todd paralysis), or idiopathic sz + SE on presentation (see also Workup of First Sz section in this chapter). When choosing AED, consider side effects, gender, comorbidities, age, other meds, $, avail. routes.

**Effectiveness of AEDs:** In general (differs w/specific dx), % of pts who are sz-free w/: 1st monotherapy = **47%**; 2nd monotherapy = **13%**; 3rd monotherapy = **1%**. Total % of pts who are sz-free on medication = **64%**. (Neurology 2002;58 (Suppl 5):S2-S8).

**Discontinuation of AED: Reasons for AED discontinuation:** Med side effects, cost, teratogenic risk, inconvenience. **Risks of AED discontinuation:** Recurrent sz, may → injury/death, inability to drive, occupational hazards. Length sz-free prior to discontinuation: If >1 unprovoked sz, wait until sz-free × 2 yr before discontinuation. Pediatric data supports early discontinuation in kids w/easily controlled szs (*Epilepsia* 2008;49(S9):25-28). Features favorable for AED discontinuation: Age of onset 2-11 yo; idiopathic etiology; normal neuro exam; prompt initial AED response, infreq szs, low AED levels at time of w/drawal; sz-free for >2 yr. Features unfavorable for AED discontinuation: Age of onset >10 yo; symptomatic etiology; mental retardation; abnl neuro exam; symptomatic partial epilepsy; poor initial response to AEDs; multiple AEDs at time of discontinuation; abnl EEG; FHx of epilepsy (Continuum *Neurol* 2010;16(3):105-120).



**AED Trade Names & Abbreviations**

| Generic Name | Trade Name | Abbreviat'n | Generat'n |
|---|---|---|---|
| Benzos (BZD): clonazepam, clorazepate, diazepam, lorazepam, midazolam | Klonopin, Tranxene, Valium/Diastat, Ativan, Versed | CLZ, CZP, DZ, LZ, MZ | 1st |
| Carbamazepine | Tegretol, Tegretol XR, Carbatrol | CBZ | 1st |
| Clobazam | Onfi | CLB | 2nd |
| Eslicarbazepine | Aptiom | ESL | 2nd |
| Ethosuximide | Zarontin | ESX | 1st |
| Ezogabine | Potiga | EZG | 2nd |
| Felbamate | Felbatol | FBM | 2nd |

| | | | |
|---|---|---|---|
| Gabapentin | Neurontin | GBP | 2nd |
| Lacosamide | Vimpat | LCM | 2nd |
| Lamotrigine | Lamictal | LTG | 2nd |
| Levetiracetam | Keppra | LEV | 2nd |
| Oxcarbazepine | Trileptal | OXC | 2nd |
| Perampanel | Fycompa | PER | 2nd |
| Phenobarbital | Luminal, Solfoton | PB | 1st |
| Phenytoin | Dilantin | PHT | 1st |
| Pregabalin | Lyrica | PGB | 2nd |
| Primidone | Mysoline | PRM | 1st |
| Rufinamide | Banzel | RUF | 2nd |
| Tiagabine | Gabitril | TGB | 2nd |
| Topiramate | Topamax | TPM | 2nd |
| Valproic acid | Depakote, Depakote ER, Depakene, Depacon | VPA | 1st |
| Vigabatrin | Sabril | VGB | 2nd |
| Zonisamide | Zonegran | ZNS | 2nd |

## CHOICE OF AED: GENERAL PRINCIPLES

### Special considerations when choosing an AED

**Sz type:** Focal or tonic-clonic szs (use narrow spectrum AEDs). Focal & generalized szs including myoclonic, absence (use broad-spectrum AEDs).

**Cost:** First-generation AEDs generally cheaper. Consider AEDs w/generic equivalents.

**First AED:** 47% of pts become sz-free w/first AED (will be on this AED chronically) → choose first AED w/best safety & tolerability.

**Multiple AEDs:** When adding AEDs, consider interactions. AED combos to monitor closely due to interactions (many more combos): PB + VPA, PHT + CBZ, CBZ + LTG, VPA + LTG.

**Other meds:** Consider interactions w/other non-AED medications.

**Female:** Childbearing years? Taking OCPs? Bone health? Teratogenicity? (see also *Pregnancy Neurology* chapter, Epilepsy in Pregnancy section).

- AEDs that may ↓ efficacy of OCPs: CBZ, FBM, PB, PHT, PRM, TPM, OXC.
- In pregnancy: New AEDs are class C = unknown fetal effects. Old AEDs are class D (known teratogens to humans). VPA is highest risk (6%-11%), PB 6%; risk w/others modest (2%-5%, no Δ c/w control population). Old AEDs can → "fetal anticonvulsant syndrome": craniofacial + digital abnormalities, ~3% w/major defects (e.g., cardiac, cleft lip/palate, microcephaly, dev delay, neural tube).

**Elderly:** Use lower doses & titrate more slowly, given lower threshold for side effects (e.g., cognitive dysfxn, tremor, gait problems). Decrease doses of protein-bound drugs, as albumin levels ↓ w/age; also note that CrCl + hepatic clearance ↓ after age 65.

**IV formulations** (when rapid titration is necessary): See table of IV AEDs below.

**CHOICE OF AED: "EXPERT RECOMMENDATIONS"** (*Epilepsy Behav* 2005;7:S1-S64)

**IGE,** idiopathic generalized epilepsy

**SLRE,** symptomatic localization-related epilepsy (focal epilepsy).



| AEDs for Idiopathic Generalized Epilepsy: Expert Recommendations | | | |
|---|---|---|---|
| **Monotherapy** | | | |
| **Setting** | **GTC** | **Absence** | **Myoclonic** |
| Mono #1 | VPA > LTG, TPM | VPA, ESX > LTG | VPA |
| Mono #2 after VPA | LTG > TPM, LEV > ZNS | ESX, LTG | ZNS, LEV, TPM |
| Mono #2 after LTG | VPA > TPM, LEV > ZNS | VPA, ESX | VPA > ZNS |
| Mono #2 after TPM | VPA, LTG | VPA, ESX > LTG | VPA |
| **Combination Therapy** | | | |
| **Current AED** | | **Consider Adding** | |
| FBM | | VPA > LTG | |
| LTG | | VPA, TPM, LEV, ZNS | |
| LEV | | VPA > LTG, TPM | |
| TPM | | LTG, VPA > LEV | |
| VPA | | LTG > TPM, LEV, ZNS | |

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|---|---|
| ZNS | LTG, VPA > LEV |
| Vagus nerve stim | VPA > LTG, TPM |

| **AEDs for Symptomatic Localization-Related Epilepsy: 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, TPM |
| GBP | LTG, CBZ, OXC > LEV, TPM |
| LEV | LTG, CBZ, OXC > TPM |
| OXC | LTG > LEV, TPM |
| PHT | LTG > LEV, CBZ |
| TPM | LTG, CBZ, OXC > LEV |
| VPA | LTG, CBZ, OXC, LEV, TPM |
| **Combination Therapy** | |
| **Current AED** | **Consider Adding** |
| CBZ | LEV > LTG, TPM, ZNS |
| GPN | LTG, LEV > OXC, TPM, CBZ, ZNS |
| LTG | LEV > TPM, OXC, CBZ, ZNS |
| LEV | LTG, CBZ > OXC, TPM, ZNS, VPA |

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|---|---|
| OXC | LEV > LTG, TPM, VPA, ZNS |
| PB | LTG, LEV > OXC, CBZ, TPM |
| PHT | LTG, LEV > TPM, VPA |
| TGB | LTG > LEV, TPM, OXC, CBZ |
| TPM | LTG, LEV > CBZ, OXC, VPA |
| VPA | LEV > OXC, LTG, CBZ, TPM |
| ZNS | LTG, LEV, OXC, CBZ |



| AEDs for Special Circumstances: Expert Recommendations | |
|---|---|
| **Depressed Pts** | |
| IGE | LTG > VPA |
| SLRE | LTG > OXC, CBZ |
| **Elderly Pts** | |
| SLRE, medically stable | LTG > LEV |
| SLRE, medically ill | LTG > LEV, GPN |
| **Emergency Department** | |
| Unknown epilepsy syndrome | LEV, VPA > PHT, OXC, LTG, CBZ, TPM |
| **Hepatic Disease** | |
| IGE | LEV, LTG |
| SLRE | LEV, GPN |
| **HIV (+) Pts** | |
| IGE | LTG, LEV |

| | |
|---|---|
| SLRE | LEV, LTG |
| **Renal Disease** | |
| IGE | LTG, VPA |
| SLRE | LTG |
| **Woman Who Might Become Pregnant** | |
| IGE | LTG > LEV |
| SLRE | LTG > LEV, OXC |
| **Woman Trying to Become Pregnant** | |
| IGE | LTG |
| SLRE | LTG > LEV, OXC |

## SIDE EFFECTS, INTERACTIONS, COMORBIDITIES, & MONITORING

| **Influence of Comorbid Conditions on AED Choice** | |
|---|---|
| **AEDs to Use Cautiously or Avoid** | |
| Absence szs | CBZ, OXC, TGB |
| Anorexia/malnourished | FBM, TPM, ZNS |
| Arrhythmias | CBZ, PHT |
| Bleeding diathesis | VPA |
| Blood dyscrasias | CBZ |
| Generalized szs | GBP, CBZ, OXC, (may exacerbate) |
| Hepatic disease | VPA, PHT, PB, CBZ, LTG, ZNS, FBM |
| Hypersensitivity reactions | AEDs w/risk of rash (esp PHT, CBZ, LTG) |
| Hyponatremia (or risk for) | CBZ, OXC |
| Hypothyroidism | CBZ, OXC, PHT |

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|---|---|
| Myoclonic szs | GBP, LTG, OXC, CBZ, TGB, PGB |
| Nephrolithiasis | ZNS, TPM |
| Obesity | VPA, PGB (↑ 10-50 lb), ?CBZ, ?GBP (↑ 5-10 lb) |
| Oral contraceptive use | CBZ, OXC, PHT, PB, TPM (at dose >200) |
| Osteopenia | PHT > CBZ, PB |
| Pancreatic disease | VPA, CBZ |
| Peripheral edema | PGB |
| Polycystic ovarian syndrome | VPA |
| Psychiatric disorders | LEV, PB |
| Renal impairment | LEV, GBP, PB, PGB, TPM, ZNS |
| **AEDs That May Help the Condition** | |
| Headache | TPM, VPA, CBZ in children |
| Insomnia | TGB |
| Mood instability | OXC, VPA, LTG, CBZ |
| Neuropathic pain | GBP, OXC, CBZ, TPM |
| Obesity | TPM, ZNS |
| Periodic limb movements of sleep | CZP, GBP, TPM, ZNS |
| Tremor | CZP, PBT, PRI, ELV, TPM |

## COMMONLY USED AEDs: DOSES, SIDE EFFECTS, INTERACTIONS

The table below lists general information about commonly used PO AEDs (listed alphabetically). (Note, there is a separate table (also below) for IV AEDs.) *Format is as follows*:

- First line: Start dose (mg), how to increment (mg & how often), goal maint dose (mg/day), schedule to divide total daily dose (qd, bid, tid, qid), metabolism (renal, hepatic), target serum level (mg/L = microgram/mL), half-life (hours), % protein bound.
- Pedi dose (wt based): Start dose, how to increment (mg & how often), goal maint dose.

- Vd, volume of distribution (if unknown, can approximate by Vd = IV dose/Δ conc).
- **CSE**, common side effects; **SSE**, serious side effects; **LTE**, long-term side effects.
- Common acronyms: **LLS**, lupus like syndrome; **TEN**, toxic epidermal necrolysis; **SJS**, Stevens-Johnson syndrome.
- Monitoring suggestions (levels, other labs/tests). If none is given, then it is reasonable to follow generic suggestions below (see "Routine" Labs & AED Level Monitoring).
- Interactions: "↑" or "↓": Lists drugs & conditions that commonly ↑ or ↓ the level of this AED. ⇨ **:** Lists effects of this AED on other commonly used drugs.

## "Routine" labs & AED level monitoring

*Levels*: 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.

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P.80
P.81
P.82

| PO AEDs | |
|---|---|
| **CBZ**<br>**CBZ-XR** | Start 200 bid, ↑ 200 qd qwk, goal 800-1,200/day(tid), hepatic; 4-12, 12-18 h, 80%<br>[Pedi: Start 5-10 mg/kg/d(bid), ↑ 5 mg/kg/d qwk, maint 15-30 mg/kg/d(bid)]<br>*If Δ'ing to CBZ-XR, total daily dose is same, but use bid (instead of tid) dosing*<br>CSE: Mild leukopenia, ataxia, diplopia, lethargy, urinary retention, ↓ wt, ↓ T4<br>SSE: Agranulocytosis (1/20 K), aplastic anemia (1/500 K), rash (10% pts), SJS (rare), hyponatremia, pancreatitis, hepatitis, LLS, arrhythmias<br>Caution: Glaucoma, cardiac dz, liver dz, prostatic hypertrophy<br>Contra: W/MAOIs, h/o bone marrow suppression, allergy to TCAs<br>Monitoring: CBC, LFTs, chem7 at baseline, 6 wk, 3 mo, 6 mo, then q3-6 mo, yrly DXA scans (lumbar spine & proximal femur)<br>In Asian pts, test for HLA-B*1502 before starting (higher risk of SJS)<br>Pts should take VitD 2,000 IU qd + Ca 1,200 mg qd<br>↑: FBM, VPA; Φ (fluoxetine, fluvoxamine, nefazodone, trazodone, viloxazine); Abx (erythromycin, isoniazid, clarithromycin, fluconazole, ketoconazole, metronidazole, ritonavir, troleandomycin); misc (cimetidine, danazol, propoxyphene, diltiazem, risperidone, quetiapine, ticlopidine, verapamil, grapefruit juice)<br>↓: PHT, PB; ⇨ ↓ VPA, ↓ OXC, ↓ OCPs, warfarin (↓ INR), ↓ theophylline, ↓ cyclosporine, ↓ Haldol, ↓ Klonopin |
| **CLB** | Start 5qhs, ↑ 5qd qwk, goal 20-40/day(qd, bid), hepatic; 0.03-0.3, 10-30 h, 85%<br>[Pedi: Start 0.1-0.2 mg/kg/d, ↑ 0.1 mg/kg/d qwk(qd, bid), goal 0.4-0.8 mg/kg/d]<br>CSE: Sedation, depression |

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|---|---|
| | SSE: Suicidal ideation, resp. depression<br>Caution: Sudden w/d → sz. Excreted in breast milk<br>Contra: Don't use w/flumazenil<br>↑: FBM; ↓:CBZ, PB, PHT; ⇨ ↑ VPA, ↑ PHT, ↑ PRM |
| **CLZ** | Start 0.25qhs, ↑ 0.25qd qwk, goal 4-10/day(qd, bid), hepatic; 20-80, 18-50 h, 85%<br>[Pedi: Start 0.01-0.02 mg/day, ↑ slowly, goal 0.1-0.2 mg/day (qd, bid); often temp Rx]<br>CSE: CNS: Sedation, ataxia, hyperactivity<br>SSE: Psychosis, resp depression<br>Caution: Sudden d/c may provoke sz. Excreted in breast milk<br>Contra: Don't use w/flumazenil<br>↓: CBZ, PB, PHT; ⇨ none |
| **DZP** | Start 2bid, ↑ 1qd q3d, goal 15/day (bid-tid), hepatic, 0.1-1; 30-36 h, 95%<br>[Pedi: Start 1-10 mg bid-qid, typically temporary rx]<br>CSE: Sedation, irritability, HA, dizziness, depression<br>SSE: HoTN, resp. depression, interstitial nephritis, thrombophlebitis<br>Caution: Sudden w/d → sz; pulm dz, psychosis. Excreted in breast milk<br>Contra: Don't use w/flumazenil. Acute narrow angle glaucoma.<br>*Monitoring*: No routine lab monitoring needed<br>↑: VPA; ↓:CBZ, PB, PHT; ⇨ none |
| **ESL** | Start 400qd, ↑ 400qd qwk, goal 800-1,200/day(qd), hepatic; unk, 20-24 h, 30%<br>CSE: Dizziness, n/v, ataxia, diplopia, somnolence, HA, ↓ $T_4/T_3$<br>SSE: Hyponatremia, ↑ PR interval, suicidal ideation, SJS<br>Caution: Reduce dose for impaired renal fxn. Excreted in breast milk<br>Contra: Allergy to OXC (cross-reactivity)<br>Monitoring: Routine, plus: Na at baseline, then 1 mo × 3 mo, then q3-6mo<br>↓: CBZ, PHT, PB; ⇨ ↓ OCPs, ↓ warfarin, ↑ PHT, ↑ CLB, ↓ LTG, ↓ TPM |
| **ESX** | Start 250qd, ↑ 250qd qwk, goal 500-1,250/day(bid); hepatic, 40-100; 30-60 h, <5%<br>[Pedi: Start 5-10 mg/kg/d, ↑ 10 mg/kg/d qwk, goal 20-30 mg/kg/d (bid, tid)]<br>*CSE*: Sedation, HA, n/v<br>*SSE*: Blood dyscrasias, erythema multiforme, SJS, LLS, psychosis<br>Caution: Sudden w/d → sz; High conc. in breast milk<br>Contra: Porphyria<br>Monitoring: Routine, plus: CBC, LFTs at: baseline, q1mo × 6mo, then q6mo<br>↑: Isoniazid, VPA; ⇨ ↓ OCPs, ↓ VPA effectiveness |
| **EZG** | Start 100tid, ↑ 150qd qwk, goal 600-1,200/day(tid), hepatic; unk, 7-11 h, 80%<br>CSE: Confusion, dizziness, ataxia, diplopia, somnolence, dysarthria<br>SSE: Blue skin, retinal damage, ↑ QT, psychosis, suicidal ideation, urinary retention<br>Caution: Reduce dose for impaired renal fxn. Unknown if excreted in breast milk<br>Monitoring: Ophtho eval q6mo<br>↓: CBZ, PHT; ↑: EtOH; ⇨ ↑ digoxin |
| **FBM** | Start 400tid, ↑ 600qd qwk, goal 2,400-3,600/day(tid), hep/renal, 30-80, 20 h, 25%<br>[Pedi: Start 5 mg/kg tid; ↑ 15 mg/kg/d qwk, goal 45 mg/kg/d(tid)]<br>CSE: CNS: HA, sedation, insomnia, diplopia, agitation, anorexia, tachycardia |

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|---|---|
| | SSE: Aplastic anemia, liver/renal failure, pancreatitis, LLS, ↑ $NH^3$, SJS<br>Caution: Only for severe epilepsy given risk of aplastic anemia; renal dysfxn<br>Contra: H/o blood dyscrasia, liver dz, +ANA<br>Monitoring: ANA at baseline; CBC, chem7, LFT at baseline, then q3-6mo<br>↓: PHT, PB, CBZ; ↑ none; ⇨ ↓ OCPs, ↓ CBZ, ↑ VPA, ↑ PHT, ↑ CLB |
| **GBP** | Start 300qd, ↑ 300qd q3d, goal 900-3,600/day(tid), renal, 12-20, 5 h, <10%<br>[Pedi: Start 10-15 mg/kg/d(tid), ↑ 10 mg/kg/d q3d, goal 25-30 mg/kg/d(tid)]<br>CSE: Fatigue, sedation, mild wt gain, tinnitus, ataxia, wt gain, behavior Δs<br>SSE: Rare, but include ICH, TTP, eye hemorrhage, psychosis<br>Caution: Avoid w/Lennox-Gastaut (may ↑ szs); taper if d/c'ing. Renally dose<br>Monitoring: No routine lab monitoring needed |
| **LCM** | Start 50bid, ↑ 100qd qwk, goal 200-400/day(bid), hepatic; 10-20, 13 h, <15%<br>CSE: Dizziness, ataxia, diplopia, nystagmus, somnolence, HA<br>SSE:↑ PR interval<br>Caution: Avoid drugs that ↑ PR interval. Unknown if excreted in breast milk<br>Monitoring: Routine, ECG prior to initiation<br>↑: None, ↓: none, ⇨ none |
| **LEV**<br>**LEV-XR** | Start 500bid, ↑ 500qd qwk, goal 2,000-3,000/day(bid), renal, 10-45, 6-8 h, <5%<br>[Pedi: Start 10 mg/kg bid, ↑ 10-20 mg/kg/d q1-2wk, goal 30-40 mg/kg/d(bid)]<br>*If Δ'ing to LEV-XR, total daily dose stays the same.*<br>CSE: Sedation, anxiety, irritability, generalized wkness, dizziness, depression<br>SSE: Psychosis (rare)<br>Caution: Reduce dose for impaired renal fxn. Can exacerbate psych d/os<br>Monitoring: Routine<br>↑: None, ↓: none, ⇨ none |
| **LTG**<br>**LTG-XR** | Start 25qd × 2wk, ↑ 25qd qwk, goal 200-400/day(bid), hep/ren; 4-20, 10-60 h, 55%<br>+ *VPA*: Start 25qod × 2wk, ↑ 25qd q1-2wk, goal 100-200/day(bid)<br>+ *enz-ind*: Start 25bid × 2wk, ↑ 50-100qd qwk, goal 300-500/day(bid)<br>[Pedi: Start 0.15 mg/kg bid × 2wk, ↑ 0.6 mg/kg/d q1-2wk, goal 4.5-7.5 mg/kg/d(bid)<br>+ *VPA*: 0.15 mg/kg/d(bid) × 2wk, ↑ 0.3 mg/kg/d q1-2wk, goal 1-3 mg/kg/d(bid)<br>+ *enz-ind*: 0.6 mg/kg/d(bid) × 2wk, ↑ 1.2 mg/kg/d q1-2wk, goal 5-15 mg/kg/d(bid)]<br>*If Δ'ing to LTG-XR, total daily dose stays the same*<br>CSE: CNS: lethargy, dizziness, diplopia, HA, insomnia, tics<br>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<br>Caution: Discontinue at first sign of rash. Levels ↓'d by pregnancy & OCPs.<br>Monitoring: Routine<br>↑: VPA; Φ (sertraline); ↓: PHT, PB, CBZ; ⇨ none |
| **OXC**<br>**OXC-XR** | Start 150bid, ↑ 150qd qod, 1,200/day (bid); renal, 3-40; 8-10 h, 50%<br>[Pedi: Start 5-10 mg/kg/d bid, ↑ 5 mg/kg/d qwk, maint 30 mg/kg/d]<br>*If Δ'ing to OXC-XR,* may need ↑ *dose to achieve bioequivalence*<br>CSE: Fatigue, n/v, ataxia, diplopia, somnolence, HA, ↓ $T_4$<br>SSE: Hyponatremia (3%), SJS/TEN (1/million), anaphylaxis (rare)<br>Caution: Allergy to CBZ (30% crossover allergy); Crosses placenta |

- Can switch CBZ → OXC overnight at ratio of 1/1.5 (CBZ/OXC)
- Plasma level measures 10-hydroxycarbazepine (active metabolite of OXC)

Monitoring: Routine, plus: Na at baseline, then 1 mo × 3 mo, then q3-6mo ↓: CBZ; ⇨ ↓ OCPs, ↑ PB, ↑ PHT (at doses >1,200/day), ↑ VPA

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**PB**

Start 1.5-4 mg/kg/d, goal 1.5-4 mg/kg/d(qd, bid), hep/ren; 15-45, 24-110 h, 50%
[Pedi: Start 5 mg/kg/d(qd, bid); goal depends on age, range 2-11 mg/kg/d]
Note: Takes 2-3 wk to reach steady state if no load given
Vd: Infant 0.9; adult 0.5
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: 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 (dextropropoxyphene, acetazolamide); ⇨ ↓ OCPs, warfarin (↓ INR), ↓ theophylline

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**PER**

Start 2qhs, ↑ 2qd qwk, goal 4-8/day(qhs), hepatic; not established, 105 h, 95% + *enz-ind*: Start 4qhs, ↑ 2qday qwk, goal 8-12/day(qhs)
CSE: Dizziness, somnolence, irritability, falls, ataxia, weight gain
SSE: Suicidal & homicidal ideation, aggression
Caution: Excreted in breast milk
Monitoring: Routine
↓: CBZ, OXC, PHT; ⇨ ↓ OCPs

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**PGB**

Start 25bid, ↑ 50qd qwk, goal 300-600/day(bid, tid), renal; unk; 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
⇨ May ↑ effect of CNS depressants (e.g., benzos, barbiturates, EtOH)

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**PHT**

Start 150bid,↑ 50qd q3-4wk, goal 200-500/day(qd-tid), hep/ren, 10-20, 8-40 h, 90%
For faster PO load: Give 15-20 mg/kg divided into three doses, spaced 2-3 h apart.
[Pedi: Start 5 mg/kg/d(qd, bid), ↑ 5 mg/kg/d q3-4wk, goal 5-10 mg/kg/d(qd, bid)]
Free level target range: 0.50-3
Vd: Child 1.0; adolescent 0.7-1.0; adult 1.0
*Corrected level = Measured PTH level/*[(*albumin × 0.2*) + *0.1*]
CSE: N/v, ataxia, nystagmus, diplopia, lethargy, confusion, ↓ $T_4$
SSE: SJS/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 FOSPHT). Nonlinear kinetics—small dose ↑ can cause large level increase. Can mask sx of hypoglycemia in diabetic

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| | pts.<br>Contra: Sinus bradycardia, heart block, hypotension, low EF<br>Monitoring: Routine + yrly DXA scans (lumbar spine & proximal femur). Pts should take Vit D 2,000 IU qd + Ca 1,200 mg qd.<br>Interactions:<br>↑: FBM, OXC, VPA; Φ (chlorpromazine, fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, 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, ticlopidine, tolbutamide, azapropazone, EtOH; uremia, hypoalbuminemia)<br>↓: VPA, CBZ, chronic EtOH, antacids, steroids<br>⇨ ↓ theophylline, ↓ digoxin, warfarin (↑ INR), ↓ cyclosporine, ↓ OCPs, ↓ Haldol |
| **RUF** | Start 200bid, ↑ 400qd q2d, goal 1,800-3,200/day(bid), hepatic; 10-25, 6-10 h, 35%<br>[Pedi: >4 yr: Start 10 mg/kg/d(bid), ↑ 10 mg/kg/d qod, goal 45 mg/kg/d(bid)]<br>CSE: Dizziness, somnolence, nausea, vomiting, headache<br>SSE: Hypersensitivity synd, rash, ↓ QTc, SI, status epilepticus<br>Caution: Pts on VPA require lower doses<br>Contra: Pts with short QT syndrome or family hx<br>Monitoring: Routine, ECG<br>↑: VPA ↓: CBZ, PHT, PB, PRM; ⇨ ↓ OCPs |
| **TGB** | Start 4qd, ↑ 4 mg/day qwk, goal 16-28 mg/day(bid-qid), hepatic, 0.1-0.3, 8 h, 95%<br>+ *enz-ind*: 4qd, ↑ 4 mg/day qwk, goal 32-56/day(bid-qid)<br>CSE: Fatigue, dizziness, ataxia, insomnia, somnolence, irritability, weakness<br>SSE: Rash, SJS (rare), spike-wave NCSE<br>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)<br>Monitoring: Routine<br>↓: PHT, CBZ, PB; ⇨ minimal |
| **TPM**<br>**TPM-XR** | Start 25bid, ↑ 25-50 mg/day q1-2wk, goal 100-600/day(bid), renal; 5-25; 20 h, 15%<br>[Pedi: Start 0.5 mg/kg bid, ↑ 0.5-1 mg/kg/d q1-2wk, goal 3-9 mg/kg/d (bid)]<br>*If Δ'ing to TPM-XR, total daily dose stays the same.*<br>CSE: Lethargy, ataxia, word-finding problems, slow speech, poor concentration, wt loss, paresthesias, mild metabolic acidosis, agitation<br>SSE: Severe metabolic acidosis (3%), renal stones (1%), AV block, acute angle closure glaucoma (rare), ↓ sweating/heatstroke(esp children), psychosis (rare)<br>Caution: ↑ risk of renal stones w/acetazolamide, dichlorphenamide, ZNS, or ketogenic diet; w/renal insuff use renal dosing; caution w/liver dz<br>Contra: Allergy<br>Monitoring: Routine<br>↓: CBZ, PHT; ⇨ ↓ OCPs, ↓ digoxin |
| **VGB** | Start 500qd, ↑ 500 mg/day qwk, goal 1,000-3,000/day (qd, bid), hepatic; 0.8-36, 5-8 h, 0%<br>[Pedi: Start 40 mg/kg/d(qd, bid), increase qwk, goal depends on age: 10-15 kg: 500-1,000 mg/kg/d; 15-30 kg: 1,000-1,500 mg/kg/d; 30-50 kg: 1,500-3,000 mg/kg/d; >50 kg: 2,000-3,000 mg/kg/d; (qd, bid)<br>Infantile spasms: Start 50 mg/kg/d, ↑ over 1 wk to goal 150-200 mg/kg/d(qd, bid)] |

| | |
|---|---|
| | CSE: Visual field cut (↑ males), diplopia, sedation, dizziness, ataxia<br>SSE: Permanent vision loss, anemia, suicidal ideation<br>Caution: Can worsen myoclonic & absence szs. Excreted in breast milk<br>Monitoring: Routine + Ophtho eval prior & q3mo<br>↑: None, ↓: none; ⇨ ↓ PHT |
| **VPA**<br>**VPA-XR** | Start 250bid, ↑ 500 mg/day qwk, goal 1,000-2,500/day(bid), hep > ren, 50-100, 8-12 h, 95%<br>[Pedi: Start 5 mg/kg tid, ↑ 15 mg/kg/d qwk, goal 20-30 mg/kg/d (bid-tid)]<br>*If Δ'ing to VPA-XR, ↑ dose 10%-20% to achieve bioequivalence.*<br>CSE: Lethargy, ataxia, wt gain, n/v/d, tremor, hair loss, mild ↓ plts, ↓ carnitine<br>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 ↑ NH3), teratogenicity<br>LTE: PCOS, amenorrhea, hyperandrogenism in females, hair thinning<br>Caution: No evidence for excess operative bleeding, but some recommend stopping before surgery (can cause ↓ factor 7)<br>Contra: Hepatic dz, porphyria<br>Monitoring: CBC, LFT, lipase at baseline, qmo × 6mo, then q3-6mo<br>↑: FBM; Φ (Sertraline, chlorpromazine); Abx (Isoniazid); misc (cimetidine, propoxyphene, salicylates)<br>↓: PB, LTG, CBZ, PHT [*free fraction PHT~ VPA level*: *Free PHT% = 10%* (*baseline level*) + (*0.1 × VPA level*)]<br>⇨ ↑ PB, ↑ FBM, ↑ LTG, ↑ CBZ |
| **ZNS** | Start 100qd, ↑ 100 mg/day q2wk, goal 100-600/day(qd-bid), renal, 10-40, 60 h, 40%<br>[Pedi: Start 1-2 mg/kg/d (qd-bid), ↑ 1-2 mg/kg/d q2wk, goal 8-12 mg/kg/d (qd-bid)]<br>CSE: Somnolence, dizziness, ataxia, photosensitivity, ↓ conc., ↓ wt, n/v, HA<br>SSE: Aplastic anemia, renal stones (2%), SJS/TEN (rare), anhidrosis (rare)<br>Caution: Taper slowly; renal or liver dysfxn; ↑ risk of kidney stones w/acetazolamide or TPM<br>Contra: GFR < 50. Hypersensitivity to sulfonamides<br>Monitoring: Routine<br>↓: PHT, PB, CBZ, VPA; ⇨ ↑ PHT |
| | **Parenteral (IV, IM, PR) AEDs** |
| **DZP-IV** | IV Load: 10-20 mg (2 mg/min), can repeat in 15 min. Maint: 0.4 mg/kg/h |
| **DZP-PR** | PR 0.2 mg/kg, can repeat after 4 h (brand name: Diastat) |
| **LCM** | IV load: 200 mg. Maint: 200-400, div: bid, start 12 h after load. PO⇨IV 1:1 |
| **LEV** | IV load: 20-30 mg/kg. PO⇨IV 1:1 |
| **PB** | IV load: 20 mg/kg (max rate: 1-2 mg/kg/min). Check level immediately after; rebolus if low: Bolus (mg/kg) = Vd x (desired-measured level).<br>Vd: Infant 0.9; adult 0.5. PO⇨IV 1:1. Monitoring: RR, BP |

| | |
|---|---|
| **PHT** | IV load: 20 mg/kg (max rate: 50 mg/min). Wait > 1 h to check level; rebolus if low: Bolus dose (mg/kg) = Vd × (desired - measured PHT level)<br>Vd: Child 1.0; adolescent 0.7-1.0; adult 1.0. PO ⇨ IV 1:1<br>Contra: Sinus bradycardia, heart block, hypotension, low EF<br>Monitoring: Cardiac monitoring, BP monitoring |
| **FOS-PHT** | IV/IM load: 20 mg PE(phenytoin equivalents)/kg; (max rate:150 mg PE/min) If IV, wait at least 2 h to check level; If IM, wait >4 h to check level.<br>Rebolus if low: Bolus dose (mg/kg) = Vd × (desired - measured PHT level) Vd: 0.04-0.13 L/kg.<br>PO(PHT) ⇨ IV(FOS-PHT) 1:1 PE<br>CSE: HoTN, burning, itching<br>Caution: Porphyria<br>Contra: Sinus bradycardia, heart block<br>Monitoring: Cardiac monitoring, BP monitoring<br>Prodrug of PHT w↓ side effects during infusion. Other info same as PHT |
| **VPA-IV** | IV load: 10-20 mg/kg (max rate 150 mg/min). PO ⇨ IV 1:1 |

References: *The Epilepsy Prescriber's Guide to Antiepileptic Drugs,* Patsalos & Bourgeois. 2010; *Complete Pocket Reference for the Treatment of Epilepsy*. Deray M, Resnick T, Alvarez L, (eds.), 2001; *Ultimate Review for the Neurology Boards*, pp. 91-104; Continuum. *Epilepsy* 2007;13(4):84-85; *Br J Clin Pharmacol* 2006;61:246-255; *JAMA* 2004;291(4):615-620; *Neurology* 2004;62:1252-1260.

## KETOGENIC DIET

*(J Child Neurol* 2009;24:979-988 & *Lancet Neurol* 2004;3:415-420)

**Def:** High-fat, low-carbohydrate (CHO) diet based on ketogenesis (production of ketones [acetoacetate, beta-OH-butyrate (BOHB)] when free fatty acids (FFA) are the primary energy source). Unclear but likely multifactorial antiepileptic mechanism.

**Indications:** Used most in pediatric epilepsy. Refractory epilepsy (med failure/toxicity, unacceptable sz freq), certain metabolic dzs [Glucose Transporter Def (GLUT-1), PDH].

**Contraindications:** Hyperlipidemia, pyruvate carboxylase deficiency, organic acidurias, disorders of fatty acid transport/β-oxidation, meds interfering w/CHO metabolism (steroids).

**Diet composition: Normal diet:** Calories from CHO 50%, fat 30%, protein 20%.

**KGD:** Fat 90%, CHO + protein 10%. Requires help of specialized nutritionist to allow sufficient nutrition for growth & development. **Variations:** Low glycemic index diet, modified Atkins, polyunsaturated fatty acids. Fat/(CHO + protein) ratio = 3-4:1. Urine check: 3-4+ ketones ~60-80 mmol/L, corresponds to 30-100 mg/dL 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:** *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 + 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; often asymptomatic. *Causes*: Meds interfering w/CHO metabolism, illness, noncompliance. *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/d 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:** Ketoacidosis → ↑Ca, $PO_4$ loss in urine; ↓ fluids, ↑ fat → ↓ $H_2O$-soluble vitamins. Dietary deficits. *Mgt*: Monitor height, weight, BMI; measure Cu, Se, Zn, Ca, Mg, PO4. Supplement calcium. Ketogenic nutritionist consult.

**Hyperlipidemia, pancreatitis:** High fat intake → ↑ cholesterol & triglycerides. Chronic effects unknown. Unclear role for lipid lowering meds. Ketogenic nutritionist consultation.



**Constipation:** Common. ↓ Fluid intake, ↓ bulk intake. *Mgt*: Encourage fluid intake, CHO-free laxative, mineral oil, suppositories.

**Urolithiasis:** Common (5%-8%): ↓ urinary pH, ↓ urine flow, ↑ calciuria, calcium supp. *Mgt*: Routine urine dipstick. ↑ Fluid intake, alkalizing agents, lithotripsy, diet discont'n (rare).

**Cardiomyopathy:** Rare, poorly understood: Low $HCO_3$ & high BOHB: Cardiomegaly,↑ QTc. *Mgt*: Prediet EKG. Monitor $HCO_3$ & 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. Controversial.

**Miscellaneous:** Behav Δs, GERD, med toxicity (carbonic anhydrase inhibitors: ↑ acidosis), surgery (CHO-free IVF, no drops in glucose. If pH drop after 3 h → R × 5-20 mEq $HCO_3$).

# SURGICAL TREATMENTS FOR EPILEPSY

## RESECTIVE EPILEPSY SURGERY

**Consider surgery early!** 36% of pts w/epilepsy have drug-resistant epilepsy. If not sz-free after adequate trial of 2 AEDs → chance of sz-freedom w/3rd AED <5%. In appropriately chosen pts (most ideal = lesional epilepsy w/concordance of EEG & MRI findings), epilepsy surgery offers a ↑↑↑ chance for sz-freedom c/w further AEDs. Surgical outcomes: 2-yr sz-freedom rates: mesial temporal epilepsy—68%; neocortical epilepsy—50% (*Neurology* 2005;65:912-918); 5-& 10-yr sz-freedom rates ˜40%-50% (*Lancet* 2011;378:1388-1395).

**Indications for surgery:** (1) Medically refractory epilepsy (determined by physician; failure of two appropriately chosen & tolerated AEDs to control szs when used for adequate period of time); (2) Epilepsy is disabling (determined by pt); (3) Reasonable chance to benefit.

**Goals of epilepsy surgery:** (1) Sz-freedom (curative) or ↓ in sz freq (palliative). (2) Reduce M + M of refractory epilepsy (accidental injuries, cognitive ↓, depression, SUDEP (depends on epilepsy severity, 1/3,000-1/200/yr), ↓ fertility, unemployment). (3) Reduce med side effects.

**Preoperative evaluation**

(A) *Localization of sz onset zone*

Determine sz onset zone & assess concordance with multiple approaches.

***Phase I monitoring (noninvasive)* includes the following:** *Long-term video EEG*—confirm dx of epilepsy; assess interictal abnls & capture multiple szs to determine sz type & localize site of sz onset. *MRI brain*—eval for structural abnls that may be epileptogenic; coronal FLAIR & T1 w/thin cuts to detect hippocampal sclerosis or cortical dysplasias; gradient echo for cavernomas or posttraumatic blood; gadolinium contrast for tumor, infection. *FDG-PET*—eval for area of hypometabolism, which often corresponds to sz focus, esp if temporal (false lateraliz'n rate in pts with unilateral temporal lobe epilepsy is only 1%-2%). *Neuropsych eval*—profile of cognitive deficits may help localize region of cortical dysfxn.

***Not routine, but sometimes helpful*:** *MEG*—source localizn of interictal discharges arising from sulci, which can be missed on scalp EEG. *Ictal SPECT*—inject isotope during sz (max uptake occurs 30-60 s after injection); scan after sz (isotope stays bound >1 h); area w/more binding (hyperperfused during sz) is potential sz focus. Subtraction of ictal & interictal SPECT with coregistration to MRI (SISCOM) has higher rate of localization than visual inspection alone. Useful for surgical evaluation of nonlesional epilepsy, but requires confirmation w/phase II monitoring. *Cerebral angiography*—characterize vascular lesions causing epilepsy. *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.

***Phase II monitoring (invasive):*** Performed only if results from phase I are inadequate for precise lesion localization. May include subdural grid/strip electrodes and/or intracranial depth electrodes. Need testable hypotheses to guide surgical placement of these electrodes.

(B) Assessment of surgical risk: *Neuropsych eval*—pre-op prediction is useful prior to L anterior temporal lobectomy. ↑ memory fxn pre-op → ↑ risk for memory decline. *Wada test*—intracarotid amobarbital (Amytal)—to determine dominant hem & whether hippocampus c/l to lesion can support memory. *fMRI*—language lateralization can predict verbal memory ↓ after left ATL, utility comparable to Wada (*Epilepsia* 2008;49(8):1377-1394).



**Focal epilepsies amenable to resective surgery:** Mesial temporal lobe epilepsy; slow-growing tumors (oligodendroglioma, fibrillary astrocytoma, pilocytic astrocytoma, mixed glioma, ganglioglioma, dysembryoblastic neuroepithelial tumor [DNET]); vascular malformations (cavernous angiomas, AVMs); cortical malformations (tuberous sclerosis; focal cortical dysplasia, polymicrogyria, focal subcortical heterotopia).

**Generalized epilepsies amenable to resective surgery:** Limited role for surgery in IGE. Exception: Corpus callosotomy to reduce drop attacks & other gen'd szs (palliative surgery).

## NEUROSTIMULATION DEVICES FOR EPILEPSY

Considered palliative procedures for pts w/refractory epilepsy not candidates for resective surgery. Do thorough investigation to assess candidacy for resective surgery first, esp as resective surgery may offer higher chance at sz freedom c/w neurostimulators, & implantation of neurostimulators may preclude certain aspects of future presurgical workup.

**Vagus nerve stimulation (VNS):** FDA approved in 1997 for adjunctive Rx of partial szs. *Procedure*: Outpt surgery, takes <1 h. Pulse generator implanted in L chest under clavicle; stimulator leads wrapped around L vagus nerve in neck & connected to pulse generator. Battery life 5-12 yr. *Modes:* Passive & on demand. *Passive*:

Generator continually sends timed impulses (preprogrammed parameters) to stimulate vagus n. *On demand*: Gives pt some control. Swiping magnet over generator → temporary ↑ in current & pulse width, which during an aura/sz/postictal period may abort sz, decrease sz severity, or abort cluster. *Mechanism of action*: Unk, potentially via changes in cerebral blood flow or neurotransmitter balance. *Efficacy:* At 1 yr, 35% of pts had >50% reduction in szs (median 45% sz reduction) *(Epilepsia* 2000;21(9):1195-1200*). Common SEs*: Alteration of voice, hoarse voice, throat pain, cough, dyspnea, paresthesias. *MRI:* Can undergo 1.5-3 T imaging of head or extremities using transmit/receive head or extremity coils. (Output current & Magnet current should be programmed to 0 prior to scan.) Exclusion: Region between C7 and T8 **cannot** be scanned due to proximity to device. Do not use open MRI scanners (safety only studied in closed scanners). *How to turn off:* Taping magnet over generator turns off VNS.

**Responsive neurostimulation (RNS):** FDA approved in 2013 for medicationrefractory partial or multifocal szs. Implanted electrodes detect abnl electrical activity (usually interictal abnls); when detected, electrical stim delivered to disrupt/abort sz at site of onset. Sz focus (where device is placed) must be clearly defined prior to placement. *Procedure*: Inpt surgery, takes 2-5 h. 1-2 depth/subdural strip electrodes are placed at sz focus. Neurostimulator is fixed to skull, & leads are connected. Device must be individually programmed for each pt to accurately detect szs & interictal abnls; requires considerable effort from both pt & physician. *Efficacy*: At 1 yr, 44% of pts had >50% ↓ in szs (median 44%). At 2 yr, 55% had >50% ↓ in szs (median = 53%) (*Epilepsia* 2014;55(3):432-441)*. MRI*: Contraindicated.

**Deep brain stimulation of the anterior nucleus of the thalamus (DBS):** Pending FDA approval. *Procedure*: Pulse generator implanted in R chest under clavicle. Multicontact depth electrode leads stereotactically implanted into bilateral anterior nuclei of the thalamus. Electrode leads are tunneled subcutaneously & connected to pulse generator. *Mechanism of action*: Unk., ?modulation of Papez circuit. *Efficacy*: At 2 yr, 54% had a >50% ↓ in szs (median = 56%). May be more effective for temporal lobe szs (*Epilepsia* 2010;51(5):899-908). *Adverse effects:* Depression (15%), memory impairment (13%), new/worse szs (9%).

## Sudden Unexpected Death in Epilepsy (SUDEP)

**Def & Common Features:** "Sudden, unexpected, witnessed or unwitnessed, nontraumatic & non-drowning death of a pt w/epilepsy, w/or w/o evidence of a sz & excluding documented status epilepticus, where post mortem does not reveal a toxicologic or anatomic cause for death" (*Epilepsia* 1997;38(suppl 11):S6-S8). SUDEP usually occurs in setting of convulsive sz, usually at night during sleep. Most are unwitnessed. **Epidemiology:** Pts w/epilepsy have 20× ↑ risk of sudden death compared w/gen'l pop'n. SUDEP accounts for 15% of epilepsy-related deaths. In pts at highest risk (refractory epilepsy), lifetime risk is 35%. **Risk factors:** Most consistent risk factor is ↑ freq of GTC szs. Compared to pts w/o GTC szs, pts w/1-2 GTCs/yr have 3× ↑ risk of SUDEP; 3-12 GTCs/yr = 7× ↑ risk; 13-50 GTCs/yr = 9× ↑ risk; >50 GTCs/yr = 15× ↑ risk. Pts on AED polytherapy have 3× ↑ risk c/w pts on monotherapy. Pts w/epilepsy for >15 yr have 2× ↑ risk c/w pts w/epilepsy for <15 yr. **Pathophysiology**: Potential



mechanisms of death (likely occur during/following convulsive sz) include (1) cardiac arrhythmia (from autonomic neural or cardiac dysfxn, channelopathy, or specific meds in susceptible pts) & (2) hypoventilation (central or obstructive); note that hypoxia/hypercapnia can precipitate cardiac arrhythmias. **Prevention:** Speculative; no trials assess efficacy of tx in preventing SUDEP: (1) reduce tonic-clonic szs w/AEDs or epilepsy surgery if indicated & (2) supervision of pt during night hrs (by another individual, or sz alarm to alert others); supervising individual can stimulate pt if pt stops breathing, potentially restoring normal cardioresp fxn (*Lancet* 2011;378:2028-38; *Nat Rev Neurol* 2014;10:271-282).

## ELECTROENCEPHALOGRAPHY (EEG)

One of few tools to assess brain fxn. ↑ temporal/↓ spatial resolution. Reflects synchronous activity (summed EPSPs) of populations of neurons, primarily in cortical gyri (oriented perpendicular to scalp). Deep/midline structures (e.g., medial frontal/temporal lobes, orbitofrontal & cingulate cortex) poorly represented on scalp EEG:

too far from electrodes.

**Uses of EEG:** Dx/management of status epilepticus (GCSE & NCSE); dx of szs; determination of risk of future szs in pt p/w sz; determination of brain fxn/extent of brain damage in comatose pts; ischemia monitoring (intraoperatively or post-SAH).

**Sensitivity of routine EEG in dx of epilepsy:** 1st EEG: 29%-55% sensitive; w/repeat EEGs: 60%-80% sensitive. Yield of repeat EEGs ↓ if initial EEG nl; limited yield after 4th EEG. 20% of pts w/szs will not have epileptiform discharges. Sleep ↑ sensitivity ˜15%. EEG w/in 24 h of sz ↑ sensitivity 15% (*Epilepsia* 1987;28:331; *Continuum Neurol* 2010;16(3):105-120).

**Indication for long-term monitoring (LTM) EEG:** (A) Dx: Paroxysmal spells/behaviors; PNES vs. sz. (B) Presurgical eval: classification of sz; lateralization/localization of abnls. (C) Quantification: Determine # & freq of szs/interictal abnls; quantify response to intervention; characterize subtle clinical manifestations (*J Clin Neurophys* 2008;25(3):170-80).

**Electrode placement:** International 10-20 system is standard, based on anatomical landmarks (Fig. 7-1). ***Electrode labels*** **:** Odd #s = left, even #s = right; lower #s = parasagittal, higher #s = lateral. 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. ***Other data*** **:** EKG, eye mvmt electrodes, resp monitor.

**Figure 7-1 Left: 10-20 EEG electrode placement. Right: double banana montage.**

**EEG montages:** Montage = choice of electrode channels & how they are displayed. Each channel is derived by taking difference of two inputs. Positive/negative convention*:* Positive potentials (input1 - input2 > 0) are displayed as a downward deflection; negative potentials (input1 - input2 < 0) are displayed as an upward deflection. Standard montages include the following: **(1) Referential**: Channels created by subtracting a common reference (e.g., an electrode placed at ipsi ear or vertex; or a calculated avg of all electrodes, or weighted sum of nearest electrodes) from each scalp electrode. Example channel derivations (input1 - input2): Fp1-ref, F7-ref, T3-ref,



T5-ref, etc. *Localization:* Focal abnls localize to the electrode w/the largest deflection. *Pros:* Easy to interpret, electrodes w/largest deflections mark region of greatest activity. *Cons*: A noisy reference electrode adds noise to all channels. **(2) Bipolar**: Channels created by subtracting adjacent electrodes from one another, proceeding down a chain. Longitudinal/anteroposterior (AP) bipolar is most common (aka “double banana,” Fig. 7-1, right). Chains: *L temporal*: Fp1 → F7 → T3 → T5 → O1; *L parasagittal*: Fp1 → F3 → C3 → P3 → O1; *Central*: Fz → Cz → Pz;

Similar for R side. Example channel derivations (input1 - input2), e.g., for L temporal chain: Fp1-F7; F7-T3; T3-T5; T5-O1. *Localization:* Focal abnls localize to point of phase reversal (usually neg phase reversal). *Pros:* Cleaner appearance (better noise cancellation); *Cons*: Activity at end of chains not easily assessed; lose information about absolute voltages; activity present in multiple adjacent electrodes tends to get canceled.

## GENERAL APPROACH TO READING EEGs

Structured approach should assess **symmetry, background frequency, organization, state changes**, response to **stimulation & activation methods**, & presence of **transients**.

**Background frequency:** Predominant frequency in absence of external stim. Conventionally divided into four frequency bands (see Fig. 7-2). Expected frequencies depend on location, state, & age. Multiple freqs can be present at any given time. For *nl healthy young adult*: ***Alpha*** (8-13 Hz) predominates in posterior leads when awake, alert, eyes closed. ***Beta*** (>13 Hz) is prominent frontally. ***Theta*** (4-8 Hz) is seen temporally, ↑ during drowsiness. ***Delta*** (<4 Hz) abnormal in awake EEG; a defining feature of slow-wave sleep.

**Organization:** Assessment of freqs & amps of EEG during awake resting state. Normal anteroposterior gradient: Lower voltage, higher freq (beta) anteriorly, transitioning to higher voltage, lower freq (alpha) posteriorly. Posterior dominant rhythm is sinusoidal alpha rhythm seen occipitally, best when awake w/eyes closed; may have ↑ amp over left hemisphere.

**Symmetry:** Asymmetry in frequency and/or amplitude may indicate underlying pathology (see Abnormal EEG Rhythms below). In epilepsy, determining asymmetries in interictal patterns, sz onset, & amplitude is critical in localization.

**Figure 7-2 EEG Background frequencies**

**State:** EEG differs w/state; various abnormalities often best seen in specific states (see Fig. 7-3). **(1) Awake, eyes closed:** Assess anteroposterior organization & presence of posterior dominant rhythm. **(2) Awake, eyes open:** Eye blinks in frontal leads. Attenuation of alpha, w/development of low-voltage, faster activity. Muscle artifact often present. **(3) Drowsiness:** Slow roving eye mvmts. Attenuation of occipital alpha. Increased frontocentral theta slowing. May see vertex waves (bilateral synchronous sharp waves maximal at Cz/C3/C4). May see ↑'d epileptiform (interictal) discharges. **(4) Stage 2 sleep:** Marked by appearance of sleep spindles (12-14 Hz synchronous waves, maximal over central region) & K-complexes (high-voltage polyphasic waves w/diffuse field). Frequent vertex waves & POSTS (see Normal EEG Variants below). Diffuse delta/theta slowing. ↑ epileptiform activity commonly present. **(5) Sleep stages 3-4:** Stage 3: 20%-50% delta, ↓ sleep spindles, & vertex waves. Stage 4: >50% delta activity, sleep spindles largely absent. **(6) REM:** Low-voltage fast activity, central sawtooth waves, rapid eye mvmts, absent

muscle artifact.

**Figure 7-3 EEG Awake & Asleep States**

**Activation procedures: (1) Stimulation:** Eye opening, calling name, startle response, noxious stim; used to assess EEG reactivity. **(2) Hyperventilation (HV):** Should see either no Δ or buildup of mod-high amplitude delta/theta w/frontal predominance, which returns to baseline w/in 1 min of stopping. May provoke sz in pts w/absence szs/IGE. **(3) Photic stim:** Strobe light in brief trains of fixed frequency (range 1-30 Hz). Normal responses: *Photic driving* (induction of occipital rhythm at harmonic/subharmonic of strobe flash freq) & *photomyoclonic response* (stimulus-induced contraction of frontal muscles). *Photoparoxysmal response* (stimulus-induced epileptiform discharges) may be seen in IGE. **(4) Sleep deprivation:** May ↑ likelihood of interictal discharges in pt w/previously nl EEG.

**Transients/interictal epileptiform discharges (IEDs):** Include *spikes, sharps, spike & waves, sharp-&-slow waves, & polyspike & waves*. See Epileptiform Abnormalities below.

## COMMON EEG ARTIFACTS

Artifacts can be recognized based on wave morphology, biological plausibility of electric field.

**Eye mvmts:** Cornea is positively charged relative to retina; eye mvmt potentials can contaminate the frontopolar/frontal leads. *Eye blink:* Initial (+) in frontopolar leads 2/2 eye closure, then (-) from eye opening; should be symmetric. *Lateral eye mvmts:* Produce opposite potentials in F7/F8, (+) in the direction pt is looking, (-) in the opposite direction. *Lateral rectus spikes* can be seen in F7/F8 immediately preceding lateral eye mvmts.

**Muscle:** Electromyogram from contraction of frontalis/temporalis/occipitalis muscles. Very fast spikes (<20 ms), high amplitude, “sputtering” quality. Can be rhythmic (i.e., chewing, tremor, walking). Usually during awake state, not be seen over midline (Cz/Pz).

**Glossokinetic:** Tip of tongue is positively charged relative to base of tongue. Tongue mvmts seen as broad field across the scalp, usually assoc'd w/speaking, swallowing.

**EKG:** Sharp EEG potentials may result from cardiac activity—correlate EEG w/ECG strip.

**Pulse (hemoballistogram):** Occurs when an electrode is placed over temporal artery (only seen in one electrode); waves are time-locked to EKG, but with fixed phase lag.

**Machine:** Stereotyped rhythmic potentials from machines (e.g., ventilator, IV drip, LVAD).

**60 Hz:** Ambient 60 Hz noise (50Hz in most of Europe, Asia, Africa, Australia) from nearby electrical devices/wiring are picked up, usually seen in electrodes w/high impedance.

**Electrode "pop":** Faulty electrode contact → momentary ↑ impedance. Resemble spikes but are restricted to a single electrode & lack an electrical field.

## NORMAL EEG VARIANTS

May resemble epileptiform discharges, but are not a/w ↑ risk of epilepsy. Characterized by monomorphic rhythms, often with higher freqs of 6 Hz or higher.



**Variants that mimic single epileptiform discharges:**

Benign epileptiform transients of sleep/small sharp spikes (**BETS/SSS**): Low-voltage temporal spikes w/broad field, occurring during drowsiness & light sleep. May be u/l or b/l, synchronous or independent.

**Lambda waves**: Positive & occipital, similar to POSTS, but seen during wakefulness w/lateral searching eye mvmts. Positive occipital sharp transients of sleep (**POSTS**): Triangular "sail" shaped, positive polarity, seen occipitally during light sleep.

**Variants that mimic repetitive epileptiform discharges:**

**Breach rhythm**: Rhythm of fast, spiky activity seen over site of prior craniotomy.

**Mu**: A motor-idling rhythm with arciform morphology at 7-11 Hz, suppresses w/mvmt of c/l limb. Seen during wakefulness, maximal at C3/C4; may be u/l or b/l.

**RMTD** (rhythmic midtemporal discharges, aka rhythmic temporal theta bursts of drowsiness, aka psychomotor variant): Rhythmic trains of 5-7 Hz monomorphic theta activity w/rounded tops & sharp bottoms. Seen during drowsiness or light sleep, may be unilat or bilat. May be mistaken for temporal lobe szs, but don't evolve in amp/freq/morphology.

**Wickets**: Arciform rhythm seen in temporal regions during drowsiness & sleep; may occur in fragments (called "wicket spikes") that resemble epileptiform discharges, but don't disrupt background or have after-going slow wave.

**14-& 6-Hz positive bursts**: Bursts of arciform morphology, where sharp phase has (+) polarity & rounded phase has (-) polarity. Can be seen at either 14 or 6 Hz, prominent over posterior temporal/occipital regions. Most freq seen in children.

**6-Hz spike-wave or phantom spike & wave**: Seen during awake & drowsy states, disappear w/deep sleep, usually last <2 s. Two variants: (1) FOLD (female, occipital, low amplitude, drowsy) & (2) WHAM (wakefulness, high amplitude, anterior, male).

## ABNORMAL EEG RHYTHMS

### Abnormalities of slow activity

**Focal slowing:** Indicative of transient or permanent focal lesions of the brain (e.g., infarct, tumor, abscess, contusion/hematoma, focal epileptic region/postictal state, multiple sclerosis, dementia). Delta indicates more severe disruption than theta activity. Irregular polymorphic delta activity suggests lesions of underlying WM. **FIRDA/OIRDA** (frontal/occipital rhythmic delta activity): Nonlocalizing; location (frontal vs. occipital) depends on age, not underlying lesion (FIRDA seen in teens & adults, OIRDA seen in kids). Nonspecific may be seen w/toxic-metabolic, ↑ ICP/hydrocephalus. Temporal intermittent rhythmic delta activity (**TIRDA**): Potentially epileptogenic,

high positive predictive value for temporal lobe epilepsy. **Generalized slowing:** Normal during drowsiness/sleep. Otherwise, nonspecific indicator of diffuse disturbance of cerebral activity (e.g., toxic-metabolic or hypoxicischemic encephalopathy, encephalitis, SAH, neurodegenerative dz). More severe encephalopathies a/w more diffuse slow activity, greater degree of slowing, & higher amplitudes.

**Abnormalities of fast activity:**

**Focal ↓ in beta**: May indicate focal cortical damage. **Focal ↑ in fast activity**: Consider breach rhythm (see Normal EEG Variants). **Diffuse excessive beta:** May result from sedating medications (benzodiazepines, barbiturates).

**Abnormalities of voltage asymmetry:**

**Focal voltage attenuation**: Suggests damage to cortex (e.g., acute infarct) or ↑ distance b/w cortex & skull (e.g., subdural hematoma/hygroma, skull hyperostosis). **Focal voltage increase**: Consider breach rhythm (see Normal EEG Variants).

**Epileptiform abnormalities:**

**Interictal epileptiform discharges (IEDs):** See figure. Imply irritated region of cortex; usu a/w epilepsy, but can be seen in 0.5% of nl individuals, more in pts w/neuropsych dz (*Electroencephalogr Clin Neurophysiol* 1993;86:75). **Characteristics of IEDs:** (1) Disrupt background rhythm, high voltage c/w background. (2) Duration 20-200 ms. (3) Surface negative polarity. (4) Physiologic field spanning >1 electrode. (5) Asymmetric, w/steep rising phase & slower falling phase that descends beyond isoelectric point. (6) May be accompanied by time-locked high-amplitude slow wave**. Types of IEDs** (see Fig. 7-4): *Spike* **:** 20-70 ms duration +/- subsequent high-voltage slow wave in delta/theta range ( *spike & wave*). *Sharp wave:* 70-200 ms duration +/- subsequent slow wave ( *sharp-&-slow wave*). *Polyspike & wave:* Multiple spikes followed by slow wave, common in myoclonic epilepsies. **Using IEDs for localization of sz onset:** In TLE, clear lateralization (all IEDs from one side) strongly suggests unilateral focus, a/w good surgical outcome ( *Neurology* 1990;40:413).

**Figure 7-4 Interictal epileptiform discharges on EEG** (*shown in referential montages*)

**Szs:** EEG correlate of sz can be highly variable. When present, EEG abnls during sz usually reveal onset location & pathway of spread. Ictal patterns include (1) well-defined epileptic rhythm (e.g., 3-Hz gen spike & wave); (2) rhythmic patterns of epileptiform discharges that evolve in frequency, location, or morphology; (3) rhythmic theta slowing; (4) paroxysmal fast activity; (5) no electrographic change on scalp EEG (usually in szs w/deep origin). See also Criteria for Nonconvulsive Sz table in this chapter for dx of electrographic szs.

**Periodic/Rhythmic Patterns seen in Critically Ill/Comatose pts**

May be difficult to distinguish clearly ictal from nonictal patterns; most fall on an “ictalinterictal continuum.” BZD trial may be useful in distinguishing (see Benzodiazepine Trial for Dx of NCSE table in this chapter) *(J Clin Neurophysiol* 2005;22:79-91).

**Patterns are named by combining a localizing descriptor** + **pattern type (see below),** e.g., GPD = generalized periodic discharges; LRDA = lateralized rhythmic delta activity.

**Localizing descriptors:** Generalized (G), lateralized (L), bilateral independent (BI), or multifocal (Mf). **Pattern types:** *Periodic discharges (PDs)*: Repeating discharges of uniform morphology at regular intervals. *Rhythmic delta activity (RDA):* Repeated delta waves of uniform morphology, w/o intervening interval b/w consecutive waves. *Spike-wave (SW)*: Spike, polyspike, or sharp wave followed by a slow wave in regularly repeating pattern, w/o intervening interval b/w consecutive waves. See Figure 7-5 ( *J Clin Neurophysiol* 2013;30:1-27).

**Figure 7-5 Common Periodic Patterns in Critically Ill Pts** (Adapted from *J Clin Neurophysiol 2013;30: 1-27*)

**Diseases associated with characteristic EEG abnormalities:**

**Herpes simplex virus:** Temporal lateralized periodic discharges (LPDs) are an early & classic finding. May also see focal slowing, focal epileptiform discharges, & szs. Note, LPDs are not specific for HSV.

**Creutzfeldt-Jakob disease:** Initially ↑'d focal or generalized theta slowing. Subsequently evolves to periodic sharp waves (GPDs) at 1 Hz & may be assoc w/myoclonic jerks. Eventually degenerates into gen low-voltage tracing. Note: GPDs not specific for CJD.

**Subacute sclerosing panencephalitis:** High-voltage repetitive polyspike-& sharp-&-slow wave complexes, recurring every 4-15 s, a/w rapid or slow myoclonic jerks.

# Delirium

Marcelo Matiello

Julie J. Miller

Eyal Y. Kimchi

## GENERAL INFORMATION

**Definition:** Sudden severe confusional state due to physical or mental illness. Impaired attention/speed/clarity/coherence of thought. *Synonyms*: Delirium, acute confusional state, toxic-metabolic encephalopathy.

**DSM 5 (five criteria): A**. Disturbance in attention & awareness. **B**. Develops over hours to days, represents acute change from baseline, & tends to fluctuate in severity during the course of a day. **C**. Additional disturbance in cognition (e.g., memory, orientation, language, visuospatial ability, or perception). **D**. Disturbances in criteria A & C not better explained by pre-existing/evolving neurocognitive d/o & do not occur in context of severely reduced arousal such as coma. **E**. Evidence (Hx, exam or lab findings) that disturbance is due to another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or to multiple etiologies.

**Mechanism:** Pathophysiology largely uncharacterized. ↑ GABAergic & dopaminergic activity &/or central cholinergic deficiency may play roles. Management is empirical.

**Risk factors:** Advanced age (>80 yo) & one or more of the following: high severity of clinical/surgical illness, dementia, use of sedative medications, visual impairment, dehydration, postoperative, severe pain, anemia.

**Triggers:** Exposure to noxious insults or precipitants in vulnerable patients. Seemingly benign insult (e.g., sedation) may cause delirium in vulnerable pt. Healthy people usu require multiple insults (e.g., gen anesthesia, major sx, psychoactive drugs, long ICU stay). Therefore, multicomponent approaches are most effective.

**Presentation:** Most common inpatient behavioral disorder (30% elderly medical pts, 10%-50% elderly surgical pts, up to 80% of ICU patients). Two main forms: Hypoactive & agitated; may also present as a mix. ***Hypoactive****:* Inattention, disordered thinking, & ↓ level of consciousness. ***Agitated****:* ↑ vigilance, psychomotor & autonomic overactivity; agitation, excitement, tremulousness, hallucinations, delusions. ***Variations****:* Hyperactivity w/↑ sympathetic activity, sleep Δs, emotional Δs (e.g., fear, depression, euphoria, perplexity). *Elderly*: Usu quiet, withdrawn, hypoactive (often underdiagnosed or mistaken for depression).

**WORKUP:** (1) Recognition of delirium, (2) identification of cause.

**HPI: Difference from baseline functioning, prior episodes of AMS/delirium, hx of dementia, risk factors/predisposing conditions or meds, recent febrile illness, & history of EtOH/drug abuse.**

*General examination:* VS, hydration, infectious foci, e/o COPD, jaundice, hepatic failure, stigmata of renal failure, needle tracks, or cherry red lips (e/o CO poisoning). Breath: Alcohol, fetor hepaticus, uremic fetor, or ketones. Bitten tongue and/or fx/dislocation of shoulder (r/o sz). Autonomic si/sx (tachycardia, sweating, flushing, dilated pupils).

*Neurologic examination*: Level of consciousness & attention. Look for focal signs, multifocal myoclonus, asterixis, & postural action tremor. Loss of VOR or nystagmus w/unexplained ocular palsies sparing pupillary reactivity raises possibility of Wernicke encephalopathy.

**Bedside tests of attention:** Month of year backward. Digit span: Repeat series of random numbers. Abnl: Inability to repeat >5. Vigilance “A” test: Read 30 random letters. Pt taps on “A”. Abnl: Miss >2.

**MONITORING:** Two recommended tools, esp. in ICU: the Confusion Assessment Method for ICU (CAM_ICU), or Intensive Care Delirium Screening Checklist (ICDSC).

### Laboratorial testing

- Fingerstick gluc, chem10 (incl. Na, K, BUN, Cr, CO2, gluc, Ca, Mg), CBC, UA, LFT, NH3, ESR, CRP, TSH/fT4, UA, RPR, TSH, CXR, tox screen (blood, urine), drug levels (e.g., digoxin, Li, quinidine), $B_{12}$, methylmalonic acid, homocysteine, thiamine, +/- BCx.
- 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 ↑ ICP



**Imaging:** *Unnecessary if:* clear treatable cause, no trauma, nonfocal exam. In pts w/stroke risk factors, may need MRI. Sustained delirium possible in R MCA infarct affecting prefrontal & posterior parietal areas, PCA infarcts resulting in bilateral or left-sided occipitotemporal lesions (fusiform gyrus), occlusion of the ACA w/involvement of the anterior cingulate gyrus & septal region, ant choroidal infarct affecting caudate or mult diffuse emboli.

**EEG:** (**1**) Exclude seizures, esp NCSE/subclinical szs. (**2**) Help w/dx (diffuse background slowing in metabolic encephalopathies, viral encephalitis; triphasic waves w/hepatic encephalopathy, uremia, sepsis; PLEDs/LPDs in temporal leads in HSV encephalitis; NCSE common in ICU w/unexplained AMS; detection may require >24 h monitoring) (Jacobson S, et al. *Semin Clin Neuropsychiatry* 2000;5(2):86-92).

## DIAGNOSIS OF DELIRIUM

(Inouye SK, et al. *Lancet* 2014;383:911.)

| **Validated Predisposing Factors** | |
|---|---|
| Dementia | Comorbidity or severity of illness |
| Cognitive impairment | Depression |
| History of delirium | History of transient ischemia or stroke |
| Functional impairment | Alcohol misuse |
| Visual impairment | Older age (≥75 yr) |
| Hearing impairment | |
| **Validated Precipitating Factors** | |
| Drugs (see below) | Infection |

| | |
|---|---|
| Use of physical restraints | Trauma admission |
| Use of bladder catheter | Surgery (especially aortic aneurysm repair; noncardiac thoracic; neurosurgery) |
| Increased serum urea or increased BUN:creatinine ratio | Urgent admission |
| Abnormal serum albumin | Coma |
| Abnormal sodium, glucose, or potassium | Metabolic acidosis |

**Drugs that Commonly Cause Confusional States**

| | | |
|---|---|---|
| **Analgesics**<br>NSAIDs, opioids (esp meperidine)<br>**Antibiotics**, **antivirals**<br>Acyclovir, aminoglycosides, amphotericin B, antimalarials, cephalosporins, cycloserine, fluoroquinolones, isoniazid, interferon, linezolid, macrolides, nalidixic acid, penicillins, rifampin, sulfonamides | **Anticonvulsants**<br>Carbamazepine, phenytoin, valproate, vigabatrin<br>**Antidepressants**<br>Mirtazapine, SSRIs, TCAs<br>**Cardiovascular meds**<br>Antiarrhythmics, β-blockers, clonidine, digoxin<br>**Corticosteroids** | **GI drugs**<br>Antiemetics, antispasmodics, H2 blockers, loperamide<br>**Herbal drugs**<br>Atropa belladonna extract, henbane, mandrake, Jimson weed, St. John's wort, valerian |
| **Anticholinergics**<br>Atropine, benztropine, diphenhydramine, scopolamine, trihexyphenidyl | **Dopamine agonists**<br>Methyldopa, amantadine, bromocriptine, levodopa, pergolide, pramipexole, opinirole<br>**Hypoglycemic agents**<br>**Diuretics** | **Hypnotics**, **sedatives**<br>Barbiturates, benzos, muscle relaxants, baclofen, cyclobenzaprine<br>**Other**<br>Disulfiram, donepezil, interleukin-2, lithium, & phenothiazines |

An extensive list of medications associated w/delirium in the elderly is available at the American Geriatric Society website (U*pdated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults—2012*).

# MANAGEMENT OF DELIRIUM

(Barr J, et al. *Crit Care Med* 2013;41(1):278-280.)

Clinical trials for delirium management have focused mainly on antipsychotic or sedating drugs to reduce agitation & behavioral symptoms. Growing evidence suggests that antipsychotics & sedatives may prolong duration & associated cognitive impairments.

**Main approaches:** (1) Avoid/remove aggravating factors; (2) identify & treat causes; (3) cognitive rehabilitation; (4) drug reduction, drug-sparing approaches (i.e., substitution for less toxic alternatives); (5) sleep enhancement (e.g., melatonin); (6) reduction of pain & stress (including complementary & alternative medicine).

**Prevention interventions:** ↓ freq & duration, no proven effect on severity: (1) Orientation protocols, cognitive stimulation 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. (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) Avoid if possible: Changes of environment (e.g., room changes), physical restraints, constipation, anticholinergic drugs, urinary & fecal catheters.

**Delirium & pain:** Complex relationship b/n pain & delirium: Undertreated pain → agitation & confusion, but opioid use → delirium. "Crescendo pain" may represent a form of delirium. Meperidine in older pts often exacerbates delirium.

**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, agitation ("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)<br>Olanzapine (Zyprexa)<br>Quetiapine (Seroquel) | 0.5 mg bid<br>2.5-5 mg qd<br>12.5-25 mg bid | EPS, ↑ QTc | Similar efficacy to Haldol. May ↑ mortality in demented pts—avoid longterm use |
| ***Benzodiazepines:*** *Only for delirium 2/2 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 |
| **Agitation PRN Therapy** | | | |
| ***Antipsychotics*** | | | |
| Haloperidol | 0.5-10 mg PO (young/healthy pts); 0.25-2.0 mg PO in elderly & frail | EPS, ↑ QTc | May ↓ delirium incidence. Avoid IV route if possible (short acting).<br>IM/IV 2x potency of PO [1 mg PO equivalent to 0.5 mg IM/IV] |

Obtain ECG. If QTc ≥450 msec, weigh risks & benefits of available Rx options & monitor QTc interval if antipsychotic started. Check serum Ca, K, & Mg. Keep $K^+$ >4 & $Mg^{++}$ >2 mEq/L. Normalize serum Ca. Avoid of other QTc-prolonging medications.

**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).

# Poisons and Vitamin Deficiencies

Julie J. Miller

Marcelo Matiello

Eyal Y. Kimchi

## INITIAL MANAGEMENT & BASIC APPROACH FOR POISON INGESTION

- Supportive care: Monitor airway, breathing, circulation, vitals. Obtain IV access.
- Consider IV thiamine, glucose, naloxone for altered mental status, esp coma or sz.
- Diagnosis often clinical (history ± exam), followed by lab confirmation (serum/urine).
- Identify possible toxin/poison by si/sx (see below) & history: What? How much? When? Route of ingestion (e.g., oral, nasal, IV, rectal, etc.)? Obtain prescription records & bottles for pill counts. Consider over-the-counter meds, coingestions, local substance use patterns, & occupational exposures. Assess intention/suicidality.
- Labs: electrolytes, anion gap, BUN, Cr, LFTs, NH3, CBC, PTT, PT/INR, serum/urine tox screen including acetaminophen & alcohol levels, Osm gap, lactate, CK, ABG.
- Studies: EKG. CT/MRI if ? trauma or neurovascular complications/focal findings. EEG if ? sz. CXR for resp distress (aspiration, ARDS). Abdominal imaging if ? body packs.

| **Common Exam Findings Associated with Ingestion** | |
|---|---|
| **Clinical Pattern** | **Poison** |
| Sedation: *Cognitive impairment*, *lethargy*, *coma*, *flaccidity*, *bradycardia*, *hypotension*, *apnea*, *slurred speech*, *ataxia*, & *varied pupils* | Miosis: Opioids, barbiturates, benzos, & sympatholytics<br>Mydriasis: EtOH, tricyclics, antihistamines, & antipsychotics<br>Other: Cannabis, AEDs, & muscle relaxants |
| Sympathomimetic syndrome: *Tachycardia*, *arrhythmias*, *HTN*, *vasoconstriction*, *agitation*, *psychosis*, *szs*, *diaphoresis* & *hyperthermia*, *hyperreflexia*, & *coma* | Cocaine, amphetamines, PCP, MAOI, sympathomimetics. Withdrawals (w/d) from sedatives (see above) |
| Anticholinergic syndrome: *Tachycardia*, *midriasis*, *dry mouth*, *constipation*, *urinary retention*, *agitation*, *szs*, & *hyperreflexia* | Anticholinergics, tricyclics, antipsychotics, antihistamines, & mushrooms |
| Cholinergic syndrome: *Bradycardia*, *diaphoresis*, *diarrhea*, *szs*, & *miosis* | Acetylcholinesterase inhibitors, nicotinic/muscarinic agents, organophosphates |

- Poison control hotline (24/7): 1-800-222-1222, esp to consider antidotes.
- Additional detox methods should be used selectively (early <1 h, or in severe cases): Activated charcoal (as effective as gastric lavage, fewer contraindications/complications), urinary alkalinization, hemodialysis, chelation
- Additional management considerations
  - Agitation: antipsychotics, benzos if due to alcohol w/d or szs
  - Seizures: benzos



  - Dystonia: diphenhydramine or benztropine iv
  - Hyperthermia: cooling blankets, paralysis w/nondepol agents
- If suspected attempted suicide, continuous suicide watch & psychiatry consult

## STIMULANTS

**Cocaine:** Blocks presynaptic reuptake of monoamines (esp in ventral tegmental area, nucleus accumbens, prefrontal cortex) → euphoria, adrenergic stim; blocks voltagegated Na channels → local anesthesia, cardiac arrhyth.

**Presentation (acute intox)**: Sympathomimetic syndrome; szs; stroke: Ischemic (vasospasm, intravascular thromb from ↑ platelet agg) & ICH (reperfusion or HTN). Mvmt d/os: dystonic reactions, buccolingual dyskinesia, choreoathetosis, akathisia.

**Rx:** Supportive measures; avoid β-blockers (coronary vasoconstriction, end-organ ischemia); szs: benzos best; VPA second line.

**Withdrawal:** Craving, depression (including suicidal ideation, psychomotor retardation), anhedonia, fatigue, ↑ sleep; ±musculoskel pain, tremor, invol mvmts.

**Methamphetamine:** Sympathomimetic. Causes release & prevents reuptake of monoamines. Long duration of action (20 h). Can lead to coma.

**Sympathomimetic crisis:** Syndrome as above → to CV collapse, stroke/ICH. MDMA is amphetamine derivative w/a similar si/sx; may → severe hypo-Na 2/2 SIADH & fatal szs.

**Rx:** Correct electrolytes (special attention to Na in case of MDMA). Severe HTN: BZ, nitroprusside, or phentolamine. *Avoid* β-blockers (including labetalol).

**Phencyclidine (PCP):** Dissociative anesthetic similar to ketamine (noncompetitive NMDA antagonist). Blocks reuptake of monoamines: sympathomimetic. Sigma receptor: Analgesia, sedation, anticholinergic.

**Presentation:** Violent/bizarre behavior, visual & auditory hallucinations, psychosis, sympathomimetic sx, vertical & horizontal nystagmus. High doses: Disorientation, agitation/violence, acidosis, szs, resp arrest, coma, rhabdomyolysis.

**Rx:** HTN: BZ, nitroprusside, phentolamine, labetalol. Gastric lavage for early si/sx or potentially lethal dose.

## OPIOIDS

**Heroin:** Pure opioid agonist. Metabolized to active metabolites (including morphine).

**Prescription opioid abuse:** Oxycodone, hydrocodone, morphine. Regular use → tolerance, predisposes to w/d. Opiate receptors: **Mu**: analgesia, euphoria, respiratory depression, cough suppression, miosis, sweating,

nausea, & vomiting. **Kappa & Delta**: analgesic.

**Presentation:** "Rush": somnolence, calmed sensation, apathy, feeling of self-sufficiency. Anticholinergic effects: N/V, itching. Overdose → respiratory depression, coma, hypothermia, szs. Miotic pupils. Inhalation of heroin vapor can lead to cerebral leukoencephalopathy (coma, severe neurologic damage, death).

**Dx:** Urine drug screen often positive up to 3-4 days after last use.

**Rx:** Naloxone IV. Goal: Normal ventilation (not normal level of consciousness). Start 0.04 mg IV, titrate up 2 mg IV every few min until desired response (normalization of respiration or ↑ responsiveness). Repeat effective dose q2-3 min as needed, up to max total dose of 10 mg. If no resp after 5-10 mg, dx must be reconsidered (Vanden Hoek TL, et al. *Circulation* 2010;122:S829-S861). 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. Correct low Ca, K, Mg.

**Opioid Withdrawal:** Can develop <6-8 wk w/chronic daily use. Early sxs: Fear of w/d → craving, anxiety, insomnia, yawning, rhinorrhea, lacrimation, salivation, stomach cramps, mydriasis, arthralgia, & myalgias. Up to 7-10 days: HTN, ↑ tremor, myoclonus, f/c, n/v/d, piloerection.

**Rx:** Oral, longer-acting opiate agonists (methadone, buprenorphine). Alpha-2-adrenergic agonists (clonidine). Possible addition of naltrexone. *Loperamide*: Abd sxs.

## MARIJUANA AND CANNABIS

Contains psychoactive substance tetrahydrocannabinol (THC).

**Presentation:** Somnolence, euphoria, impaired concentration & short-term memory, tachycardia, conjunctival injection, dry mouth. May precipitate panic attack, paranoia, psychosis in pts w/pre-existing psychiatric dx. **Dx:** Urine drug screen. **Rx:** Reassurance, benzos & antipsychotics as need for acute psychiatric symptoms.



## BARBITURATES

**Physiology & metabolism:** Potentiate effect of GABA at GABAA receptors by ↑ duration of chloride channel opening. *Short-acting*: Anesthetics. *Intermediate action:* Butalbital (Fioricet/Fiorinal), amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal). *Long-lasting*: Phenobarb, primidone. Lethal doses: 6-10 g phenobarb, 2-3 g other barbs.

**Presentation:** Sedation pattern above

## ALCOHOL INTOXICATION

### General considerations

Tox screen should include EtOH, methanol, ethylene glycol, isopropyl alcohol, acetaminophen, salicylate (coingestion common). Osm gap: suspect other alcohols other than EtOH for Osm gap >10 after correcting for EtOH:

- Osm gap = Osmol measured - Osmol calc
- Osm measured = 2 × Na + BUN/2.8 + glucose/18 + ethanol/4.6

Thiamine 100 mg + folate 1 mg + MVI 1 amp to 1 L of D5NS + 3 g MgSO4. Expect ↓ of blood alcohol level (BAL) of 20 mg/dL/h w/EtOH.

### Ethanol

Most commonly abused drug. Stimulates GABA-A Rs, suppresses NMDA Rs. Peak serum levels: 30-90 min after ingestion w/empty stomach. Chronic use → (1) downregulation of GABA receptors → tolerance; (2) up-regulation of glutamate receptors (to maintain normal state of arousal). Abrupt discontinuation → imbalance (less GABAergic, more glutamatergic effects). Metabolism by alcohol dehydrogenase follows zero-order kinetics.

**Presentation/syndromes:**

**Acute intoxication:** 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 + 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, arm tremors, dysarthria, diplopia, blurred vision.

**Cerebral atrophy:** Ventricular enlargement w/cognitive dysfxn**.**

**Neuromuscular issues:** Peripheral neuropathy, acute/chronic myopathy.

## 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, vomiting, abd pain.

**Diagnosis:** Typical si/sx + anion gap metabolic acidosis (serum bicarb typically <10 mEq/L). Funduscopy: Hyperemia, papilledema. Check methanol level, Osm gap, ABG.

**Management:**

- Fomepizole (inhibitor of alcohol dehydrogenase): 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 (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 PCO2 <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 → glycolic acid & 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. If severe: Coma, hypotonia, sz. **12-24 h cardiopulmonary:** ↑ HR, RR, BP, arrhythmias, pulm edema. 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. Ethylene glycol level, Osm gap.

**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, shock.

**Dx:** Serum isopropanol level. Does not produce anion gap. Acetone → falsely ↑ Cr.

**Rx:** Dialysis for refract hypotension or level >400 mg/dL.

## ETHANOL WITHDRAWAL

**Presentation:** Discontinuation/significant ↓ in EtOH intake. Insomnia, anorexia, n/v, tremors, anxiety, hallucinations, palpitations; autonomic hyperactivity (tachycardia, HTN, hyperreflexia, irritability, sweating, low-grade fever). Onset ~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 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, w/d 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 underlying conditions.

**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.

**In-house Rx:** Thiamine 100 mg IV qd indefinitely (consider higher doses for Wernicke). 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 or propofol. Do not treat psychotic sx w/phenothiazines or butyrophenones (may precip sz).

Symptom-triggered therapy (based on CIWA scale) decreases both treatment duration & amount of benzodiazepine used & as efficacious as standard fixed-schedule therapy (*JAMA* 1994;272:519-523).

| Benzodiazepine Management Protocol for Alcohol Withdrawal |
| --- |
| **Assessment protocol**<br>Initial: Vitals, CIWA-Ar score (helpful to use standard tracking sheet)<br>Initial CIWA-Ar score ≥ 8→<br>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.<br>CIWA-Ar score < 8 × 72 h → discontinue assessments.<br>CIWA-Ar score ≥ 8 at any time; see above.<br>Administer benzodiazepines according to schedule below. |

Consider Rx to ICU if: CIWAS-Ar >35, q1h required for >8 h, 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 w/d:

- Initial CIWA score 15 or higher
- History of severe alcohol w/d
- History of w/d-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/with 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.
Central alpha-2 blockers (clonidine, dexmedetomidine)

# MEDICATION OVERDOSES

## Aspirin and salicylates

Includes: Acetylsalicylic acid (ASA), methyl salicylate, bismuth subsalicylate (ingredient in OTC meds, e.g., Pepto-Bismol, Kaopectate).

**Physiology & metabolism:** Metab in liver via glucuronidation, oxidation, & glycine conjugation. First-order kinetics at therapeutic doses. ↑ doses/chronic use, zeroorder kinetics.

**Presentation** (not evident until 6-12 h after ingestion): Tinnitus, vertigo, n/v/d (at 150-300 mg/kg), hyperventilation, ΔMS, szs (>300 mg/kg).

**Dx:** High suspicion if high anion gap acidosis & tinnitus are present. Elevated anion gap, UA w/ketones.

**Rx:** Hydration & correction of pH to enhance excretion. UOP monitoring (goal 1-2 mL/kg/h). *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.

## Lithium

Monovalent cation, used in BPD. 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:** Can be *acute* (pts w/o tissue body burden of Li), *acute-onchronic* (pts who take lithium regularly & recently took larger dose), or *chronic* (pts w/large body burden of Li). N/v ± diarrhea, hyperreflexia, cerebellar (tremor, asterixis, ataxia, nystagmus), myoclonus, confusion, coma, sz, ↓ renal fxn, & diabetes insipidus. "Syndrome of irreversible lithium-effectuated neurotoxicity" (SILENT): Impaired cognition, sensorimotor PN.

**Dx:** 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 posttetanic 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).

**Clinical presentation of toxicity:** *Mild*: 20-50 mg/L: nystagmus, mild ataxia. *Severe*: 50-100 mg/L: severe ataxia, dysarthria, confusion; >100 mg/L: 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). Can also cause TEN or Stevens-Johnson syndrome. Leukopenia, PN, gum hypertrophy. Permanent *cerebellar* injury after prolonged toxicity.

**Dx:** Clinical plus serum levels. Correct for alb: PHT level = PHT plasma/[(0.02 × alb) + 0.1].

**Rx:** Fall prec. Avoid lidocaine if intubation required. Brady stops when infusion stopped; rarely require pacing. Activated charcoal w/in 4 h of oral overdose.

## Ergots

**Clinical presentation**: Severe burning sensation in limbs due to vasoconstrictive effects of ergot alkaloids. Neuropsychiatric SEs: Halluc, irrational behavior, szs.

## Digoxin

Inhibits Na-K ATPase, ↓'s conduction at SA & AV nodes. Toxicity result of ↑ serum levels (e.g., renal

insufficiency, drug interactions) or ↑ sensitivity (e.g., hypoxemia, hypoK, hypoMg, hyperNa, hyperCa, acid-base disturbances, aging, coronary ischemia).

**Clinical presentation:** Nausea, vomiting, diarrhea, abdominal pain; palpitations, syncope, dyspnea; confusion, somnolence, dizziness, HA, paresthesias, hallucinations. Visual: disturbed color vision (often yellow-green coloring), blurred vision, double vision, scotomas, arrhythmia (bradycardia).

**Dx:** Check plasma levels (at least 6 h after last dose); repeat levels q2h until tox resolved.

**Rx:** Optimize clearance. Symptomatic bradycardia: Atropine 1 mg. Activated charcoal if ingestion w/in previous 6-8 h. Repeated doses may be recommended. Digoxin-fab fragments for dig toxicity w/dysrhythmias a/w hemodynamic instability, altered MS, hyperK, digoxin level >10 ng/mL. Correct electrolyte abnls, esp hypoK & hypoMg.

**Caution:** Beware using Kayexalate concurrently w/insulin/glucose/bicarbonate and/or digoxin-fab fragments: Risk of → hypokalemia. **AVOID** giving Ca: can → VT, VF (intracellular Ca).

## Antipsychotics

Postsynaptic blockade of dopamine receptors. First generation: Haloperidol, thioridazine. Atypical agents: Risperidone, quetiapine, clozapine, olanzapine.

**Clinical presentation:** Sedation, lethargy, agitation, anticholinergic syndrome, occasionally depressed resp status (quetiapine), szs (clozapine). *Extrapyramidal syndromes*: dystonia, parkinsonism, akathisia. *Neuroleptic malignant syndrome*: AMS, agitation, muscle rigidity, hyperthermia, autonomic instability, miosis. NMS similar to malignant hyperthermia 2/2 general anesthetics, succinylcholine

**Dx:** Clinical +/- serum levels. Check CK if concern for NMS.

**Rx:** Decontamination w/activated charcoal if w/in hours of ingestion. Give anticholinergics (diphenhydramine, benztropine) for EPS; consider dantrolene, benzos, or benztropine for NMS.

## Tricyclic antidepressants

Inhibit presynaptic reuptake of norepinephrine & serotonin. Includes imipramine, amitriptyline, nortriptyline. Commonly used for depression, migraine, & neuropathic pain.

**Clinical Presentation:** Sedation, delirium, hallucinations, anticholinergic syndrome, szs, cardiac arrhythmias, & conduction delay. *Serotonin syndrome*: confusion, restlessness, agitation, hallucinations, autonomic dysfunction, szs, hyperreflexia, clonus, rigidity, mydriasis.

**Dx:** Clinical, tox screen/levels, EKG (particularly look for QRS prolongation).

**Rx:** Activated charcoal, sodium bicarbonate IV (goal pH > 7.45) for cardiac toxicity/arrhythmias.

## Selective serotonin reuptake inhibitors (SSRI)

Inhibit reuptake of serotonin by neurons in CNS. Includes paroxetine, fluoxetine, citalopram.

**Clinical presentation:** Tremors, akathisia, dyskinesias, n/v, rarely mild CNS depression. *Serotonin syndrome*: Confusion, restlessness, agitation, hallucinations, autonomic dysfunction, szs, hyperreflexia, clonus, rigidity, mydriasis; usu caused by combination of serotonergic agents including MAOIs, fentanyl, tramadol, metoclopramide, ondansetron, cocaine, amphetamine & derivatives.

**Dx:** Clinical, tox screen. Hunter criteria for diagnosis of serotonin syndrome (must have one): spontaneous clonus, inducible clonus + agitation or diaphoresis, ocular clonus + agitation or diaphoresis, tremor + hyperreflexia, hypertonia + temp 38°C + ocular or inducible clonus.

**Rx:** If severe serotonin syndrome, cyproheptadine (nonspecific serotonin receptor antagonist) 12 mg followed by 2 mg q2h until clinical response; only PO or NG formulation available.

# PLANT & FUNGAL DERIVATIVES

**Nutmeg:** 60 g or 12 teaspoons may produce various neuropsychiatric s/sx: dizziness, 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. Acute spastic nonprogressive paraparesis, central visual field loss. Chronic: Ataxia, PN.

**Lathyrism:** Grass pea (*Lathyrus sativus*). Beta *N*-oxalylamino-L-alanine; s/sx: Acuteonset pain, spastic paraparesis.

# NEUROTOXINS

## Botulism

*Clostridium botulinum*—spore-forming Gram-positive rod. Toxin destroyed by heat, but spores heat-tolerant.

**Pathophysiology:** Protease that attacks NMJ, preventing vesicular fusion w/presynaptic membrane & acetylch release → flaccid paralysis beginning w/diplopia, bulbar muscles & descending over hours-days to resp failure.

**Ddx:** GBS, myasthenia gravis, tick paralysis, stroke (brainstem), heavy metal/organophosphate poisoning.

**Dx:** Hx, Tensilon test (r/o MG), CSF studies (nl), neuroimaging, EMG w/rep stim., cxs from serum, stool, & leftover food samples. Mouse bioassay: Inoculate w/sample; see whether mouse develops botulism.

**Rx:** Heptavalent antitoxin works if given early. Organism is sensitive to penicillin & metronidazole. Supportive.

## Tetanus

Toxin enters at NMJ & migrates into CNS by retrograde axonal transport.

The toxin tetanospasmin inhibits synaptobrevin → blocks neuroexocytosis, GABA release.

**Clinical features:** Opisthotonos, risus sardonicus, trismus. Any sensory stimulus produces muscle overactivity & tetanic spasm. Laryngospasm can lead to asphyxia.

**Rx:** Clean & debride wound. Give dose of antitoxin. Abx [IV PCN or metronidazole (1 g q8h for both)] typically given for 1 wk. Control spasms w/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).

# HEAVY METALS

## Thallium

Structurally similar to potassium; disrupts K-dependent processes.

**Clinical features:** Painful polyneuropathy w/distal weakness, optic atrophy, 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 tid.

## Arsenic

Inorganic forms, particularly trivalent, more toxic than organic. Binds to sulfhydryl groups, inhibits many enzyme

systems (cellular respiration, gluconeogenesis, etc.).

**Clinical features:** GI distress, arrhythmias, renal failure, encephalopathy, coma, szs, painful sensorimotor ascending peripheral neuropathy resembling GBS, Mees lines (discoloration on nails) classic (but can be seen in any heavy metal poisoning).

**Treatment:** Decontamination if recent ingestion. Chelating agents (dimercaprol or succimer) only used in severe toxicity. Anticipate & treat cardiac arrhythmias; maintain high UOP to facilitate excretion.

### Mercury

Inhib choline acetyltransferase (last step in acetylcho prod) → motor & cog dysfxn. Organic short-chained methylmercury worse CNS side effects than inorganic forms.

**Clinical features:** Tremor, ataxia, confusion, depression (may be delayed). Acrodynia (pink disease): Hands & feet pink, painful neuropathy in children. Exposure in pregnancy → developmental abnormalities.

**Rx:** Decontamination, esp exposed skin. Aggressive hydration. Chelation Rx for acute inorganic mercury poisoning (DMSA, dimercaprol, penicillamine).

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### Lead

**Pathophysiology:** Interferes w/sulfhydryl-dep enzymes (particularly in heme synthesis), competes w/Ca2+-dep rxn, accumulates in neuroglia.

**Clinical features**: Adults: Nausea, abd pain, anemia, irritability, insomnia, lethargy or hyperactivity, headaches, szs; coma & death if severe. Chronic toxicity: Neuropathy, painful arthralgias, bluish “lead line” along gums. Children: Dev delay, cerebral edema. Peripheral blood smear: Basophilic stippling, microcytosis, & hypochromasia.

**Rx:** Remove the source of contamination. Acute toxicity: Chelation w/DMSA or EDTA.

## 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). Often coexists w/$B_{12}$ deficiency. **Myelopathy or myeloneuropathy** characterized by spasticity, gait d/o, sensory ataxia, paresthesias. Copper supplementation does not always reverse. **Rx:** Stop zinc exp, give oral copper.

## ORGANOPHOSPHATE POISONING

**Pathophysiology:** Cholinesterase inhibitor. Toxicity 2/2 cholinergic excess.

**Muscarinic:** Bronchorrhea, bronchoconstriction, hypersalivation, sweating, lacrimation, bradycardia, HTN, miosis, micturition. **Nicotinic:** Fascics, muscle weakness, diaphragmatic paralysis. **CNS:** Emotional lability, tremors, slurred speech, resp depression, szs, coma. ***DUMBBELSS*: D**iarrhea, **U**rination, **M**iosis, **B**radycardia, **B**ronchoconstriction, **E**xcitation (muscle, CNS nicotinic effects), **L**acrimation, **S**alivation, **S**weating.

**Rx:** Wear gloves, remove soiled clothes, wash contaminated skin.

**Rx:** Give both of the following: **Atropine** 1-2 mg IV bolus, repeat q1-5 min prn for desired effects (drying of pulmonary secretions, adequate oxygenation, dry skin, HR >70, pupils dilated); **pralidoxime** 1-2 g IV, repeat at 1 h then q10-12 h if weakness persists.

## 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, malaise, n/v. In more acute poisoning: Confusion, szs, coma, CV effects:tachycardia, HTN. Severe sequelae occur in 15% who survive: cognitive problems, irritability, & Parkinson-like syndromes.

**Pathophysiology:** CO has higher affinity for heme than O2 & leads to impaired O2 delivery.

**Rx:** Hyperbaric $O_2$.

### Cyanide

Inhibitor of metalloenzymes, such cytochrome C oxidase, prevents oxidative phosphorylation in mitochondria → impairs aerobic respiration. Consider in smoke inhalation, along w/CO.

**Clinical features:** HA, N/V, vertigo, confusion, arrhythmias, renal failure, coma, & death. Delayed sequelae: Parkinsonism from basal ganglia damage.

**Rx:** Antidotes include *sodium nitrite* 10 mL of 3% solution (300 mg) slow IV push over 2-5 min followed by *sodium thiosulfate* 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 $B_{12}$*: 5 g IV over 15 min.

### Nitrous oxide

Oxidizes the cobalt core of vitamin $B_{12}$. Can lead to polyneuropathy, ataxia, psychosis.

**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 accumulation). Untreated → complete 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 $B_{12}$ (cobalamin) deficiency

Cofactor essential for DNA synthesis & for Krebs cycle; same processes also involve folate, homocysteine (Hcy), MMA.

**Absorption**: Only found in animal products (meat & dairy). $B_{12}$ binds R protein in stomach in presence of acid → R protein is digested by pancreatic enzymes in duodenum → $B_{12}$ binds to intrinsic factor (IF, made by gastric parietal cells) → $B_{12}$-IF absorbed in distal ileum → enters portal circulation bound to transcobalamin II.

| Most Common Etiologies of Vitamin $B_{12}$ Deficiency | |
|---|---|
| **Deficient $B_{12}$ intake** | **Achlorhydria** |
| Strict veganism | Gastritis (esp 2/2 *H. pylori*) |
| Alcoholism | Pancreatic deficiency |
| **Intrinsic factor deficiency** | **HIV/AIDS** (*multifactorial*) |
| Pernicious anemia (autoimmune gastritis) | Poor nutrition |
| Gastrectomy | Chronic diarrhea/ileal disorder |
| **Medications** | **Impaired intestinal/ileal absorption** |
| Proton pump inhibitors | Celiac dz |
| H2 blockers | Crohn dz |
| Colchicine | Bacterial overgrowth |
| **Defects of intracellular metabolism** | |
| Methylmalonic aciduria | |
| Homocystinuria | |

| Manifestations of Vitamin $B_{12}$ Deficiency | |
|---|---|
| **Hematologic** | **Neurologic (may precede anemia)** |
| Megaloblastic anemia (↑ MCV, ↓ Hct, ↑ indirect bilirubin, ↑ LDH, hypersegmented neutrophils on smear) | Peripheral neuropathy, paresthesias |
| Pancytopenia | Subacute combined degeneration (slowly progressive weakness, sensory ataxia, paresthesias → spasticity, paraplegia, incontinence) |
| **Psychiatric:** Cognitive impairment, dementia. Irritability, personality change | **Hyperhomocysteinemia** (also w/folate def) |
| **Skeletal**: Osteoporosis, hip & spine fractures | **Vascular:** ? increased risk of stroke, MI |

**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%); ? antiparietal cell abs; serum gastrin; serum pepsinogen levels.

**Interpretation of MMA & Hcy values in $B_{12}$ & 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 qd × 1-2 wk → 1 mg qd indefinitely.

Monitoring on therapy: Fe, LFTs, K, reticulocyte count at 1 wk (if hypoK → K suppl); HCT at 8 wk (should have normalized); $B_{12}$, MMA, Hcy: Recheck 1-3 mo.

**Prognosis:** Recovery most rapid <3 mo; may continue 6-12 mo.

**Vitamin $B_9$ (folate) deficiency:**

DNA synthesis & remethylation of Hcy. Pregnancy: Protects against neural tube defects (esp important in those on AEDs). May be caused by methotrexate; can be reversed w/leucovorin. Dietary deficiency now rare in Western countries.

**Clinical features & pathophysiology:** megaloblastic anemia, neurologic manifestations are rare. May cause peripheral neuropathy.

**Rx:** Folate 4 mg PO qd. 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): Symmetric distal polyneuropathy & weakness 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: depression, insomnia, tremor. Early dx may prevent irreversible damage. Causes: malnutrition, carcinoid syndrome, TB meds.

**Rx:** Nicotinamide 500 mg PO qd × 3 wk or 100 mg IV × 5-7 days.



## Vitamin $B_3$ (niacin) toxicity

Flushing: Prostaglandin-mediated; more common w/immediate-release preparations, after EtOH, exercise, sun exp, spicy foods. Minimized if niacin taken after meals or if aspirin taken prior. Severe flushing ↓'d by starting at low dose & increasing slowly. Other SEs: N/v, pruritis, hives, constipation, myopathy rarely, hepatotoxicity, precipitation of pre-existing gout.

**Rx/precautions:** Reduce/stop niacin. Hepatotoxicity more common w/sustained release. Monitor serum uric acid, blood glucose, LFTs q6-8wk while titrating dose.

## Vitamin $B_6$ (pyridoxine) deficiency

At risk: Elderly, alcoholics, diabetics. 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.

**Clinical features:** Seborrheic dermatitis, angular cheilitis, atrophic glossitis w/ulceration, somnolence, confusion, PN, szs.

**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, hypocalcemia from malabsorption (paresthesias, hyperreflexia, tetany).
**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, propionyl 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. Severe deficiency → alopecia, seborrheic dermatitis.

**Rx:** Unclear, ~30 µg/day.

**Summary of Primary Neurological Signs a/w Vitamins**

| Clinical sign | Vitamin deficiency |
|---|---|
| Optic neuropathy & other ocular signs | A, $B_1$, folate, $B_{12}$, E |
| Neuropathy | $B_1$, $B_6$, folate, $B_{12}$, E |
| Myelopathy | Folate, $B_{12}$, E |
| Myopathy | D, E |
| Encephalopathy | $B_1$, $B_3$, folate, $B_{12}$ |
| Sz | $B_6$ |

# Rapidly Progressive Dementia

R. Ryan Darby

Alireza Atri

**Definition:** Deterioration of intellectual/behavioral/cognitive/psychiatric fxn (dementia) usually over several weeks to months but <2 yr.

**Epidemiology** (UCSF data: 178 rapidly progressive (RPD) referrals, most "r/o CJD," *Ann Neurol* 2008;64:97): 62% prion (75% sporadic, 22% genetic, 3% acquired); 15% neurodegenerative (i.e., classically "chronic" degenerative dzs); 8% autoimmune; 4% infectious; 2% each psychiatric, cancer, toxic-metabolic, vascular; 4% undetermined (often leukoencephalopathy/encephalopathy of unknown origin). Other studies suggest 6%-27% from reversible causes.



## DIFFERENTIAL DIAGNOSIS & WORKUP FOR RPD

**DDx of RPD "VITTAMMNIINSSSS"** (modified from *Neurol Clin* 2007;25:783): **V**ascular, **I**nfectious, **T**oxic & **T**rauma, **A**utoimmune, **M**etabolic & **M**etastases/neoplasm, **I**atrogenic & **I**llicit/drugs, **N**eurodegenerative, **S**ystemic, **S**eizure, **S**tructural & **S**leep disorders.

- **Vascular:** Infarcts (large vessel, thalamic, multifocal) or ischemic encephalopathy; TTP (2/2 microangiopathic thromboses), hyperviscosity (e.g., polycythemia, paraproteinemias—monoclonal gammopathy, Waldenstrom), cerebral venous thrombosis, dural AV fistulas, inflammatory cerebral amyloid angiopathy (I-CAA), CADASIL.
- **Infectious:** Viral encephalitis, HIV dementia, PML, subacute sclerosing panencephalitis (SSPE), fungal infxns, syphilis, parasites/amebiasis, Lyme dz, *Balamuthia*, Whipple dz.
- **Toxic & trauma: Toxicities/poisoning**: Lead, CO, bismuth, lithium, mercury, arsenic, toluene, cyanide. **Trauma**: Postconcussion & chronic traumatic encephalopathy (CTE), chronic SDH, diffuse axonal injury, & hemorrhage.
- **Autoimmune:** Hashimoto encephalopathy/SREAT, nonparaneoplastic autoimmune (e.g., NMDA, VGKC), lupus cerebritis, 1° or 2° CNS vasculitis, sarcoidosis, paraneoplastic limbic encephalopathy, ADEM, Susac, Behcet, celiac dz.
- **Metabolic & metastases/neoplasm: Metabolic**: Electrolyte/metabolic abnls; uremia, hypoxic-ischemic or hypercapnic encephalopathy, Wilson dz, mitochondrial dz, portosystemic encephalopathy, porphyria, acquired hepatocerebral degeneration, lysosomal storage dz, leukodystrophies, methylmalonic acidemia. **Metastases/neoplasm**: Nonautoimmune paraneoplastic limbic encephalitis, frontal meningioma, gliomas, CNS mets, primary CNS lymphoma, intravascular lymphoma (IVL), lymphomatoid granulomatosis (LYG), gliomatosis cerebri.
- **Iatrogenic-illicit drugs: Iatrogenic:** Medication & supplement side effects, neurosurgery, chemoRx, XRT. **Illicit/drugs**: Chronic alcohol (Wernicke-Korsakoff, Marchiafava-Bignami), leukoencephalopathy from inhaled heroin, MDMA, methanol.
- **Neurodegenerative:** Creutzfeldt-Jakob dz (CJD; sporadic, iatrogenic, familial, new variant), AD, vascular dementia (VAD), DLB, FTD syndromes, primary progressive aphasia (PPA) syndromes, PD w/dementia, CBD, MSA, ALS-FTD-parkinsonism, PSP, Huntington dz, CTE.
- **Systemic, seizure, structural, & sleep disorders: Systemic**: Thyroid, parathyroid, & adrenal abnls,

HTN/PRES. **Seizure**: Chronic sequelae or interictal encephalopathy. **Structural**: NPH, sagging brain syndrome. **Sleep Disorders**: OSA, sleep deprivation.

**Diagnostic workup: Generic & "As Indicated" Tests**

***Essential* (all pts presenting w/RPD)**

- **Blood:** CBC, PT, PTT, chem7, Ca, Mg, phos, LFTs, NH3, LDH, vitamin $B_{12}$, Hcy, MMA, TSH, free-T4, "rheum screen" (ESR, CRP, ANA, RF, SS-A, SS-B), RPR, HIV Ab, Lyme Ab, anti-TG abs, anti-TPO abs, paraneoplastic/autoimmune abs [minimum: anti: NMDA, Hu (ANNA-1), Ma2 (Ta), CV2 (CRMP-5), amphiphysin, AMPA-R, & VGKC (LGI1, CASPR2); GABAb; consider: anti: Yo, nCMAg, Ma1, Ri (ANNA-2), GAD65].
- **CSF:** Cell count + differential, protein, glucose, IgG index, oligoclonal bands, VDRL, paraneoplastic/autoimmune abs.
- **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, Cu, ceruloplasmin, anti-ds DNA, anti-smith, p-ANCA, c-ANCA, C3, C4, CH50, antiendomysial abs, antigliadin IgA & IgG, ACE, anti-GAD Ab, other paraneoplastic abs, HIV viral load, T-cell subsets, smear, viscosity, lactate & pyruvate, hypercoagulability tests, Notch3 gene (CADASIL), VLC fatty acids, arylsulfatase, galactosidases, genetic tests (e.g., HD, AD, FTD, SCAs).
- **CSF:** Cryptococcal Ag, viral PCRs & cultures. Cultures: Bacterial, fungal, AFB, AFB stain, cytology & flow cytometry, PCR IgH gene rearrangement, Whipple PCR, 14-3-3 protein, NSE (neuron-specific enolase), amyloid-beta42, tau (total & phosphorylated).
- **Urine:** Cu (24 h collection, if ? Wilson dz), heavy metal screen (24 h collection, for lead, arsenic, mercury, bismuth, aluminum, lithium), PBG/ALA (24 h collection if ? porphyria).
- **Others:** Brain FDG-PET (AD vs. FTLD), amyloid PET (AD), DAT PET (DLB, PD), MR spectroscopy, body PET + CT (cancer screen), mammogram, conventional angio, EMG/NCS, Bx: brain/meninges, jejunum (Whipple dz), skin (IVL); carotid U/S, TTE.



## VASCULAR CAUSES OF RPD

**Inflammatory cerebral amyloid angiopathy** (*Neurology* 2013;81:1596)

**Def:** CAA a/w (1) perivascular inflamm. (CAA-RI, 13%-17% of CAA) or (2) Aβ-related angiitis (ABRA, 36% of CAA) ? response to deposits of β-amyloid. More common w/APOE ε4/ε4.

**P/w:** RPD (cognitive ↓ over 1-4 mo), szs (90% CAA-RI), HA, leukoencephalopathy.

**Dx:** Clinical history + MRI findings, ±biopsy, *MRI*: multiple microhemorrhages on GRE/SWI; patchy or confluent WM ↑ T2/FLAIR lesions, +meningeal enhancement (57%). *CSF*: mild-moderate ↑ protein (nonspecific). *Brain bx*: CAA-RI: perivascular inflammatory response. ABRA: granulomatous angiitis similar to 1° CNS vasculitis.

**Rx:** steroids +/- cyclophosphamide; avoid antiplatelet & anticoagulant meds.

**CADASIL** (*Lancet Neurol* 2009;8:643)

**Def:** Genetic, AD dz affecting small cerebral vessels causing strokes & leukoencephalopathy.

**Epid:** Prev 2% age <65, 11% age <50 in pts w/lacunar stroke + leukoaraiosis.

**P/w:** Migraine w/aura (20%-40%), TIA/stroke (60%-85%), mood d/o (20%), progressive cog impairment in 10% (executive, attn, memory, near 100%), szs 5%-10%.

**Dx:** MRI: T2/FLAIR WM lesions, esp external capsule, ant temp lobes. Other: Notch3 gene mutation, skin bx w/granular osmiophilic material in vessel walls.

**Rx:** ? donepezil for cog impairment, CV risk modification, migraine Rx.

## INFECTIOUS CAUSES OF RPD

Most infectious RPD cases are atypical (i.e., uncharacteristically *slow*) presentations of common CNS infxns. Most common causes: HSV, CMV, EBV, enteroviruses, WNV, EEE.

**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 neuro deficits or meningoencephalitis.

**HIV:** Four associations w/RPD: **(1)** AIDS-dementia complex (usu advanced AIDS); **(2)** during seroconversion; **(3)** neuro-IRIS (neuroimmune reconstitution inflamm synd) on starting HAART; **(4)** opportunistic infxns. Amphetamine + HIV → accelerated HIV dementia.

**SSPE** (2/2 CNS infxn 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. Later: spastic quadriparesis, diffuse hyperreflexia & upgoing toes, coma. *Dx*: **(1)** ↑ measles abs (serum & CSF) in approp clinical setting; **(2)** EEG: Periodic complexes & 3-10 Hz sharp waves a/w myoclonic jerks.

**CNS Whipple dz:** Rare but treatable bacterial infxn 2/2 *Tropheryma whippelii*. *Epid*: Onset: Any age, typically 40-70s (median 50). ***P/w***: Typically diarrhea, abd pain, ↓ wt, arthralgias, wasting, fever, lymphadenopathy; 15% w/o GI si/sx. ***CNS involvement***: ~5% p/w neuro si/sx; subclinical dz in ~45% cases. 70% cognitive impairment, 40% psychiatric si/sx. Other common si/sx: Eye mvmt palsies, myoclonus, sz, aseptic meningitis, hypothalamic involvement, ataxia, focal signs. "Classic triad": Dementia, ophthalmoplegia, myoclonus (<10% cases, but very specific). *Oculomasticatory myorhythmia*: Pathognomonic (but uncommon). ***Dx***: CSF: ↑ protein, ↑ lymphs 50% cases. MRI: Nonspecific. PAS+ inclusions or *T. whippelii* in foamy macrophages on jejunal bx; PCR on jejunal bx or CSF. ***Rx***: TMP/SMX 160/800 mg PO bid × 1-2 yr, w/folate. Second line: penicillin G, penicillin VK, amoxicillin.

## TOXIC-METABOLIC CAUSES OF RPD

**Niacin deficiency: Pellagra** ("rough skin"): See *Poisons and Vitamin Def* chapter.

**Heavy metals** (arsenic, mercury, aluminum, lithium, lead): Usu p/w florid *acute* encephalopathy (hours-days; usu faster than RPD [weeks-months]); can present as RPD.

**Manganese toxicity:** Mostly in miners. Parkinsonism 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 si/sx, unexplained pain, worse si/sx w/new meds; fluctuating course.

**Adult-onset metachromatic leukodystrophy (AoMLD):** Rarely p/w RPD; other leukodystrophies also rarely

p/w adult-onset RPD (e.g., X-linked adrenoleukodystrophy).

**Kufs dz:** Rare; adult form of neuronal ceroid lipofuscinosis. Presentation: Early adulthood onset, progressive myoclonic epilepsy, ±psychiatric si/sx, ±catatonia.

**Mitochondrial d/o:** Include MELAS, MERRF, Kearns-Sayre dz. Rarely p/w RPD. Other sx: Migraines, psych sx, weakness, n/v/GI sx, hearing/vision impairment. **Dx**: Lactacte/pyruvate, plasma AAs, urine organic acids, MR spect, muscle bx, genetic testing. **Rx**: CoQ10, mitochondrial cocktail

**Wilson Dz** (*Lancet* 2007;369:397)

**Def:** AR d/o of copper metabolism.

**Epid:** Prev 1:30-100 K, age onset 5-35.

**P/w:** *Neuropsych* (40%-50% initial presentations): Parkinsonism, tremor, dystonia, behavioral, psychiatric. *Other sx:* Cirrhosis, Kayser-Fleischer rings.

**Dx:** ↑ LFTs, serum ceruloplasmin, serum Cu, 24 h Cu, liver Bx, ATP7B gene test.

**Rx:** Chelators (penicillamine, trientine, Zn); liver transplant.

# AUTOIMMUNE CAUSES OF RPD

## HASHIMOTO ENCEPHALOPATHY/STEROID RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS, "SREAT"

**Epid** (*J Neuropsychiatry Clin Neurosci* 2011;23:384): Prev ~2/100,000. Age of onset: 45-55 yr. 80% female. A/w autoimmune thyroid dz, SLE, DM 1, Sjögren.

**P/w:** Nonspec course. Rapid improvement w/steroids is required (96%). Prodrome (not always present): Depression, personality Δs, psychosis. Progressive or fluctuating encephalopathy w/inattention, exec/memory dysfxn, agitation or lethargy (65%), szs (59%), psychosis (27%), myoclonus (42%), stroke-like episodes (18%), hallucinations.

**Dx:** 86% w ↑ antithyroid peroxidase (anti-TPO) abs, 48% w ↑ antithyroglobulin (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. MRI (abnl 45%), EEG (abnl 89% usu slowing, sometimes sharps), CSF (abnl 71% usu ↑ TP), & brain bx findings nonspecific.

**Rx:** Corticosteroid responsiveness a defining feature. Start w/high-dose IV methylpred (Solu-Medrol) 1 g/day × 3-5 days. Too short course → relapse. Follow w/maint PO prednisone 1-2 mg/kg/d; taper slowly. Repeat methylpred pulses for relapses. Rx duration varies (4-6 mo-10 yr). In relapsing-remitting dz, can use steroid-sparing agents, e.g., IVIg, plasma exch, azathioprine, cyclophosphamide, hydroxychloroquine, methotrexate, cyclophosphamide, rituximab.

## LIMBIC ENCEPHALITIS (LE)

**Epid:** Up to 8% of pts p/w RPD.

**P/w:** Subacute amnesia (↓ antegrade short-term memory (STM), ±↓ retrograde memory), psychosis, hyperreligiosity, hallucinations, szs, personality Δs, sleep disturbances, +/- brainstem involve.

**Cancer:** SCLC (75%; of these, 50% a/w anti-Hu abs), germ cell (ovarian, testicular), thymoma, Hodgkin lymph, breast Ca. LE may precede Ca dx by weeks-months; rarely years.

**Abs:** *Intraneuronal:* Anti-Hu, anti-Ma2/Ta, anti-CV2/CRMP-5, antiamphiphysin. *Extracellular*: Anti-NMDA, anti-AMPA, anti-GABAb, anti-VGKC (LGI1, CASPR2).

**Dx**: *MRI*: T2/FLAIR Δs in mesial temporal lobes (MTL). *EEG*: Slowing, szs. *LP*: Mild ↑ prot, WBCs. *Serum/CSF*: LE ab panel. *Cancer screen*: CT-PET c/a/p, pelvic/testicular US, mammogram.

**Rx**: Tumor removal, steroids (1 g Solu-Medrol × 5 days), IVIg (0.4 g/kg × 5 days), PLEX. *Long term*: Rituximab, cyclophosphamide.

**NMDA-receptor encephalitis** (*Lancet Neurol* 2011;10:63; *Neurology* 2012;11:1094)

**Epid**: 1%-4% of encephalitis cases. Med. Age 23, range 5-76, 80%-91% female, 59% w/CA (ovarian/testicular teratomas most common; rarely neuroblastoma, Hodgkin lymphoma).



**P/w**: *Prodrome (86%)*: Fever, HA, n/v/d, URI sxs, days-weeks prior. *Presentation*: 77% w/psych sxs (anxiety, insomnia, fear, hyperreligiosity, delusions, mania), 23% w/neuro sxs (STM deficits, ↓ language output, mvmt d/o in 86%). *Progression*: Echolalia, mutism, dissociative sxs, catatonia, coma, hypoventilation 66%, autonomic sxs 69%, szs 76%.

**Dx**: *MRI:* 50% WNL. Others: Nonspec T2/FLAIR in MTL, cortex, BG, cerebellum, brainstem. *EEG:* ~100% abnl (slowing, epileptiform, "extreme delta brush" in 30%). *LP:* 80%-95% abnl; ↑ prot, WBCs, OCBs. *Other*: Abs: Rarely neg in serum but + in CSF. Pelvic/testicular U/S.

**Rx**: Tumor removal, steroids, IVIg, PLEX (caution w/autonomic instability), rituximab, cyclophos, & azathioprine. 75% recover w/mild sx.

***Features of antibody-mediated limbic encephalitis*** (*J Neurol* 2010;257:509)

| Antibody | Tumors | Age/Gender | Abnormal Dx tests | Presenting sx |
|---|---|---|---|---|
| Anti-Hu (ANNA-1) | 98%: SCLC, neuroblastoma, prostate | 55-65 F > M | MRI: 50%<br>LP: 72%<br>EEG: 86% | EM, subacute sensory neuropathy, LE, cerebellar |
| Anti-Ma2 (anti-Ta) | 96%: Germinoma, testicular, lung | 21-82 M >> F (Ta)<br>M = F (Ma2) | MRI: 82%-95%<br>LP: 72%-85% | LE, brainstem, cerebellar, hypothalamic |
| Anti-CV2 (anti-CRMP-5) | 96%: SCLC, thymoma, renal cell | 50-70<br>F = M | MRI: ?<br>LP: 86% | Neuropathy, cerebellar, LE, chorea, EM, ON |
| Anti-VGKC (LGI1, CASPR2) | 31%: SCLC, thymoma | 30-80<br>M > F | MRI: 40%-85%<br>LP: 25%-41% | Isaac & Morvan syndromes, neuromyotonia, REM sleep d/o, sz, LE |
| Anti-NMDA-R | 9%-56%: Ovarian, testicular | 5-76<br>F >> M | MRI: 50%-55%<br>LP: 80%- | Prodromal, LE, psych, movement d/o, autonomic, hypoventilation |

| | | | | |
|---|---|---|---|---|
| | teratomas | | 95%<br>EEG:<br>~100% | |
| Antiamphiphysin | 95%: Breast, SCLC | 28-84<br>F = M | MRI: 8%<br>LP: 61% | LE, EM, stiff person, cerebellar, autonomic |
| Anti-AMPA-R | 70%: Lung, breast, thymus | 38-87<br>F >> M | MRI: 90%<br>LP: 90% | LE, hypersomnia, visual hallucinations |
| Anti-GABAb-R | 47%: | SCLC 16-77<br>F = M | MRI: 63%-66%<br>LP: 60%-90%<br>EEG: 74% | LE, sz, ataxia, opsoclonusmyoclonus |

## CELIAC DZ (*LANCET NEUROL* 2010;9:318)

**Def:** Systemic autoimmune dz w/sensitivity to gluten → inflamm/atrophy of small intestine mucosa. 10%-23% w/neuro sxs, often w/o GI sx. May be a/w other AI dz (e.g., DM, RA, Sjögren, thyroid dz, collagen vascular dz, liver dz, IgA def). **P/w:** *GI*: Si/sx of malabsorption: diarrhea, steatorrhea, nutritional & vitamin def. *Skin*: Dermatitis herpetiformis. *Neurologic manifestations*: Ataxia, neuropathy, neuropsychiatric si/sx, sz, HA, dementia. **Dx:** ↑ serum antigliadin IgA or IgG and/or anti-TG2 abs (replacing antiendomysial abs); anti-TG6 most Se/Sp for neuro sxs; TG3 for skin sxs. HLA DQ2.5 or DQ8 testing in unclear cases. Intestinal bx (may be neg in neuro dz but w/+IgA deposits). **Rx:** Gluten-free diet.

## NEUROSARCOIDOSIS

**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 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: WNL or w/mildly ↑ protein & lymphocytosis. Serum or CSF ACE ↑ in ~50% cases; nonspecific. Bx required 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 causes p/w RPD: **(1)** IVL, **(2)** 1° CNS lymphoma, **(3)** LYG, **(4)** Waldenstrom macroglobulinemia (WM), **(5)** gliomatosis cerebri.

## INTRAVASCULAR LYMPHOMA (AKA ANGIOTROPIC LYMPHOMA)

**Def:** Rare subtype of diffuse large B-cell lymphoma (DLBCL); clonal proliferation of lymphs 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; ~1 case/million pts; no known risk factors; rarely arises in setting of DLBCL.
- Four common presentations: (1) CNS, (2) skin, (3) FUO, (4) hemophagocytic syndrome.

**CNS IVL:** Protean si/sx: Focal motor/sensory signs; generalized weakness, AMS, RPD, psychiatric sxs, 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 w/skin involvement (~1/4 w/skin involvement as sole presenting si/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.

- 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*: Nader Kamangar, Anthony W O'Regan. Lymphomatoid Granulomatosis. *eMedicine*, Apr 16, 2009, http://emedicine.medscape.com/article/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 exuberant benign (polyclonal) T-cell rxn. Dx 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). *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 abnls nonspecific. *Labs*: CBC: Leukopenia (20%), lymphopenia (33%). T-cell subsets: May find low CD4 count; Hct WNL or slightly high; ESR: WNL to moderately ↑; Cr, LFT usu WNL. *Imaging*: *CXR, chest CT*: Usu nonspecific; b/l nodules or masses in lower & peripheral lung fields (80%-100%); pleural effusions (33%); pneumonitis or large mass-like lesion (30%); cavitation of nodules (30%); pneumothorax (5%). Hilar & mediastinal lymphadenopathy rare → consider alternative dx or transformation into aggressive lymphoma. *Brain MRI*: Lesions isointense or hyperintense on T1, hyperintense on T2 images; enhancement may be punctate & linear (relatively specific for inflammation of deep cerebral vessels). *Biopsy*: Required for dx. Analysis for cell phenotype, clonality, EBV infxn.

**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 (WALDENSTROM 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 the United States; 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 (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 si/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 infxns (2/2 B-cell dysfunction). *Renal*:

Renal dz (but uncommon). *Heme*: Bleeding d/os: Platelet, coagulation factor, & fibrinogen dysfxn. *Skin*: Purpura, bullae, papules, plaques & nodules, chronic urticaria (Schnitzler syndrome), Raynaud phenomenon, livedo reticularis, acrocyanosis. *CV*: CHF (but uncommon). *Ophtho*: Periorbital masses (retroorbital & 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)** Ophtho: 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 2/2 WM. *Neuropathy*: Usu slowly progressive distal symmetric sensorimotor. Variants: Chronic ataxic neuropathy, 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** (**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M** protein, **S**kin 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: (i) Cryoglobulinemia w/demyelinating & axonal features; (ii) related to chemotherapeutic agents. **(5)** Motor sensory demyelinating neuropathy: (i) Osteosclerotic myeloma & Castleman dz; (ii) 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, ↑ LDH [signifies extent of WM tissue involvement]).
- RF, cryoglobulins, direct antiglobulin test, cold agglutinin titer: May be (+).
- 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 amyloidosis* (i.e., 2/2 neuropathy, nephrotic syndrome, CHF): Abd 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: (i) Rx of IgM paraprotein complications; (ii) dzmodifying Rx. Rx include IVIg, plasmapheresis, alkylating agents, IFN-α, purine nucleoside analogues, high-dose chemo, splenectomy, rituximab, thalidomide, bone marrow transplantation, experimental agents. **(3) Hyperviscosity syndrome:** Urgent plasmapheresis (80% IgM is in the intravascular space; should remove >1/2 intravascular volume to sufficiently lower viscosity). Measure viscosity before & after; remove 2-4 U plasma q1-2wk (to avoid recurrent emergency); 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 40-50 s. 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-JAKOB DZ

**Epid:** ~1/million/yr. ~**85%** sporadic (sCJD). ~**15%** inherited (aut dom): gCJD, Gerstmann-Straussler-Scheinker dz, fatal familial insomnia (FFI); <**2%** acquired: iatrogenic, vCJD, kuru.

**sCJD (sporadic CJD)** (*Neurologist* 2011;17:67-74)

**Epid:** Usu insidious; age 50-70; F = M; median survival 5 mo; 85% die w/in 1 yr.

**Mech**: PrPc → PrPSc leads to change in prot folding confirmation (from α-helices → β-pleated sheets). Phenotype determined by codon 129 polymorphism (MM, MV, VV) + protease digest (type 1,2). Leads to distinct phenotypes: Cognitive (MM1, MV1, MM2, VV1), ataxic (VV2, MV2), sporadic familial insomnia (MM2), & variably protease-sensitive prionopathy w/psych + frontal sxs (usually VV, type 1,2 neg). Some mixed type 1,2 w/mixed phenotype.

**Modified WHO clinical criteria sCJD** (*Brain* 2009;132:2659) *Probable CJD* (Se 98%, Sp 71%): **(1)** Progressive dementia <2 yr w/≥2 of myoclonus, visual or cerebellar si/sx, pyramidal or extrapyramidal si/sx, akinetic mutism & **(2)** EEG = PSWC, 14-3-3 CSF protein, or MRI T2/DWI lesions in basal ganglia, thalamus, cortex. *Possible CJD* same as "Probable CJD" but w/o satisfying EEG, CSF, or MRI criteria.

**P/w:** *Typical*: Cognitive: Memory, executive, language (39%), cerebellar (21%). Behavioral/psych: Depression, anxiety (20%). Constitutional: HA, dizziness, fatigue, sleep d/o (20%), sensory (11%), motor (9%), visual (7%).

*Progression*: Dementia, progressive cortical signs (aphasia, apraxia, pyramidal signs), movement d/o (myoclonus, rigidity, choreiform-athetoid movements), akinetic mutism.

**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, aka GPDs):** Se ~50%-65% w/repetitive testing over dz course; Sp ~90% (in the right setting; but GPDs occur in other settings, e.g., AD, DLB, vascular dementia, Hashimoto encephalopathy, toxic-metabolic encephalopathies). **(4) CSF:** Routine studies typically WNL. May have mild ↑ protein & +OCBs. 14-3-3 protein: Metaanalysis w/Se 92%, Sp 80% across studies (*Neurology* 2012;79:1499). Varies w/DDx: Sp 95%-97% vs. neurodegenerative dzs but 82%-87% vs. reversible RPDs (*Brain* 2012;135:3051). +total tau protein & NSE may have Se/Sp >90%. **(5) Real-time quaking-induced conversion (RT-QuIC) PrP:** CSF Se 77%, Sp 100%, nasal brush Se 97%, & Se 100% (*NEJM* 2014;371:519).

**vCJD (variant CJD)** (*Ann Neurol* 2008;64:97)

Younger onset than "traditional" sCJD; ages 12-74, median 29, & much longer duration of illness. Begins w/psych illness >6 mo. Neuro si/sx later: Dementia, ataxia, dysesthesia, mvmt d/o (chorea, myoclonus, dystonia). Linked to bovine spongiform encephalopathy, usu codon 129 MM. **EEG** rarely shows PSWCs/GPDs (unlike sCJD). **MRI:** Similar to sCJD but distinguished by "pulvinar sign" (bright pulvinar c/w putamen). **Tonsillar bx:** If available, if not brain bx. **Urine PrPsc**: Se 93%, Sp 100% (*NEJM* 2014;371:530).

**Gerstmann-Straussler-Scheinker dz:** Rare (~1 per 100 million cases). Autosomal dominant, onset ~40 s. 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 dominant inheritance. Can be sporadic (MM2/thalamic sCJD). **Features:** Progressive insomnia, dream-like confusional state, ↓ memory, dysautonomia (HTN, ↑ HR, hyperhidrosis, 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. *Lack MRI & EEG signatures of CJD. Look for underlying systemic dz* (*e.g., undx cancer) unmasking/decompensating a neurodegenerative dementia.*



- CBD, DLB, late AD, & VAD (mixed dementia 2/2 AD + VAD very common) si/sx shared w/CJD: Myoclonus, extrapyramidal signs.
- DLB: Typically p/w rapid fluctuations in arousal & cognition, parkinsonism, vivid recurrent well-formed visual hallucinations; very rarely PSWC/GPDs on EEG (overlap w/CJD).
- FTD: Typically p/w "frontal syndrome" (behavioral, cognitive-executive dysfxn, personality Δs → dementia); language dysfxn.
- CBD: Typically p/w "corticobasal" syndrome (dementia, parkinsonism, alien limb syndrome, myoclonus); visual sensory & motor deficits. *These all can occur in CJD*.
- Typical PSP: Early falls; dysarthria; executive dysfxn; symm bradykinesia; axial & postural instab, aphasia.

- PPA syndromes: Salient initial sxs of progressive language dysfxn: word order, grammar, production, finding, or meaning; often younger onset (<65 yr). Etiology ~1/3 AD & ~2/3 FTLD.
- PCA syndrome: Salient initial sx of progressive visuospatial dysfxn: Balint, partial Gerstmann, VF defects >alexia, ideomotor apraxia, prosopagnosia. Often younger onset (<65 yr). Etiology ~2/3 AD, ~1/4 DLB, <10% CJD, CBD/prion dz.
- 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.
- Cerebellar-cognitive syndromes: Rare. Fragile X tremor ataxia, SCA, DRPLA, Gordon Holmes syndrome.

# Dementia

Joel Salinas

Vikram Khurana

## 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 & acquired forms. Affects >5 million Americans (1 in 9 above 65, 1 in 3 above 85). Cost > $200 billion annually (*2014 Alzheimer's Dz Facts & Figures*).

**Etiology:** *Most common cause is s*poradic Alzheimer dz (AD) (60%-80% of demented pts in the United States). Multiple etiologies in same pt common (e.g., mixed Alzheimer's/vascular dementia). *Other causes*: 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. Dementia from paraneoplastic syndromes → see *Neuro-Oncology* chapter Paraneoplastic Syndromes.



**Causes of Dementia**

*Idiopathic late-onset*
AD, dementia a/w parkinsonism (dementia w/Lewy bodies [DLB], Parkinson disease dementia [PDD], progressive supranuclear palsy [PSP], corticobasal syndrome), frontotemporal dementia (FTD) spectrum disorders, prion diseases
*Familial*
Adult onset: Familial forms of AD, FTD, extrapyramidal (e.g., familial parkinsonism, Huntington disease, Wilson disease), prion dzs, Down syndrome, Kufs disease
Pediatric: Neuronal ceroid lipofuscinoses, storage diseases, adrenoleukodystrophies
*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)
*Inflammatory*
Vasculitis, multiple sclerosis, paraneoplastic, Hashimoto encephalopathy
*Neoplastic*
Primary CNS tumor, gliomatosis cerebri, metastatic CNS tumor, primary CNS or systemic non-Hodgkin lymphoma
*Vascular*
Diffuse (Binswanger disease), vascular dementia
*Traumatic*
Chronic subdural hematoma, chronic traumatic encephalopathy (dementia pugilistica)
*Other*
Recurrent nonconvulsive seizures, chronic refractory epilepsy, NPH

## APPROACH TO DIAGNOSIS OF DEMENTIA

### HISTORY

Careful history from pt & family members. Determine **symptoms** w/special care. **Initial** sx esp 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, imbalance). **(6)** Temporal course: Rapidity of onset, course—progressive? fluctuating? stepwise? **(7)** Nonneurologic sxs, e.g., fever, wt loss, cardiorespiratory, rash. **(8)** PMH may suggest

potential etiologies (Fig. 12.1). **(9)** Medications. **(10)** Family history may give clue to familial dementias. **(11)** Social history may be revealing (e.g., smoking → vascular dementia/chronic pulmonary dz, alcohol abuse → alcohol & nutritional deficiency-related dementias, multiple sexual partners → 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 (Se for dementia ˜70%; Sp ˜90%) & Montreal cognitive assessment (MoCA; more Se but less Sp for MCI; normative data avail at http://www.mocatest.org) tools. Queen Square Screening Test for Cognitive Deficits is useful pocket-sized companion (Warrington EK. *The Queen Square Screening Test for Cognitive Deficits.* London, UK: Institute of Neurology, 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, cooperation.

## DIAGNOSTIC STUDIES

**Laboratory tests:** Consider the following lab tests but tailor to individual pts: Basic (chem10, BUN/Cr, 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 (including Aβ/tau). 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, TTE).

**Neuroimaging:** *Structural imaging*: Brain MRI preferable to head CT w/contrast. *Vascular imaging* (in cases of suspected vascular dementia). *Functional imaging*: SPECT (single photon emission computed tomography) & PET measure resting cerebral blood flow & metabolism. *Chemical imaging*: MR spectroscopy; amyloid/tau PET imaging, not yet in widespread clinical use.

**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.

**Clinical Differentiation of the Major Dementias**

| Dz | First Sx | Mental Status exam | Φ sxs | Neuro exam | Imaging/Biomarkers |
|---|---|---|---|---|---|
| **AD** | Memory loss (in majority of cases), though other cognitive, behavioral sxs can be 1st | Usu episodic memory loss, though other cog domains can be impaired | Usu nl, though apathy/depression are common | Initially nl | Entorhinal cortex & hippocampal atrophy; T/P atrophy or ↓ metabolism; + amyloid PET, CSF ↓ Aβ + ↑ tau |
| **FTD** | Apathy, poor judgment/insight, speech/language | Frontal/executive, language; spares v/s | Apathy, disinhibition, hyperorality, loss of empathy, perseverations/compulsions | Due to PSP/CBD overlap: Vertical gaze palsy, axial rigidity, dystonia, alien hand Concurrent motor neuron disease | FL &/or TL atrophy or ↓ metabolism; spares posterior PL |
| **DLB** | Visual hall., REM sleep d/o, fluctuations parkinsonism, attention, | & frontal/executive; spares memory | Visual hall. depression sleep d/o delusions | Parkinsonism | Posterior PL atrophy; OL ↓ metabolism or ↓ perfusion |

| | | | | | |
|---|---|---|---|---|---|
| | v/s deficits | early; delirium prone | | | |
| **CJD** | Dementia, mood, anxiety, mvmt d/o, visual symptoms | Variable | Depression, anxiety | Myoclonus, rigidity, parkinsonism, cortical blindness | Cortical ribboning, BG, or thalamus: hyperintensity on DWI/FLAIR MRI |
| **Vascular** | Variable: apathy, judgment/problemsolving difficulty; falls, focal weakness | Frontal/executive, cognitive slowing; can spare memory | Apathy, depression | Usually motor slowing, spasticity; can be normal | Cortical &/or subcortical infarctions, confluent WM dz |

Adapted from Bird TD, Miller BL. Alzheimer's disease and primary dementias. In: Fauci AS, Braunwald E, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*. 17 ed. New York, NY: McGraw-Hill, 2008:2393-2406.



## TREATMENT OF DEMENTIA

**Disease-modifying pharmacotherapy:** None available; some promising agents in trial.

**Symptomatic pharmacotherapy:** Cholinesterase inhibitors for AD & DLB. NMDA receptor antagonists for AD. Antidepressants for depression, anxiety. Neuroleptics for agitation, psychosis (typically use atypical neuroleptics (e.g., preferably quetiapine [Seroquel] given less EPS compared to other atypicals); for acute severe agitation requiring parenteral medication, consider IV or IM Haldol); can cause significant adverse reaction in DLB. Stimulants, catecholamine enhancers, dopaminergic agonists for inattention (limited data), ↓ arousal, apathy. Antiseizure medications for mood stabilization (limited data).

**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); replace $B_{12}$ if borderline low.

**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:** *Cognitive rehab, if avail. 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 compromise ADL, 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 “baseline.” Current preventive strategies: Reducing vascular risk (e.g., smoking cessation, DM control, optimizing lipid profile, Mediterranean diet); reducing alcohol consumption (e.g., <1-2 drinks daily); regular exercise to optimize cardiovascular fitness & cerebrovascular perfusion (e.g., at least three episodes of 30-min mod-intensity activity per wk); maintaining intellectual & social engagement/participation (e.g., community groups; hobbies w/low to mod cognitive load; social support).

## 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 typically stratified into *amnestic vs. nonamnestic & single vs. multiple domain* (e.g., amnestic multiple domain [memory & language]).

**Etiology, pathogenesis:** Same 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 w/neuropsychological assessment. W/u similar to dementia. Consider comorbid Φ d/os, including anxiety & depression, medication effects, substance abuse, chronic pain as potential etiologies or exacerbating factors. Consider assessing 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 amnestic MCI, smoking history, hyperlipidemia, ApoE4 genotype, medial temporal lobe volume loss on MRI, temporoparietal hypometabolism on FDG-PET, or CSF β-amyloid levels indicating cerebral amyloid burden. A minority may convert back to normal cognition. Follow w/annual neuropsychological assessment.

**Treatment:** No pharmacotherapy proven to lower long-term risk of conversion to dementia; some agents in trial. Cholinesterase are sometimes started if suspected underlying pathology is AD (limited data). Current preventive strategies: as for "normal



aging" above. Treat comorbid depression w/nonanticholinergic drug (e.g., SSRIs like sertraline or citalopram).

## 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 1 in 9 age >65 & 32% of people >85. The annual indirect & direct costs total more than $1.1 trillion by 2050. 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). Head trauma, vascular dz, diabetes, low education level may increase 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. In relation to E3/E3, the relative risk w/*E4/E4* is 14.9; *E3/E4*, 3.2; *E2/E4*, 2.6; *E2/2*, 0.6; & E2/3, 0.6. <1% of cases early onset (age <65) 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/parietooccipital preponderance; enlarged ventricles (hydrocephalus *ex vacuo*). *Amyloid plaques*: Aggregated β-pleated sheets of β-amyloid protein. *NFTs*: Hyperphosphorylated forms of microtubule-associated 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 (NIA diagnostic guidelines for AD, *Alzheimers Dement* 2011;7(3):263-269):** Insidious-onset cognitive or behavioral symptoms (≥2 impairments in either learning, reasoning, visuospatial, or language abilities or personality) that interfere w/functioning, represent decline from previous functioning, & not explained by delirium or major psych disorder. Clear-cut gradual worsening by report or observation. Initial & most prominent deficits are either amnestic (impairment in learning & recall) or nonamnestic (language, visuospatial, or executive dysfunction). Defn of probable AD cannot be applied when evidence of substantial concomitant vascular disease temporally related to onset or worsening of cognitive impairment; core features of DLB or FTD other than dementia; or other concurrent active medication or disease that could have substantial effect on cognition. Biomarker definition: (1) biomarkers showing the level of beta-amyloid accumulation in the brain & (2) biomarkers showing that neurons in the brain are injured or actually degenerating.

**Clinical features:** Prominent impairment of episodic 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; myoclonus. Duration to death (typically from medical causes including infection, aspiration, pulmonary embolism, cardiac arrest, malnutrition) typically 8-10 yr. *Exam*: Cognitive dysfxn, unmasking of primitive reflexes (e.g., grasp, palmomental, snout), Babinski sign as late feature (if present early may suggest vascular component). Nonmemory initial complaints in ~20% cases (e.g., language (logopenic primary progressive aphasia), executive dysfunction or navigational difficulty). Rarely presents w/visuospatial complaints (so-called posterior cortical atrophy). Can have Balint syndrome. Disturbed olfaction often a very early but nonspecific feature of AD.

**Diagnosis/workup:** Dx currently clinical, w/neuropsychological assessment. Consider comorbid Φ d/os. Assess vascular risk (smoking history, 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; imaging for amyloid (using florbetapir F-18, or flutemetamol F18) or tau deposition, burden/pattern of distribution impt as tau may be more correlated w/clinical phenotype (amyloid imaging used rarely outside of research though approved for clinical care given currently not covered by insurance; tau imaging remains experimental); ↓ Aβ/tau ratio in CSF (currently considered to provide high confidence of underlying AD pathology similar to amyloid imaging). ApoE4 genotype not specific enough to be used in clinical practice.

**Treatment:** Currently no dz-modifying therapies available. Rivastigmine, donepezil, & galantamine (acetylcholinesterase inhibition) & memantine (NMDA-receptor antagonist). 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, Φ 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). However, beware parkinsonism complicating neuroleptic use; hence, quetiapine is strongly preferred.



**FDA-Approved Pharmacotherapy for AD**

| Drug | Tx Regimen (Doses in mg) |
|---|---|
| Rivastigmine | Initial: 1.5 bid; may ↑ by 3 mg/day (1.5/dose) q2wk based on tolerability (max dose: 6 bid). Available as 4.6 mg/24 h transdermal patch w/fewer GI side effects (can be increased to max dose 13.3 mg/24 h patch). |
| Donepezil | Initial: 5 mg/day at bedtime. May ↑ to 10/day at bedtime after 4-6 wk. |
| Galantamine | Initial: 4 mg bid for 4 wk. If tolerated, ↑ to 8 bid for ≥4 wk. If tolerated, ↑ 12 bid. Also available as extended release w/initial 8 mg/day & (if tolerated after 4 wk) max 16 to 24 mg/day. 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 mg qd per wk to target of 20 mg/day. Doses >5 mg/day should be given in two divided doses. For severe renal impairment, max 5 mg bid. Also available as extended release w/initial 7 mg/day; titrated by 7 mg/wk up to max 28 mg/day. |

ULN, upper limit of normal.

## FRONTOTEMPORAL DEMENTIA

**Definition:** Dementia defined by marked selective cerebral atrophy of frontal and/or temporal lobes. 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: 40-60 s (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.

**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). FTD occurs on a spectrum w/other neurodegenerative phenotypes (mainly parkinsonism & ALS) assoc w specific genes: MAPT, GRN, C9ORF72, TREM2, CHMP2B, VCP, OPTN, CHCHD10, SQSTM1, UBQLN2, plus many more. Multiple other genes implicated in rarer familial forms of FTD. Unlike AD, *APOE* genotype does not modify FTD risk.

**Pathology:** FTLD used to describe pathology; FTD for clinical syndromes. 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, FTLD is defined by neuronal intracytoplasmic inclusions that **(1)** stain + for **tau** (FTLD-tau), e.g., **Pick dz**, corticobasal degeneration (**CBD**), **PSP**, also hereditary FTLD caused by MAPT mutations; **(2)** stain + for **ubiquitin** & TDP-43 *but not for tau* (FTLD-U), e.g., subset of sporadic FTLD & also hereditary FTLD 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 taupositive Pick bodies (but no NFTs), & argyrophilic grains, glial tau-positive inclusions.

**Pathogenesis:** FTLD-tau & FTLD-U presumably represent different dzs w/similar patterns of differential neuronal vulnerability & hence similar clinical phenotype.

**Tauopathies:** Include several distinct dzs—including **AD, FTLD-tau, CBD, PSP, CTE**. 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:** TDP-43, an RNA-binding protein, has been shown to aggregate in these dzs. TDP-43 aggregation also occurs in ALS (mutations in C9ORF72 are the most common cause of familial FTLD and/or ALS & have also been found in sporadic cases) & 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 > L 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-> R-sided anterior temporal atrophy w/TDP-43 > tau pathologyp/w fluent aphasia associated w/impaired naming & impaired knowledge of word meaning. Behavioral sxs may occur. **(3)** ***Primary nonfluent aphasia*** (**a subset of PPA**)—correlated w/atrophy of L frontal lobe & tau > TDP-43 pathology, including significant overlap w/PSP & CBDp/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. LP or amyloid imaging to differentiate from AD, C9ORF72 should be checked in all FTD-ALS pts regardless of whether there is a family hx.

**Treatment:** Currently no dz-modifying therapies available. Cholinesterase have not been shown to be beneficial; ISSRIs, neuroleptics, stimulant medications (see Table 12.2) may help w/behavioral dysfxn, but neuroleptics may ↑ parkinsonism; mood stabilizers (e.g., Valproate) may be helpful. Cognitive training & psychosocial support are important aspects; family education is critical.

## DEMENTIA WITH LEWY BODIES AND PARKINSON DISEASE WITH DEMENTIA

**Definition:** Dementia with Lewy Bodies (DLB) is dx as dementia w/vis halluc, parkinsonism & fluctuating course w/Lewy bodies on pathology. If parkinsonism present >1 yr before cognitive impairment is detected, dx is Parkinson disease with dementia (PDD).

**Epidemiology:** DLB: 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). PDD: Progression to dementia occurs in up to 80% of pts w/PD.

**Etiology:** Both DLB & PDD are synucleinopathies. Mostly sporadic & thought to have complex genetic/environmental etiology, although mutations or multiplication in the alpha-synuclein-encoding *SNCA* (*PARK 1/4*) gene can cause a DLB phenotype. Addl PARK gene mutations that can lead to DLB [or PDD] include PARK17, VPS35, PARK18, EIF4G1. An impt genetic risk factor assoc w/PDD is single mutation in glucocerebrosidase gene.



**Pathology:** *Cortical Lewy bodies*: Intracytoplasmic eosinophilic inclusions w/in cortical neurons composed of alpha-synuclein, ubiquitin, & neurofilament proteins. Decrease in acetylcholine & other neurotransmitters. Minimal cortical atrophy. The pathologic difference between DLB & PDD is controversial & is reasonable to consider them as a single disease w/phenotypic heterogeneity. Generally, there are three main types of pathology that might cause cognitive impairment in the PDD/DLB spectrum: Lewy body-type degeneration in cortical & limbic structures, coincident AD-type pathology in cortical & limbic structures, & pathology in subcortical structures (e.g., degeneration of medical substantia nigra & nuclei of other ascending pathways).

**Pathogenesis:** Presumed to involve a gain of toxic function associated w/alphasynuclein posttranslational modification, oligomerization, and/or aggregation.

**Consensus diagnostic criteria** (*Neurology* 1996;47:1113): Core features (must have two for probable DLB, one 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 behavior disorder; dysphagia & impaired swallowing.

**Clinical features/diagnosis:** Typical features of DLB: 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. DLB commonly occurs together w/AD.

**Treatment:** *Parkinsonism*: L-dopa/C-dopa. Start 100/25 ½ tab daily & increase by ½ tab to 1 tab tid. May be effective for motor features early in illness, although only a fraction respond. Side effects of nausea, hypotension, delirium, & hallucinations occur early in treatment course & limit use. *Cognitive decline*: Cholinesterase inhibitors (see Table 12.3) are as effective if not more than in AD. *Depression*: SSRIs are the drug of choice. *Hallucinations/behavior disturbances*: Atypical antipsychotics. ***Avoid antipsychotics*** *whenever possible***:** Risk irreversible parkinsonism, NMS. First withdrawal L-dopa/cdopa medications to see if behavior improves; If not, use atypical antipsychotic w/caution (see

section on AD for doses). Start w/quetiapine. **Clozapine** may be particularly useful in avoiding extrapyramidal effects. Monitor CBC. *REM sleep behavior disorder:* low-dose clonazepam at night or melatonin.

## VASCULAR DEMENTIA

**Definition:** Decline in cognitive fxn due to accumulation of deficits from cerebrovascular events. Can be concurrent w/AD ("mixed dementia") w/a dementia syndrome spectrum from pure vascular dementia to pure Alzheimer's. Synonyms: Vascular dementia, poststroke vascular dementia, subcortical ischemic vascular dz & dementia, small-vessel dementia, strategic-infarct dementia.

**Epidemiology:** 15%-20% of dementia, though 9%-18% of these are mixed cases w/attempts to "purify" mixed cases unrewarding.

**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, 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: Impairment on MMSE/MoCA; 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 (in contrast to AD: recognition usually impaired as well).

**Treatment:** Acetylcholinesterase inhibitors (AchEIs: donepezil, galantamine, & rivastigmine) may have some benefit. Current preventive strategies: As for "normal aging" above. Management of vascular risk factors w/ASA, statins, antihypertensives, etc.

## NORMAL PRESSURE HYDROCEPHALUS (NPH)

**Definition:** 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).

**Epidemiology:** Very rare cause of dementia at 0%-5%; incidence of shunt-responsive NPH about 2.2 per million persons per year.

**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. Expansion theory: Initial pressures in NPH are high, but normal pressures eventually result from ↑ ventricle size, while forces on white matter ↑ ventricles expand. Fluctuating ICP theory: Critical intermittent spikes in intraventricular pressure. Gradient 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 (Evan's ratio: [max ventricular width]/[largest biparietal distance btw inner tables of skull]; ventriculomegaly = ratio ≥0.3); periventricular/periaqueductal T2 FLAIR hyperintensity (2/2 ↑ transependymal flow). High-volume LP (30-50 mL) → showing transient improvement in gait (occasionally cognition via MMSE/MoCA); temporary lumbar drain may be useful in diagnosis, though risk must be weighed against benefit.

**Treatment:** *Ventriculoperitoneal shunt*: Long duration & extensive cortical atrophy or WM dz on MRI ↓ prospects of success. Shunting improves gait far more than cognition. Adjunctive symptomatic pharmacotherapy (stimulants/dopaminergics, if impaired attention, apathy).

# Behavioral Neurology

Joel Salinas

Jesse Mez

## 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.

P.120

**Prosody:** Cadence & intonation of syntactic speech, typically a nondominant hemisphere finding.

**Circumlocution:** Use of many unnecessary words to express an idea.

**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.

**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 the United States: 200,000 secondary to head trauma; 100,000 secondary to stroke. 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 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 pts 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/significantly less 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 the Broca 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 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. Multisyllabic 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 recog 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 pt read irregular words (dough, height, pint).

**Writing:** Have pt write spontaneously. Write to dictation; copy; write nonsense words; write a description of “cookie theft” picture or other complex pictures.

## CLASSICAL APHASIA TYPES

**Categorization of the Classic Aphasia Types**

| Aphasia type | N | Fl | C | Rep | Re | Wr |
|---|---|---|---|---|---|---|
| **Anomic** | | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Broca's** | | | ✓[a] | | ✓[a] | |
| **Wernicke's** | | ✓ | | | | ✓ |
| **Conduction** | | ✓ | ✓ | | ✓ | ✓ |
| **Transcortical motor** | | | ✓[a] | ✓ | ✓[a] | |

| | | | | | |
|---|---|---|---|---|---|
| **Transcortical mixed** | | | ✓ | | |
| **Transcortical sens** | | ✓ | ✓ | | ✓ |
| **Global** | | | | | |

[a]While comp & reading are listed as intact, pts usually do have deficits in these domains spec related to agrammatism. Deficits are not as wide ranging as in the receptive aphasias.
Deficits are blacked-out ✓ indicates intact ability. N, naming; Fl, fluency; C, comprehension; Rep, repetition; Re, reading; Wr, writing.

| **Localization for Classic Aphasia Types** | |
|---|---|
| **Type** | **Lesion Localization(s)** |
| **Broca's** | Broca area plus surr frontal areas (Note: Lesion to Broca area alone usu. presents as incomplete Broca aphasia or aphemia). |
| **Transcortical motor** | 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** | Regions posterior or inferior to Wernicke area |
| **Global** | Frontal & temporoparietal regions |
| **Transcortical mixed** | Regions adjacent to both Broca & Wernicke areas. |
| **Anomic** | Left temporal cortices: temporal pole, proper nouns; inferior temporal lobe, animals; posterior temporal lobe, tools. |
| **Conduction** | 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.

**Additional 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, 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 hemianopsia (close proximity to temporal optic radiation).

**Caveats to classical aphasia types:** Classical aphasia types based on stroke/vascular territories. Tumors, other structural lesions, degenerative diseases often



don't follow classic categorization. Automatic speech (e.g., expletives or counting or singing) usually localize to nondominant hemisphere & are preserved in most aphasias including global.

**Handedness, cerebral dominance, & aphasia:** 99% of right-handers have left hemisphere language dominance, & 2/3 s of left-handers have left hemisphere language dominance. *Anatomic asymmetry*: dominant hemisphere is usually larger (esp temporal lobe). *Crossed aphasia in right-handers (rare)*: aphasia from right hemisphere lesion in right-hander that cannot be explained (e.g., by forced right-handedness, known childhood central nervous system impairment), 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:** Exaggerated fluent aphasia (w/mild deficits in comprehension & repetition): left anterolateral thalamic nuclei; assoc w/attentional & memory deficits. Defective comprehension w/or w/o repetition deficits: head of left caudate, anterior limb of left internal capsule; assoc w/dysarthria & right hemiparesis.

## APROSODIA

**Prosody:** Syntactic > 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.

**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:** W/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. Determine if pt can differentiate between variably compounded lexemes (e.g., “lighthouse keeper” vs. “light

housekeeper”)

**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.

## DISORDERS OF COMPLEX VISUAL PROCESSING & APRAXIA

**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 the 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 |
|---|---|
| **Visual object agnosia** | **Def:** Inability to visibly recognize a familiar object (despite nl vision)<br>**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:<br>○ Recognize that an object is a face, nose, mouth, etc.<br>○ Recognize facial emotions<br>○ Perform complex perceptual tasks<br>**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<br>**Localization:** Any lesion disconnecting both vis assoc cortices from language areas<br>○ Usually from two lesions: Callosal lesion (disconnecting hemispheres) & left occipital lesion (disconnecting left vis association cortex from left language cortex)<br>○ Occasionally from one lesion: Inferior & posterior to left occipital horn (causing both connections)<br>Commonly a/w right hemianopia, semantic memory deficits |
| **Achromatopsia** | **Definition:** Acquired color perception deficit involving all or part of vis field |

| | |
|---|---|
| | w/relative preservation of form<br>**Localization:**<br>• Ventral (inferior) vis association cortex (fusiform & lingual gyri) or subjacent white matter.<br>• Inferior lesion can cause achromatopsia in upper & lower quadrants, while superior lesions do not cause achromatopsia.<br>• 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<br>○ Localization: b/l obliteration of vis cortices or optic radiations.<br>○ Both blindness & denial are often transient.<br>"**Blindsight**"**:** Cortically blind pt not consciously aware of vis stimulus, but able to perceive image at basic level (geometric forms, mvmt, bright light). Pt can still accurately point to flash of light in inoperative field. Likely 2/2 to intact connections to vis parietal cortex |
| **Gerstmann synd** | **Definition:** Acalculia, left-right confusion, finger agnosia, agraphia; rarely pure synd<br>**Acalculia:**<br>○ Test oral & written addition, subtraction, multiplication, & division.<br>○ Attentional deficits, aphasia, alexia, & neglect can cause a secondary acalculia & should be evaluated prior to dx primary acalculia<br>**Left-right confusion:**<br>○ Test right & left on pt's & examiner's body.<br>○ Increase complexity w/multistep testing (e.g., "point to my left ear w/your right hand")<br>○ Aphasia & neglect can cause secondary left-right confusion & should be evaluated prior to diagnosing primary left-right confusion<br>**Finger identification deficit (i.e., finger agnosia):**<br>○ Ask pt to match his own fingers to outline drawing of a hand.<br>○ Aphasia can cause secondary finger agnosia & should be evaluated prior to diagnosing primary finger agnosia<br>**Agraphia** (see separate section for further discussion)<br>**Localization:** Left angular gyrus |
| **Balint synd** | **Definition: Simultanagnosia, optic ataxia, ocular apraxia**<br>**Simultagnosia** (or vis disorientation): Unpredictable perception & recognition of only part of the vis field ("seeing the trees but not the forest")<br>**Optic ataxia** (aka visuomotor ataxia): Impairment of target pointing under vis guidance. Usually no evidence of tremor<br>**Ocular apraxia:** Inability to shift gaze at will toward new vis stimuli in periphery<br>**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<br>**Localization:** Left parietal lobe or white matter projections |
| | |

| | |
|---|---|
| **Ideational apraxia** | **Definition:** Inability to carry out multistep activity using a real object even though individual mvmts required for activity are intact (e.g., 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<br>**Localization:** Often left parietal lobe |
| **Constructional apraxia** | **Definition:** Inability to reproduce patterns through drawing, copying or building 3-dimensional objects (not a true apraxia)<br>**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. Doesn't occur in isolation or have particular localization |

## 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.

**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 network involv postparietal cortex, frontal eye fields, & cingulate gyrus. 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 indicate cingulate involvement. Right-& left-sided thalamic lesions causing neglect also 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.

## 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. *Shortterm* (*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.,

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 the same category or concept as response (e.g., after being given a word list including "apple," subject will more likely say "orange" when asked to produce a 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:* frontoparietal network (largely 2/2 attentional dysfn). Long-term memory: Implicit memory: nonlimbic areas likely including the cerebellum, basal ganglia, & heteromodal assn areas of temporal & parietal lobes. *Explicit memory*: limbic areas especially Papez circuit (centered around the hippocampus, hippocampus > fornix > mammillary body > mammillothalamic tract > anterior thalamic nuclei > cingulate gyrus > presubiculum > entorhinal cortex) have critical function in *facilitating* storage & retrieval of memories. Actual storage is not well understood, but postulated to occur throughout the 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). Nl 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 neuroexam 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 med problems, 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 age-matched controls, although can consider stroke workup in older pts or those w/vascular risk factors.

**Pathophysiology:** Unknown. Not sz: EEGs negative. SPECT during attacks showed unilateral or b/l hypoperfusion of temporobasal region series (*J Nucl Med* 1998;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. Postictal 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 amnesia*: Younger pts w/1° retrograde amnesia. *Intoxication/drug use*: Often somnolent, + tox screen.

## FUNCTIONAL AMNESIA

**Presentation:** Often variable, transient, or long-standing. 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 amnesia by DSM V criteria). May be a/w multiple personalities (dissociative identity d/o by DSM V criteria).

**Risk factors:** Underlying underdeveloped personality, problematic childhood, sexual abuse.



## 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 w/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 relives trauma.

**Tx:** Includes SSRIs, medium- to long-acting benzodiazepines, 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: **S**leep change (either more or less), **I**nterest lower (anhedonia), **G**uilt, **E**nergy reduction, **C**oncentration reduction, **A**ppetite change (either more or less), **P**sychomotor slowing/agitation, **S**uicidal thoughts. *Major depressive episode*: Lasts ≥2 wk, incl low mood or anhedonia & meeting four of eight SIGECAPS criteria. *Persistent depressive disorder (dysthymia) d/o*: Only requires two of SIGECAPS criteria, but lasts >2 yr.

**Tx:** Antidepressants. Maximum response to drugs takes about 6 wk, but begins to occur in 1-2 wk. Early intervention improves acute outcome. Tx should be continued after recovery for at least 6-9 mo. If recurrence occurs, consider long-term maintenance. Refer to psych if sxs severe, refractory, or pt 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.

**Tx:** Mood stabilizers: Li, carbamazepine, valproate, lamotrigine. While most of mood stabilizers are freq used by neurologists, should defer to psych if only treating bipolar. 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; splitting,



self-mutilation. *Histrionic*: Excessively emotional & attention seeking. *Narcissistic*: Grandiose, entitled, disregard for others but retained ability to empathize.

*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 Φ hospital beds are occupied by schizophrenics. At least 10% of

homeless are schizophrenics. Onset usually late teens to mid-20s. 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 or early spring), 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's, 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, stroke, temporal lobe epilepsy (olfactory, gustatory, or tactile halluc).

**W/u:** CBC, chem. 10, $B_{12}$, RPR, TSH, UA, blood cx, Utox, serum tox, CXR. Consider HIV, neuroimaging, EEG, lumbar puncture, ESR, heavy metal screen, ceruloplasmin, adrenal studies, porphyria studies. Consider other dx strongly if older than 45.

**Tx:** 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. Progression & 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 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're typically hyperalert & can recall details of episode after recovery.

**DDx:** Parkinsonism, akinetic mutism, locked-in synd, neuroleptic malignant synd, serotonin synd, persistent vegetative state, nonconvulsive status, stiff person synd.

**W/u:** Close monitoring of vital signs 2/2 difficulty discriminating from NMS, chem 10, LFTs, CPK (particularly if suspect malignant catatonia), 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).

**Tx:** 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 use disorder

Loss of control while using & preoccupation w/a substance → continued use despite adverse consequences & physiological sxs (tolerance & w/d) within a 12-mo period; 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 popl meet criteria for drug (nonalcoholic, nontobacco) dependence. Alcohol dependence a/w acute pancreatitis, cirrhosis, cardiomyopathy, HTN, 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 questionnaire*: 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 initially.

**Risk factors:** Painful med procedures, parental illness, or trauma in childhood (esp sexual or physical abuse).

**Presentation:** *La belle indifference*: pt unconcerned w/sxs. *"Give-way" weakness*: pt may exhibit discontinuous resistance during strength testing. Apply pressure in an irregular/intermittent manner. *Hoover sign*: w/pt supine, hold heel 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, pt may nlly manipulate an object w/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 different frequency than tremor physician may alter tremor frequency. *Nonepileptic spells* (psychogenic nonepileptic sz; pseudoszs): See *Epilepsy* chapter.

**Prognosis:** Unfavorable w/sxs often lasting greater than a decade.

### Other somatoform d/os

**Somatization d/o:** Mult somatic complaints (4 pain, 1 sexual, 1 neurologic, 2 GI) over several yrs, before age 30, resulting in med tx & impairment of fxn; med d/o have



been excluded. Pts usually seek med help from mult providers. Chronic w/onset typically during adolescence.

**Hypochondriasis:** Preoccupied w/concerns of a serious condition, despite neg w/u, causing impairment in fxn. Misinterpret bodily signs & sxs.

**Body dysmorphic d/o:** Overly preoccupied w/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” (w/o external motivations, e.g., money); more common in women. Pts give dramatic hx, but vague & 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 (financial gain or avoiding work, stressors, incarceration, etc.).

### Management of somatoform/conversion d/o

Exclude 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 referral out of inability to dx. If pt is unwilling to seek psych evaluation, 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. *Etiologies*: usu drug induced (SSRI, MAOI-A >> MAOI-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, mech ventilation), consider benzos, cyproheptadine (4-8 mg PO tid without exceeding 0.5 mg/kg/d).

## Antipsychotics

All about equally effective (typical & atypical) w/exception of clozapine (& 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 chronic 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/d 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 [w/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.

# Movement Disorders

Ellen B. Penney

Albert Hung

## HYPOKINETIC MOVEMENT DISORDERS

### PARKINSON DISEASE (PD)

**Introduction:** Most common neurodegenerative mvt d/o affecting ~1% of people >60. Men:Women 3:2 predominance (unclear why), mean onset 60 yo (range: 40-70). Course variable. Primarily sporadic dz, but several familial forms identified. To date, 18 genes identified that can cause early-onset (<40) familial dz or late-onset familial dz or predispose to sporadic dz. Routine genetic screening not recommended.

**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/dx

**Diagnostic criteria:** Cardinal features are rest tremor, bradykinesia, rigidity, and postural instability w/asymmetric onset. Features pointing to an alternate dx are early (<3 yr) prominent instability/falls, early (<3 yr) freezing, early (<3 yr) hallucinations, dementia preceding motor symptoms or in 1st yr; supranuclear gaze palsy; symptomatic dysautonomia; documented condition known to cause parkinsonism, e.g., drugs. Definite dx *only* w/autopsy.

*Other features*: 40% develop dementia → see chapter *Dementia* for dementia w/Lewy bodies. ANS → bowel/bladder dysfxn, orthostatic hypotension.

| Features | |
|---|---|
| *Early signs*<br>↓ blinking (nl blink rate 15-20/min, PD → 5-10). ↓ facial expression (hypomimia). ↓ smell sensitivity.<br>*Bradykinesia*<br>Most characteristic feature of PD and most disabling. Slow mvmts, first noted w/fine motor tasks; micrographia (small handwriting). Difficulty turning in bed is late finding. Gait: slow, reduced arm swing, shuffling, freezing, turning en bloc → freezing. Monotone, hypophonic dysarthria. Sialorrhea (failure to swallow).<br>*Postural instability*<br>Worsening balance → falls; tested via pull test. Festination—chasing center of gravity. Retropulsion/propulsion. | *Tremor*<br>Resting 3-5 Hz "pill rolling." First sx in 70% pts. Usually in extremities. Can involve lips/chin but head/neck unusual. Usually asymmetric at dz onset. ↑ w/anxiety, contralateral mvmt, ambulation. Postural tremor most disabling. Need to differentiate from ET. Not always alleviated w/l-dopa or dopamine agonists.<br>*Rigidity*<br>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 dx: (1)** Parkinson-plus syndromes: eventually diagnosed in about 25% of pts w/original dx of PD.

Clues that may not be PD: early dementia → Lewy body dz, early/frequent falls → PSP, orthostatic hypotension → MSA, apraxia/alien hand → CBD, rapid onset → structural lesion/toxins. Typically have POOR response to dopaminergic therapy; worse prognosis; more rapid progression. **(2)** 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. **(3)** Structural: tumor, hydrocephalus, chronic subdural hematoma, trauma, vascular (Binswanger dz = multiple lacunar infarcts in basal ganglia leading to parkinsonism w/LE predominant symptoms). **(4)** Infectious: postencephalitic, prion dz, HIV/AIDS, PML, neurosyphilis, SSPE. **(5)** Toxic: carbon monoxide, carbon disulfide, manganese, MPTP, rotenone, paraquat. **(6)** Metabolic/miscellaneous: hepatocerebral degeneration, hypoparathyroidism/pseudohypoparathyroidism, hypoxia, Wilson dz, hypocalcemia (Fahr dz).

## Rx

**L-dopa-carbidopa:** Most effective med, active w/in 30 min of med ingestion, doesn't help all sxs (particularly postural instability). Starting med early in dz doesn't ↓ long-term efficacy. Start 25/100 mg tid. Titrate up by 1 pill qd or qod to achieve clinical effect. Should taper up to at least 1 g/day for 3 mo → 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). *Side effects*: Nausea (common w/med initiation) → give med w/meal or crackers (but high-protein meal decreases med absorption) or add additional carbidopa. Dyskinesias (worsen as dz progresses), vivid dreams, sleep disturbance, visual hallucinations, hypotension, constipation, compulsive behavior (e.g., gambling).

**Carbidopa:** ↓ peripheral side effects of L-dopa (nausea/hypotension). Daily dose of 75 mg needed; can increase as needed.

**Dopamine agonists:** Less efficacious than L-dopa but still first-line alternative. Thought to ↓ risk (by 3-4×) of dyskinesias/motor fluctuations in the first 5 yr of tx vs. L-dopa. Ergot derivatives (pergolide) associated w/valvular dz, nonergots preferred (e.g., pramipexole & ropinirole). *Side effects*: Decreased impulse control → gambling, hypersexuality, hypomanic states. Confusion, somnolence, delirium, hallucinations that are more common in elderly. Peripheral edema.

**MAO-B inhibitors** (rasagiline, selegiline): Reduce dopamine metabolism. Weakly effective meds but may increase effectiveness (and side effects) of L-dopa. Controversial evidence that rasagiline is neuroprotective. *Side effects:* Nausea, headache. Insomnia, confusion w/selegiline. Avoid w/SSRI, TCA, or MAO-B inhibitors that can cause serotonin syndrome.

**COMT inhibitors:** Prolong levodopa effect and reduces “wearing off.” Give entacapone w/each dose of L-dopa. Avoid use of tolcapone given liver toxicity, needs LFT monitoring.

**Anticholinergics:** Reduce tremor. Use limited by confusion (especially in pts >70).

**Amantadine:** Weakly effective monotherapy. May reduce dyskinesias/motor fluctuations due to levodopa.

**Atypical antipsychotics** (quetiapine, clozapine): For PD-associated psychosis.

**Which medication to start?** Most pts will need dopaminergic tx. If tremor is a major sympt, try anticholinergic or amantadine monotherapy. *Dopamine agonist vs. l-dopa*: L-dopa associated w/increased motor complications (i.e., dyskinesia, mtr fluctuations) early in Rx (<5 yr) but has better overall motor fxn. Controversy over whether early L-dopa tx has long-term consequences for motor fluctuations. Some evidence that motor complications in the two grps equalize over time (10-14 yr). Eventually those treated w/agonist will require adjunctive L-dopa. (*NEJM* 2000;342:1484; *J Neurol Neurosurg Psych* 1994;57:1034; *Neurology* 2008;71:474; *Lancet* 2014;14:60683).

**Neuroprotection:** Debate if L-dopa is neurotoxic or neuroprotective. Controversial evidence that rasagiline (TEMPO, ADAGIO studies) may be neuroprotective. Ongoing studies on uric acid. No clear evidence for Coenzyme Q10, riluzole, and agonists.

**Surgery:** Indicated in pts who were L-dopa responsive but developed motor fluctuations/dyskinesias, intractable tremor, dystonia. Benefits of surgery rarely exceed original drug effect. DBS currently preferred over ablation (such as pallidotomy or thalamotomy) used in 50 s. Two major targets for DBS: globus pallidus internus (GPi) and subthalamic nucleus (STN). DBS improves motor fxn ("on time" w/o motor fluctuations) and QOL. May have adverse cognitive and mood effects.

## Long-term medication complications

**Motor fluctuations:** Wearing off between doses, often predictable. Linked to low plasma levels of meds. As dz progresses, brain DA levels are more dependent on plasma levels. *Tx*: **(1)** Advise to avoid taking L-dopa w/high-protein meals; tighten dose interval (more frequent doses at same dose). **(2)** Add COMT inhibitors: ↑ half-life of L-dopa. **(3)** MAO-B inhibitors: ↓ dopa breakdown in CNS (selegiline, rasagiline). **(4)** DBS if above fails.

**Dyskinesia:** Involuntary choreiform mvmts, often linked to high plasma dopamine levels. As PD progresses, dyskinesia occurs at lower L-dopa/agonist doses. Cause unclear; exogenous dopaminergic stim 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, switch to dopa agonist monotherapy (if tolerated), or add amantadine (NMDA receptor antag) or clozapine (*Neurology* 2004;62:381).

## What to do in the inpatient setting

Continue home meds if possible. Even if NPO for surgery, continue meds until morning of surgery unless clear contraindication. Most meds NOT available in IV form. Sx will worsen if meds held. Other illnesses can also worsen PD symptoms.



## MULTIPLE SYSTEMS ATROPHY (MSA)

**Introduction:** Progressive dz w/autonomic dysfxn +/- parkinsonian, cerebellar si/sx, pyramidal sympts. Less common features: dystonia, dyskinesias, chorea. Cognition relatively preserved. Two types: MSA-P (prominent parkinsonism), MSA-C (prominent cerebellar sympts). Sporadic dz, prevalence ~3/100 K, M > F, average onset 55 yo (range 30-80 s), early disability (~3-5 yr), mean survival ~6-10 yr.

*Pathology*: Alpha-synucleinopathy w/glial cytoplasmic inclusions of alpha-synuclein. ANS sx → cell loss in brainstem (PRF, dorsal motor vagus nucleus) + spinal cord (parasympathetic preganglionic for bladder/sexual, intermediolateral column for hypotension). MSA-P → striatonigral system atrophy. MSA-C → olivopontocerebellar atrophy.

### Clinical manifestations

**Autonomic:** Occurs in all patients. Orthostatic hypotension is symptomatic in 70%; recurrent syncope in 15%; *l-dopa may worsen it*. Urogenital sxs (80%): Urinary retention/incontinence, early erectile dysfxn.

**MSA-P (parkinsonism, prev. known as striatonigral degeneration, or SND):** Parkinsonism is main feature in 80% of pts. Progressive akinesia/bradykinesia, rigidity, postural instability. 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):** Occurs in ~20%. Gait/limb ataxia, scanning dysarthria, cerebellar oculomotor problems. If + FH consider SCA & not MSA.

**Imaging:** MRI w/putaminal, olivopontocerebellar atrophy. T2 hyperintensities in pons, midcerebellar peduncles — > "Hot cross bun" sign 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.

### Rx

**Parkinsonism:** 30% initially responsive to L-dopa but usually require higher dose (up to 1,000 mg qd) and response declines over time; *dopamine may worsen orthostatic hypotension* and induced confusion. Botulin toxin for dystonia.

**Orthostatic hypotension:** Avoid large meals, increase salt intake, avoid straining during urination/defecation, no EtOH/drugs, elastic stockings, head up tilted bed. Fludrocortisone (up to 0.2 mg qd) or midodrine (up to 15 mg tid) first line. Pyridostigmine (up to 60 mg tid) has slight benefit and does not worsen supine HTN. Droxidopa newly approved medication (start 100 mg tid → up to 1,800 mg daily). **If supine HTN:** give meds for hypotension > 3 h before bed, treat only if SBP >200, start nighttime short-acting $Ca^{2+}$ antagonist. **Impotence** → penile injections (prostaglandin), sildenafil (but can worsen hypotension). **Speech/bulbar dysfxn:** Inspiratory stridor can develop; monitor for sleep apnea.

## PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

**Introduction:** Progressive dz w/vertical gaze difficulties & falls/gait instability w/in first year of onset. Prevalence ~2/100 K; 5% of pts in mvmt d/o clinic have PSP; no gender difference; average onset ~60.

*Pathology:* Tauopathy. Globose neurofibrillary tangles (tau deposits) in the brainstem & basal ganglia. Definitive dx via autopsy.

### Clinical features

***Parkinsonism* (*symmetric unlike PD*):** Postural instability w/frequent falls. Gait freezing occurs early in dz. Bradykinesia. Rigidity is axial > appendicular (unlike PD) w/retrocollis. Open, unblinking eyes (surprised look), masked facies, or blepharospasm & involuntary eye closure. Rarely w/pill-rolling rest tremor. Dystonia of extremities.

***Visual*:** First sign is slowing of vertical saccades (initially overcome by VOR) then limited range. Horizontal saccades effected later. Nontargeted saccades ("look left/right") affected first over targeted saccades ("look at my finger, then my nose"). Smooth pursuit slow w/saccadic intrusions. Eventually lose bell phenomena (closing eyelids causes eyes to roll up), convergence, and optokinetic nystagmus. Can have square-wave jerks & eyelid apraxia.

***Bulbar sxs*:** Dysarthria (usually spastic, "growling" speech), dysphagia.

***Cognitive:*** Executive dysfxn, reduced verbal fluency, perseveration. Apathy > disinhibition > dysphoria, anxiety. Depression. Pseudobulbar sx: emotional incontinence. "Applause sign"—preservation of automatic behavior (perseverative clapping). Palilalia—repetition of words.



***Other (less common) features*:** Pyramidal symptoms, insomnia

**Imaging:** MRI w/atrophy of the midbrain may be seen; "Mickey Mouse sign" demonstrates atrophy on axial midbrain cuts; beaked "hummingbird" appearance of the midbrain on midsagittal view.

**Rx:** *l-dopa*: Some pts (<50%) have short-lived, moderate benefit. *Amantadine* (100 mg bid) may have slight benefit, helps drooling and dyskinesias. *Botulinum:* For dystonia. *Multidisciplinary approach*: PT/OT/social

services.

## CORTICOBASAL DEGENERATION (CBD)

**Introduction:** Progressive dz w/asymmetric parkinsonism and cortical/cognitive dysfxn. Prevalence ~1/100 K but possibly accounts for up to 6% of parkinsonism. Onset >60 yo (possible female predominance).

*Pathology:* Frontoparietal atrophy + substantia nigra degeneration. Tauopathy w/neuronal neurofibrillary tangles (tau deposits), astrocyte tau plaques. “Balloon” neurons, neuronal achromasia (lack of staining).

### Clinical features

**Motor:** Often asymmetric, usually starts in one arm. Parkinsonism: Bradykinesia, rigidity, tremor (often faster [6-8 Hz] than in PD and jerky), myoclonus (may be stimulus sensitive), postural instability (late in dz), gait short & shuffling. Dystonia: Present in most pts, asymmetric, painful; progresses to “dystonic clenched fist” (dystonic flexed hand, held in a fist, fingers clenched around adducted thumb). Dysarthria, dysphagia.

**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 interfere w/voluntary mvmt, limb may grasp objects + not release them. Cortical sensory loss (e.g., agraphesthesia; not primary sensory). Neglect.

**Cognition:** Dementia may be presenting (or only) sign (some CBD do not develop movement sxs). Nonfluent aphasia common (overlap w/FTLD). Depression, apathy, irritability.

**Eye movements:** Difficulty initiating saccades (horizontal, unlike PSP); once initiated, saccades are nl. Smooth pursuit slow w/saccadic intrusions.

**Imaging:** MRI 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.

**Rx:** *L-dopa*: Response usually poor, transient. *Tremor:* beta-blocker, benzodiazepine, primidone. *Dystonia:* benzodiazepines, botulinum. *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 congenita*: 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 dz*): 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: (1)** When does tremor occur: at rest, w/posture, w/action, w/intention (worse at end of goal-directed mvmt)? **(2)** Amplitude + frequency of tremor (i.e., high 12 Hz or low 3 Hz). **(3)** Aggravating/relieving factors: Stress, anxiety, lack of sleep, caffeine intake, alcohol?



*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).

| Tremors | | |
|---|---|---|
| Rest predominant | **PD** | Second most common tremor in adults (after essential tremor). Often starts unilateral in one hand. Low frequency (4-6 Hz), “pill rolling,” improves w/mvmt. Assoc w/other sxs of PD. |
| | **Rubral tremor** | Due to midbrain injury (possibly due to lesion of superior cerebellar peduncle, substantia nigra, & red nucleus). Slower frequency than PD (3-5 Hz); large amplitude. May cause combined rest, postural, action, & intention tremor. Always associated w/signs of midbrain/cerebellar lesions. |
| Postural predominant | **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. 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.). Responds to clonazepam, gabapentin. |
| Intention predominant | **Cerebellar tremor** | Low frequency <5 Hz. Lesion affecting dentate nucleus or superior peduncle. Usually only intention tremor, but can occur. w/posture or even rest. 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 intention** | Due to lesion along cerebellar path from dentate nucleus to thalamus. Most common causes: Stroke, multiple sclerosis, midbrain lesion |

| | | |
|---|---|---|
| | **tremors** | (trauma or stroke). Other less common causes: Degenerative dz of cerebellum, severe essential tremor, Wilson dz, mercury poisoning. |
| | **Task-specific tremor** | Occurs *only* during specific tasks (and at no other time), most commonly writing. Can be associated w/task-specific dystonia. |
| Mixed: Postural and action | Essential tremor | See below. |
| | Enhanced physiologic tremor | Commonly confused w/essential tremor. Normal people have low amplitude, high frequency tremor (8-12 Hz), usually not visible. Many factors enhance tremor and make it visible: emotions (anxiety, fear, excitement, fatigue); caffeine; medical illness (hypoglycemia, fever, thyrotoxicosis, EtOH/opiate withdrawal, pheochromocytoma); many meds (see list below); toxins (mercury, lead, arsenic). *Tx*: Reduce/remove offending agent. |
| | Neuropathic tremor | Postural, intention tremor. Occurs in limb(s) affected by neuropathy. Due to weakness or loss of proprioceptive input. Occurs w/large fiber neuropathies (hereditary neuropathy, in recovery phase of GBS, or CIDP). |
| | 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:** Most common cause postural/action tremor. Rhythmic shaking of hands/arms (95% cases). May also involve: the head ("no-no" head tremor, 34%), tongue/LE (30%), voice (12%), face (5%) (*Pract Neurol* 2007;7:222). Tremor when hands outheld, worsens w/intention (at end of goal-directed mvmts). ~75% of pts → disability & decreased quality of life. Incidence increases w/age, dx at mid to late adulthood, no gender difference. +FH in up to 70% cases (felt to be heritable d/o, autosomal dominant, but some pts w/o FH). Pt w/1° relative → 4.7× risk of getting essential tremor. Pathophys unknown but likely involves dysfxn of cerebellar networks. Often improves w/alcohol intake.

**Dx:** Must consider secondary causes of tremor: meds; metabolic d/os (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 below. *DAT scan:* may help distinguish ET from PD.

***Red flags:*** Unilateral/focal tremor, leg tremor, rigidity, bradykinesia, rest tremor, gait disturbance → consider parkinsonism. Sudden/rapid onset on meds that worsen tremor. Isolated head tremor w/abnormal posture (head tilt or turning) → consider dystonia.

| Medications Commonly Causing Tremors |
| --- |
| Neuroleptics, reserpine, tetrabenazine, metoclopramide, antidepressants (especially TCA); lithium; cocaine; alcohol; bronchodilators; theophylline; caffeine; dopamine; steroids; cyclosporine; valproate; perhexiline; amiodarone; procainamide; calcitonin; thyroid hormones; chemotherapy (vincristine, adriablastin) |

| Differential Dx & Main Features of Tremors | |
| --- | --- |
| **Dx** | Tremor Description |
| Essential tremor | Hand > head/voice tremor, postural/intention, 4-12 Hz |
| Enhanced physiologic | Usually hands, postural/intention, 8-12 Hz |
| Orthostatic tremor | Legs, postural |
| Parkinson's | Rest, unilateral/asymmetric, hand, 3-6 Hz, other PD signs |
| Wilson dz | Upper/lower extremities, postural/intention, 4-6 Hz, pts <40 yo, liver dz, dystonia, etc. |

**Rx**

**Nondisabling mild symptoms** → Lifestyle modifications (no caffeine, no nicotine, avoid meds that cause tremors).

**Moderate to severe tremors** → 1st line: Propranolol or primidone. 2nd line: Other β-blockers, gabapentin, topiramate, BZD, botulinum toxin (focal/segmental dystonic tremor; inject to cause subclinical wkness; not very effective). 25%-55% no benefit from meds.

**Disabling medication-resistant tremors** → Surgery: DBS of thalamic VIM nucleus. Bilateral DBS: 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 or tid) | 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 of both agonist & antagonist muscles. 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: Focal 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*): Often dominantly inherited (w/low penetrance). Usually starts focal (in one limb) → progress to generalized in 50%. *Late onset* (*>26 yo*): More likely to affect neck or cranial muscles. More likely to remain focal. |

**Primary dystonia:** No other neurologic abnormalities (except myoclonus/tremor). No abnormalities on pathology. No underlying cause (no structural brain abnl, no inborn errors of metabolism) except (in some cases) identifiable genetic mutations.

| Primary Dystonia | |
|---|---|
| Primary focal dystonia | 10× more common than primary generalized dystonia. More common in adults, begins midlife, more common in women (except writer's dystonia), occurs in neck, face, arm. Can progress over 1-2 yr, but then becomes static. *Red flag*: if occurs in leg → may be first sign neurodegenerative dz.<br>**Cervical dystonia:** Most common focal & primary dystonia. 30-50 yo, begins w/neck stiffness & ↓ head mobility → abnl head posture (retrocollis) + neck/shoulder pain, sensory trick (touch face) may reduce sxs. Ddx: cervical disc dz.<br>**Cranial dystonia (usually >40 yo):** Blepharospasm, oromandibular dystonia, spasmodic dysphonia (strained/breaking >> breathy voice). |

| | |
|---|---|
| | **Blepharospasm:** Most common cranial dystonia. Causes ↑ blink rate, forced eye closure, difficulty w/eye opening. Sxs increase w/bright light, reading, driving.<br>**Oromandibular dystonia:** Involuntary clenching (bruxism), opening, deviation of jaw. |
| Primary generalized torsion dystonia | Progressive, disabling, usually begins in kids (<26 yo), genetic. Many cases autosomal dominant w/low penetrance. Multiple genes now identified. Most common cause DYT1 mutation → CAG deletion in torsion A gene. AD but penetrance only ~30%. Prevalent in Ashkenazi Jews. Starts as focal dystonia → generalized/multifocal (65%), segmental (10%), remains focal (25%). DYT6 associated w/AD adolescent-onset dystonia. |

**Secondary dystonia:** Large number of diverse causes. Due to an underlying pathology, usually additional neurologic signs/symptoms + abnormal brain imaging/labs are present.



| Secondary Dystonia | |
|---|---|
| Degenerative disorders | Other neuro si/sx present, usually d/o affects basal ganglia.<br>*Many causes*: Wilson dz, PD/Parkinson plus, Huntington, DRPLA, spinocerebellar degeneration, PANK2, familial basal ganglia calcification (Fahr), lysosomal storage d/o (Krabbe's, Niemann-Pick's), ceroid lipofuscinoses, mitochondrial dz (Leigh's, Leber's), neuroacanthocytosis, Lesch-Nyhan syndrome, ataxia telangiectasia, gangliosidoses, MLD, homocystinuria, Hartnup dz; glutaric aciduria; methylmalonic aciduria.<br>**X-linked dystonia parkinsonism syndrome** (DYT3, formly known as Lubag dz): Adult onset of dystonia and/or parkinsonism in people from Island of Panay (Philippines). Atrophy of caudate and putamen. Mutation in Xq13.1 region. |
| Drug-induced dystonia | L-dopa, dopamine agonists, antipsychotics, antiepileptics, calcium channel blockers, 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. |
| Other causes | Paraneoplastic, encephalitis, psychogenic, cervical cord or peripheral injury. |

**Dystonia-plus syndromes:** Syndromes in which other neuro signs are present but NOT associated w/neuropath findings (unlike degenerative d/o). Known genetic mutations.

| Dystonia-Plus Syndromes | |
|---|---|
| Dopa-responsive dystonia | **Segawa syndrome**: Autosomal dominant, DYT5. Rare, presents in early childhood, female predominance. Begins as foot dystonia, leading to gait problems → progressive generalized dystonia ± parkinsonism. Early development n. Marked diurnal variation, |

| | |
|---|---|
| | worse at end of day. Due to point mutation in enzyme important in the synthesis of tetrahydrobiopterin (cofactor for dopamine synthesis). *Tx*: Dramatic response to L-dopa.<br>Autosomal recessive mutations in tyrosine hydroxylase cause dystonia w/onset in infancy, hypotonia, hypokinesia, psychomotor delay. |
| Myoclonus dystonia | Onset childhood, dystonia of arms, trunk, bulbar w/brief myoclonic jerks. AD mutation (DYT11) w/maternal imprinting in gene encoding sarcoglycan. |
| Rapid-onset dystonia parkinsonism | Onset adolescence/early adulthood w/generalized dystonia and parkinsonism that has rapid development over hours to weeks and then stabilizes. AD mutation (DYT12) in Na+/K+ ATPase α3 subunit. |

**Dx: (1)** Hx, exam. **(2)** Brain MRI to rule out underlying pathology. **(3)** Consider DYT1 or DYT6 testing if pt < 26 yo at onset; adult onset arm dystonia (DYT1); or +FH of dystonia w/onset <26 yo. **(4)** L-dopa trial to r/o dopa-responsive dystonia if onset <26. **(5)** Consider CBC, CMP, Mg, Ca, coags, LFTs, TFTs, ESR, ANA, RPR, bld smear, serum AA, urine OA, sulfates, lysosomal enzymes, Wilson dz evaluation (slit lamp exam for Kayser-Fleischer ring ~100% sensitive, serum ceruloplasmin ~85% sensitivity, 24-h urine copper, genetic testing).



| Dystonia Treatment | |
|---|---|
| **Physical therapy** | Braces/splints can help improve posture & prevent contractures. Temporary immobilization followed by retraining may be beneficial in hand dystonia. CAUTION: Immobilization can exacerbate dystonia in some pts. |
| **L-dopa** | Small subset respond. Should be trialed in all pts w/onset <26. Usually 100-300 mg/day effective. Usually no L-dopa-induced fluctuations/dyskinesias. If no improvement in 1 mo L-doparesponsive dystonia unlikely. |
| **Antidopaminergic meds** | Dopamine receptor blockers: Mixed efficacy, usually not used due to side effects.<br>Tetrabenazine: Inhibitor of vesicular monoamine transporter 2 that depletes dopamine. Often effective in tardive dystonia. May be beneficial in generalized dystonia. *Side effects:* Depression, somnolence, and acute dystonia. |
| **Anticholinergic meds** | Trihexyphenidyl (start at 1 mg qhs, taper up to max 10 mg tid) may help generalized/segmental dystonia. Young pts tolerate side effects better (somnolence, confusion, dry mouth, urinary retention). Pyridostigmine (peripheral acting anticholinesterase inhibitor) can reduce side effects. Can worsen dyskinesias. |
| **Muscle relaxants** | Benzodiazepines, tizanidine, cyclobenzaprine, baclofen, and opiates may be useful. Clonazepam may particularly help blepharospasm & myoclonic dystonia. Baclofen may help oromandibular dystonia. |

| | |
|---|---|
| **Botulinum toxin** | Very effective for focal dystonia. Esp good for blepharospasm, cervical dystonia, and oromandibular dystonia. Slightly less useful for limb dystonia (hard to produce fxnl benefit). |
| **Deep brain stimulation** | DBS of internal globus pallidus can produce dramatic benefits for some pts w/generalized or segmental dystonia. May take > 6 mo to achieve maximum benefit. |

## CHOREA

**Introduction:** Abrupt, rapid, or continuous movements that flow randomly, can be dance-like, often incorporated into normal movement/behavior. Athetosis is similar, slower, writhing movements. Manifestations range between mild restlessness (can appear voluntary and fidgety) and severely disabling movements interfering w/speech, feeding, & gait. Motor impersistence noted on tongue protrusion (aka “jack-in-the-box tongue”) or handgrip (aka “milkmaid grip”). Pendular or “hung-up” (discontinuous relaxation) reflexes. Temporarily suppressible.

**Causes:** *Huntington dz* (see below); *storage dzs*; *genetic metabolic conditions* (Wilson's, Niemann-Pick's, Lesch-Nyhan's, pantothenate-kinase-associated neurodegeneration, ataxia telangiectasia); *Leukodystrophies* (Pelizaeus-Merzbacher's); *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; Beriberi, pellagra, B12 def); *toxins* (mercury, manganese, thallium, CO poisoning, alcohol, toluene); *Meds* (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, autosomal dominant dz w/mvmt, behavioral, & cognitive sympts. Prevalence 5-7/100 K Caucasians. Average onset 40-50s (range infancy to old age). Gene on chromosome 4 w/expanded trinucleotide repeat (CAG). Mutant gene → toxic gain of fxn. If <36 repeats normal, 36-41 repeats may get dz, fully penetrant when >41. Repeat length roughly correlates w/age onset. Repeats may expand w/subsequent generations, leading to anticipation (i.e., earlier onset of dz, particularly w/paternal inheritance). *Pathology*: Striatal degeneration, cortical atrophy/thinning, ubiquitinated intranuclear inclusions of Huntington protein.

| **Clinical Features Huntington Disease** | |
|---|---|
| Motor symptoms | Wide range of sympts. ~50% pts unaware of early sympts.<br>Earliest symptoms: Impaired saccade initiation (must blink to initiate) → delayed, slowed saccades. Impaired tongue protrusion (motor impersistence). Slow, irregular finger tapping & rapid alternating mvmts.<br>Chorea most prominent in early-moderate dz. Apraxia.<br>Later features: Bradykinesia, rigidity, dystonia, imbalance, impaired speech/swallowing. |
| Psychiatric symptoms | Subtle change in personality → depression, irritability, apathy, anxiety, disinhibition. High suicide rates (5%-10%). Less common delusions, psychosis, mania. |

| | |
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| Cognitive symptoms | Presenting symptom in ~8% pts. Impaired executive fxn, processing speed, attention, memory. |

**Dx:** Confirmed w/genetic testing. Perform genetic counseling prior to genetic testing in all pts. Predictive genetic testing in asx pts available.

**Rx:** No known dz modifying tx. Meds w/potential benefits: Coenzyme Q10, creatine, pridopidine, highly unsaturated fatty acids. Supportive tx w/weight maintenance & family counseling important. Chorea → dopamine antagonists (may have parkinsonian side effects), tetrabenazine. Psychosis → newer neuroleptics. Anx/dep → mood stabilizers, SSRI.



## MYOCLONUS

**Introduction:** Sudden, brief, shock- or jerk-like involuntary mvmts. 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)** Segmental: Palatal & 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 w/feeding.

**Essential myoclonus:** Idiopathic or genetic, progresses slowly, subcortical, usually the most prominent or only clinical exam finding. Some associated disability (usually mild). Hereditary form: Onset <20 yo, dominant inheritance (variable severity), benign course, myoclonus throughout upper body.

**Epileptic myoclonus:** Occurs as a component/part of epilepsy, as only manifestation of epilepsy (myoclonic sz), or as one of multiple sz types. EEG → ictal epileptiform discharges.

**Secondary (symptomatic) myoclonus:** 2/2 wide range of underlying dzs (storage d/o, neurodegenerative, metabolic, paraneoplastic, encephalopathy, posthypoxia, infectious, CNS injury/inflamm.). Usually chronic/subacute progression. Often a/w AMS, sz, ataxia, other mvmt d/os. Drug induced: 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*. Valproate: Titrate slowly, daily dose of 1,200-2,000 mg. BZD → clonazepam (may need 15 mg/day). Levetiracetam: Titrate up for clinical response (up to 3,000 mg/day). Barbiturate: Phenobarbital. Phenytoin/carbamazepine: Helpful only in small %. Zonisamide: Usually effective daily dose of 200-600 mg; better for cortical. Sodium oxybate, tetrabenazine, anticholinergics. |

## TICS

**Definition:** Intermittent, repetitive stereotyped movements and/or sounds; rhythmic or nonrhythmic. Voluntary movement made in response to an involuntary & irresistible urge to move. Suppression usually associated w/uncomfortable feelings/urges to move or vocalize. Precipitating factors: Stress, anxiety, boredom. *Differentiating between tics & myoclonus*: **(1)** Myoclonus interferes w/voluntary action; tics do not. **(2)** Tics suppressible; myoclonus is not. **(3)** Tics often preceded by subjective urge to move. *Differentiating between tics & dystonia*: **(1)** In dystonia, the body moves of its own accord; tics are under semivoluntary. **(2)** In tics, body position & mvmts return to normal between tics.

**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 d/os. Evaluate for precipitating factors such as stress, meds, drug abuse, streptococcal infection (questionable association of tic d/os w/strep infections). In pts 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. **Rx:** Warranted when tics are interfering w/schoolwork, social fxning. Tx of associated ADHD, OCD, anxiety d/os often more important than Tx of tics. Education (pt, family, school), reassurance, manipulation of environment, identifying & treating triggers. *Clonidine, guanfacine, clonazepam* are first-line rxs. Neuroleptic meds are second line (risperidone). Botulinum toxin can be considered if dystonic tic. DBS in severe intractable tic d/os; further studies needed.

| Other Hyperkinetic Movement Disorders | |
| --- | --- |
| **Hyperekplexia** | Startle d/o 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 |

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| | in neonatal period; assoc w/alpha-1 subunit of glycine receptor gene point mutations; treated w/clonazepam. |
| **Hemiballismus** | Violent, 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 mvmts. Appear purposeful to some degree but serving no obvious purpose; e.g., wringing hands, head nodding, body rocking. Occurs in autistic spectrum d/os such as Rett syndrome. Can be suppressed. Also seen in ~10% of nonautistic kids as well as FTD & psychosis.<br>*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 starts earlier. **(3)** Stereotypy more often rhythmic/symmetric v. tics. **(4)** Tics can wax & wane; stereotypy tends to be more persistent. **(5)** Tics short duration; stereotypy last longer. |

## GAIT DISORDERS

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| Gait | Description |
|---|---|
| Cerebellar | Leaning forward, wide based, lurching irregularly.<br>Unable to tandem; associated w/other cerebellar signs such as dysarthria, dysmetria, dysdiadochokinesia.<br>Causes are many & include cerebellar degeneration from EtOH & phenytoin, strokes, tumor, MS, spinocerebellar ataxias, ataxia telangiectasia, DRPLA, episodic ataxias. |
| Frontal | Upright posture; impaired postural reflexes.<br>Slow, magnetic gait, can have impaired initiation.<br>Can be related to bifrontal lesions, subcortical dz (e.g., microvascular angiopathy), normal pressure hydrocephalus. |
| Proprioceptive or sensory ataxia | Romberg sign present, wide based, high stepping gait.<br>Due to loss of sensation (e.g., proprioception & vibratory).<br>Causes: Peripheral neuropathy, vitamin B12/E deficiency, Friedrich ataxia. |
| Spastic (scissoring) | Increased tone in hip & knee extension resulting in one foot stepping across the path of the other w/circumduction.<br>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.<br>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 | Affected leg: Flexed at the hip in exaggerated way to elevate the foot & prevent tripping from weakened dorsiflexion & toe drag. May slap foot down to feel the floor. Related to foot drop or severe sensory ataxia. |
| 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. May almost fall, lean into walls, etc. w/o actually falling. |

## DRUG-INDUCED MOVEMENT DISORDERS

**Introduction:** Caused by dopamine receptor antagonists → neuroleptics, antinausea meds (Compazine), or meds for gastroesophageal d/o (e.g., metoclopramide)

### Acute

***Dystonia*** (most common rxn): Occurs w/in minutes. Tx: d/c offending agent; BZD (lorazepam); anticholinergic (benztropine or diphenhydramine) may help but could worsen dyskinesia/chorea.

**Other disorders:** Tics, dyskinesias, chorea.

**Subacute:** Akathisia → motor restlessness. Tx: D/c offending agent; BZD, β-blocker, dopamine agonist, anticholinergic (could worsen dyskinesia/chorea).

**Tardive syndromes (chronic):** Develops months to years after neuroleptic.

***Tardive dyskinesia*:** Most common form, choreiform mvmts of mouth, lips, tongue. Atypical antipsychotics decrease risk of getting this d/o. In 1/3 of pts, d/c offending med → sx resolution.

***Tardive dystonia*:** Dystonic posturing usually of axial muscles → rocking of trunk/pelvis.

**Tx:** Stop antipsychotic (slowly titrate off, **abrupt d/c worsens sxs**), clonazepam, Botox, tetrabenazine (Side effects: depression, somnolence. Start 12.5 mg daily for 1 wk and then slowly taper up to max 150 mg daily). Anticholinergics may help dystonia but could worsen dyskinesias/chorea. Refractory: DBS.

# Meningitis, Encephalitis, and Brain Abscesses

Kate T. Brizzi

Tracey Cho

Meningitis: Inflammation of the meninges. Encephalitis: Inflammation of the brain. Meningoencephalitis: Inflammation of brain & meninges. Aseptic meningitis: Meningitis w/neg routine bacterial cx (misnomer—causes include infectious & noninfectious agents, excluding causes of acute bacterial meningitis). Chronic meningitis: Meningitis > 1 mo. Recurrent (Mollaret) 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, or even without neck stiffness.



***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%)<br>BMS = 1: won't miss bacterial meningitis, but nonspecific (Se >99%, Sp 37%-73%)<br>BMS ≥ 2: strongly suggests bacterial meningitis (Se >99%, Sp 97%)<br>(*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/$mm^3$*.<br>*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 |
| | → | "Aseptic" | → | Admit, w/u AAM |
| | | | → | 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 (neg Gram stain, CSF



ANC < 1,000, CSF protein < 80, peripheral ANC < 10). **(3)** Normal serum WBC. **(4)** No sz during illness. **(5)** No cerebral (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 (coxsackie, ECHO, non-polio entero)<br>Herpes viruses (HSV1, HSV2, VZV, CMV, EBV, HHV-6, simian herpes B virus)<br>Resp viruses: Adenovirus, rhinovirus, influenza types A and B, parainfluenza viruses, RSV<br>Arboviruses: EEE, WEE, VEE, St LE, 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, 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), *Whipple 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*, amebae (*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-cytosine 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, Behcet dz, sarcoidosis, Vogt-Koyanagi-Harada syndrome, Fabry dz.
**Neoplastic:** Leptomeningeal cancer, leukemia, lymphoma, carcinomatous meningitis, posttransplantation lymphoproliferative disorder
**Vascular:** Infarctions (brain, cord), CNS vasculitis (primary or secondary)
**Postinfxn/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 parainfections. **(2)** Mosquito & tick-borne 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 sx pointing to asymmetric

temporal & frontal lobe involvement. Fever/HA progress for days & then szs, obtundation). **(3)** Useful clues on exam (Table 14.1): 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, uveitis (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 × 14 days (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 plasmapheresis (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 if reasonable grounds for suspicion.

**Diagnostic Tests:** ***Labs*****:** Vast ddx. Use "two-step" approach: **(1)** *Initial w/u* for dangerous/common/treatable causes (see **Table 14.3**) **(2)** *Further w/u* focused based on: Pace & temporal pattern of illness (acute, subacute/chronic/recurrent), clinical clues (see **Table 14.1**), epidemiology & risk factors (**Table 14.2**), initial lab results (**Table 14.3**). ***MRI w/gado*****:** If suspect encephalitis (may help narrow ddx). ***EEG*****:** If pt is confused/obtunded/comatose to r/o nonconvulsive status epilepticus.

**Table 14.1 Possible Etiologies Based on Clinical Findings**

| |
|---|
| **Hepatitis:** *C. burnetii* |
| **Lymphadenopathy:** HIV, EBV, CMV, measles, rubella, WNV, (*Toxoplasma) Treponema 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, St LE, *T. whipplei, T. brucei gambiense* |

| |
|---|
| **Cranial nerve palsies:** HSV, EBV, *Listeria, TB, T. pallidum, B. burgdorferi, T. whipplei, Cryptococcus, Histo, Coccidioides* sp., HIV, Lyme, VZV, CMV, HSV, sarcoid |
| **Dementia:** HIV, sCJD & vCJD, measles virus (SSPE), *T. pallidum, T. whipplei* |
| **Myorhythmia:** *T. whipplei* (oculomasticatory) |
| **Parkinsonism:** JEV, St LEV, WNV, Nipah virus, *T. gondii, T. brucei gambiense* |
| **Flaccid paralysis:** JEV, WNV, tick-borne encephalitis virus, enteroviruses, (enterovirus-71, coxsackieviruses), poliovirus |
| **Rhombencephalitis:** HSV, WNV, enterovirus 71, *Listeria, rabies* |
| **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:** HSV2, Behcet's |
| **Hydrophobia, aerophobia, pharyngeal spasm, hyperactivity:** Rabies |
| **Tremors of eyelids, tongue, lips, extremities:** St LE, WNV |
| **Temporal lobe preference:** HSV > VZV, EBV, HHV6, syphilis |
| **Hydrocephalus:** Bacterial, fungal, & parasitic agents, sarcoidosis |
| **Very low CSF glucose:** Tuberculosis, *Cryptococcus*, neoplastic, sarcoidosis |
| **Skin rash, aphthous ulcers:** HIV, VZV, HSV, EBV, CMV, JCV, Behcet's |





### Table 14.2 Possible Etiologies Based on Risk Factors & Epidemiology

| **Age** |
|---|

| | |
|---|---|
| Neonates | HSV2, CMV, rubella virus, *Listeria, T. pallidum* (syphilis), *Toxoplasma* |
| Infants & children | EEE, JEV, Murray Valley EV, influenza virus, La Crosse v. |
| Elderly | EEE, St LE, WNV, sporadic CJD, Listeria |
| ***Animal contact*** | |
| Bats | Rabies v., Nipah v. |
| Birds | WNV, EEE, WEV, VEE, St LE, Murray EV, JEV, *Cryptococcus* |
| Cats | Rabies v., *C. burnetii, B. henselae, T. gondii* Dogs Rabies v. |
| Horses | EEE, WEE, VEE, Hendra v. |
| Old World primates | B v. |
| Raccoons | Rabies v., *B. procyonis* |
| Rodents | EEE, VEE, tick-borne EV, Powassan v. (woodchucks), La Crosse v. (chipmunks, squirrels), *Bartonella Q, LCMV* |
| Sheep & goats | *C. burnetii* |
| Skunks | Rabies v. |
| Swine | JEV, Nipah v. |
| 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 | *Gnathostoma* species |
| Unpasteurized milk | Tick-borne EV, *Listeria*, *C. burnetii Insect contact* |
| Mosquitoes | EEE, WEE, VEE, St LE, Murray Valley EV, JEV, WNV, La Crosse v., |

| | |
|---|---|
| | *Plasmodium falciparum* |
| Sandflies | *Bartonella bacilliformis* |
| Ticks | Tick-borne EV, Powassan v, *R. rickettsii, Ehrlichia, A. phagocytophilum, C. burnetii*, *B. burgdorferi* |
| Tsetse flies | *T. brucei (gambiense & rhodesiense)* |
| ***Occupation*** | |
| Exposure to animals | Rabies v., *C. burnetii, Bartonella* sp. |
| Exposure to horses | Hendra v. |
| Work w/primates | B v. |
| Laboratory workers | WNV, HIV, *C. burnetii, Coccidioides* sp. |
| Healthcare 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 v., WNV (transfusion/transplant/breast-feeding), HIV, rabies v. (transplant), influenza v, *M. pneumoniae, TB, T. pallidum* (sexual intercourse, 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 v. |
| Transfusion & transplantation | CMV, EBV, HIV, tick-borne 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 v. |
| Central America | Rabies, EEE, WEE, VEE, St LE, *R. rickettsii, P. falciparum, T. solium* |
| Europe | WNV, tick-borne EV, *A. phagocytophilum, B. burgdorferi* |
| India, Nepal | Rabies v., JEV, *P. falciparum* |
| Middle East | WNV, *P. falciparum* |
| Russia | Tick-borne encephalitis v. |
| South America | Rabies, EEE, WEE, VEE, St LE, *R. rickettsii, B. bacilliformis* (Andes mountains), *P. falciparum, T. solium* |
| Southeast Asia, China, Pacific Rim | JEV, tick-borne *EV*, Nipah v., *P. falciparum, Gnathostoma sp., T. solium* |
| **Unvaccinated status** | VZV, JEV, polio v, measles, mumps, rubella |

## Table 14.3 Laboratory Workup for Encephalitis & Aseptic Meningitis

| General |
|---|
| **Serum:** CBC w/differential, ESR, CRP, ACE; RPR & FTA-ABS, cryptococcal antigen<br>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<br>**CSF:** Cell count + diff, protein, glucose, opening pressure<br>Cx: Bacterial, fungal, viral, mycobacteria<br>FTA-ABS (Se, not Sp; nonreactive test excludes dx; reactive nondiagnostic); AFB smear PCR for HSV1, HSV2, VZV, EBV, enteroviruses, mycoplasma, *M. tuberculosis* VZV IgM & IgG; VDRL (Sp, not Se), cryptococcal antigen<br>*B. burgdorferi* serology (ELISA & Western blot); EIA capture, calculate IgG index<br>**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; rabies at back of neck at hairline
DFA & PCR of skin bx specimen (if rash present) for *R. rickettsii*
**Imaging:** CXR, MRI of the brain w/& w/o gadolinium

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**Additional Workup as Clinically Indicated**

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**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 St LE, EEE, VEE, HSV2, EBV, La Crosse virus, LCMV, WNV, enteroviruses, adenoviruses, *M. pneumoniae, R. rickettsii*, *Ehrlichia chaffeensis*, *A. phagocytophilum*. WNV IgM. La Crosse virus IgM.

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**Whole blood specimen:** Smears for *Ehrlichia morulae*, PCR for *Ehrlichia*, *Anaplasma* species
**CSF:** IgM for WNV & St LE, PCR for *Ehrlichia*, PCR for *Anaplasma* species

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DFA, direct fluorescent antibody. *Clin Inf Dis* 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 cantonensis*, 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's, other vasculitis.
  - Drugs: NSAIDs, abx, IVIg, immunosuppressants, allopurinol, vaccination, intrathecal Rx.
- **Neoplastic:** adenocarcinoma, lymphoma, leukemia.
- **Other rare causes:** Hereditary autoinflammatory periodic fever syndromes, cholesterol extravasation from craniopharyngioma, or teratomas (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, syphilitic, Lyme, cryptococcal, HIV*), *neuro-rheum* (*Behcet, Sjögren, Wegener, SLE*), *& neuro-onc* (*neoplastic meningitis*).

## HISTOPLASMA MENINGITIS

Endemic fungal infection in the United States, 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 and then itraconazole 200 mg bid for at least 12 mo, ART (for AIDS).

## COCCIDIOIDES MENINGITIS

Soil fungus (*Coccidioides immitis*) endemic in SW United States & Mexico. Usu selflimiting 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/day for life, ± intrathecal amphotericin B initially.

## TOXOCARIASIS MENINGOENCEPHALITIS

**Very rare** helminth infxn (roundworm) of human w/*Toxocara canis* (dog) or *T. cati* (cat) via geophagia or exposure to contaminated soil. P/w meningitis/meningoencephalitis/myelitis w/ocular lesion & hepatomegaly. ***Dx*:** ↑eos & + abs in serum or CSF, MRI w/enhancing subcortical white matter lesions (˜ADEM). ***Rx*:** Antihelminthic therapy & corticosteroids.

## EASTERN EQUINE ENCEPHALITIS

Most neuropathogenic arbovirus in the United States; most endemic in Eastern N. America (July-October).

**Clinical:** Incubation: Mosquito bites causing cutaneous lesions. Prodrome: Fever, HA, flulike *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 mo 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 pachymeningitis (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 (abnormal lymph node, skin lesion, enlarged lacrimal gland, transbronchial, conjunctival) 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 & TNF inhibitors 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). Increasingly recognized as part of IgG4-associated disorders.

**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. Autoimmune systemic diseases, esp SLE, predispose. Usu 2/2 repeated exposure, e.g., IVIg (>2 g/kg dose, >6 g/h infusion rate, w/o prehydration), NSAIDs, abx (e.g., trimethoprim, Bactrim, PCN), immunosuppressants (infliximab, MTX, cytarabine, azathioprine), 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); +HSV2 cx 75% (not used in practice); +HSV2 PCR. (**Mollaret cells**—large, multilobulated, "footprint" 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 HSV2 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). **(3)** S/p splenectomy predisposes for pneumococcal meningitis.

**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 >7 days. **MS** Δ: 78% (most confused/lethargic, but ~1/4 responsive to pain only or unresponsive). "**Classic triad**": **Fever, nuchal rigidity, MS**Δ (*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. meningitidis*: Rash (64%; of these, ˜90% are petechial; can be maculopapular). **(3)** *Arthritis:* in ˜7% cases; most common w/*N. meningitidis*. 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, Brudzinski & 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), otorrhagia.

**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): not Se or Sp. *Brudzinski sign* (passive neck flexion → hip flexion): not Se or Sp. *Kernig sign* (w/hip flexed, extend the knee → pain): not Se or Sp. *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 14.4**).

- Consider changing abx when pathogen & sensitivities avail: *see* **Table 14.5**.
- Abx **dosing:** *See* **Table 14.6**. Abx **duration:** *See* **Table 14.7***.*
- When can treatment be **completed at home?** *See* **Table 14.8***.*

**Early prognosis/triage to ICU vs. ward:** See %s complications/outcomes above. Model based on retrospective analysis of 269 cases of ABM dxd 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.



**Table 14.4 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 OR cefotaxime + ampicillin | *S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic GN bacilli |
| **Basilar skull fracture** | |
| Vancomycin + ceftriaxone OR cefotaxime | *S. pneumoniae*, *Haemophilus influenzae*, group A β-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) |
| **Postneurosurgery** | |
| 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 + | Coag-neg staph (esp *S. epidermidis*), *S.* aureus, aerobic GN bacilli (incl *P. aeruginosa*), *Propionibacterium acnes* |

| | |
|---|---|
| meropenem | |
| **Impaired cellular immunity** | |
| Vanco + ceftriax. OR cefotaxime + ampicillin | *L. monocytogenes*, gram-neg bacilli |
| **Dosing** | |
| Vancomycin | 1 g q12h (or 30-45 mg/kg/d div bid-tid) |
| Ceftriaxone | 2 g q12h |
| Cefotaxime | 2 g q4-6 h |
| Ampicillin | 2 g q4h |
| Cefepime | 2 g q8h |
| Dexamethasone | 0.15 mg/kg q6h × 2-4 days, first dose ~15 min before (or w/) first abx dose |



**Table 14.5 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. meningitides*** | | |
| *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] | Trimethoprimsulfamethoxazole, meropenem |
| *Streptococcus agalactiae* | Ampicillin or penicillin G[e] | Third-gen cephalosporin[a] |
| *Escherichia coli* & other Enterobacteriaceae[f] | Third-gen cephalosporin | Aztreonam, fluoroquinolone, meropenem, trimethoprimsulfamethoxazole, 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 14.6 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) |
| **Ceftazidime** | 6 g (8) | **Rifampin** | 600 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 14.7 Duration of Abx for ABM Based on Pathogen[a]

| | |
|---|---|
| *Neisseria meningitides* | 7 |
| *Haemophilus influenzae* | 7 |
| *S. pneumoniae* | 10-14 |
| *S. agalactiae* | 14-21 |
| *Aerobic Gram-neg bacilli* | 21 |
| *L. monocytogenes* | ≥21 |

[a]Not rigid—modify as clinically indicated. *Clin Infect Dis* 2004;39:1267.



### Table 14.8 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.

### 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%), mycotic aneurysm.

**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, gray-white jxn (due to microinfarction → BBB breakdown). Common associated infxns: Chronic pulmonary (e.g., lung abscess or empyema); skin, pelvic, intra-abdominal infxns; bacterial endocarditis, esophageal dilation & endoscopic sclerosis of esophageal varices, cyanotic congenital heart dz (mostly children). Pulmonary AVM an occult cause. *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 & 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 streptococci*, *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 & CN6 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. **(3) MRI w/gado:** Similar findings to CT, but more sensitive. Compare T1 pre-& postcontrast; 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). **(4)**

**LP:** Contraindicated if focal sx (e.g., unilateral HA) or signs ↑ ICP. Imaging showing posterior fossa abscess or mass effect with displacement of middling structures. Hydrocephalus. If not contraindicated, CSF 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. **(5) Aspiration** (stereotactic CT-guided or surgical) & cultures (Gram stain, aerobic, anaerobic, mycobacterial, & fungal cultures). Special stains: Acidfast stain (for mycobacteria), modified acid-fast stain (for Nocardia), fungal stains. **(6)**

**Serology:** Blood anti-Toxo IgG Ab, serum anticysticercal abs. **(7) ±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): Tailor 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 q4-6 h |
| Hematogenous | Vancomycin 15 mg/kg IV q12h[a] **PLUS** metronidazole (see above) |
| Neurosurg or penetrating TBI | Vancomycin 15 mg/kg IV q12h[a] **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 |

[a]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 abx before biopsy 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.

# Neurologic Infectious Diseases

Tamara B. Kaplan

Nagagopal Venna

## NERVOUS SYSTEM LYME DZ

**Definition:** Tick-borne spirochete infxn caused by *Borrelia burgdorferi* (*Borrelia garinii* or *afzelii* in Europe/Asia).

**Epidemiology:**

- Most common vector-borne illness in the United States; peak incidence in summer (May-Aug)
- Majority of cases in NY, NJ, CT, RI, WI, PA, MA, ME, NH, MI, MD, DE, northern CA

| Clinical Manifestations | |
|---|---|
| **Stage** | **Manifestation** |
| Stage 1: Early localized: Wks after infxn | *General*: flu-like illness. *Derm* (~80%): Erythema migrans (EM) |
| Stage 2: Early disseminated: Wks to mos after infxn | *General*: Fatigue, malaise, LAN, HA; fever uncommon. *Derm*: Multiple (1-100) annular lesions ±EM. *Rheum* (~10%) migratory arthralgias (knee & hip) & **myalgias**. *Neuro* (~15%): Cranial neuropathies (esp, **CN VII**), aseptic meningitis, mononeuritis multiplex (±pain), transverse myelitis. *Cardiac*: (~8%): **Heart block**, myopericarditis |
| Stage 3: Late persistent: Mos to yrs after infection | *Derm*: Acrodermatitis chronica atrophicans, panniculitis. *Rheum* (60%): Joint pain, recurrent mono- or oligoarthritis of large joints (classically knee), synovitis. *Neuro*: Subacute encephalomyelitis, polyneuropathy, dementia |
| *Lancet* 2003;362:1639; *CID* 2006;43:1089; *NEJM* 2007;357:1422. | |



**Neurologic presentations of Lyme dz:** (*Neurology* 1996;46:619). Neuro involvement in ~15% untreated cases, typically in stages II-III. Even untreated, most cases of acute CNS Lyme improve or completely resolve in weeks-months; ~5% untreated pts → chronic neurologic dz



| Neurologic | Comments |
|---|---|

| Presentations | |
|---|---|
| **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). Thoracic radiculitis w/segmental weakness of the abdominal wall. CSF antibodies almost always positive. CSF PCR unreliable |
| **Peripheral neuropathy/chronic radiculoneuropathy** | ~30% cases. Mononeuritis multiplex. Unlike early radiculoneuritis, not a/w meningitis, cranial neuropathy, or CSF abs |
| **Chronic axonal polyneuropathy** | With radicular pain, distal paresthesias |
| **Encephalomyelitis** | Rare, 0.1%-5% most commonly involves the spinal cord at the level of a radiculopathy and is usually apparent on MRI scans; assoc w/inflammatory CSF |
| **Encephalopathy** | Mild cog. dysfxn. Brain MRI & CSF usually nml likely 2/2 systemic infxn. Similar to "toxic metabolic" encephalopathy a/w chronic UTI, PNA |
| **Optic neuritis** | In pedi population 2/2 infl. or ↑ ICP |
| **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, multiple cranial neuropathies. 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, 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).

### *Diagnostic studies*

- Serology (in right clinical setting): Screen w/ELISA, but false+ due to other spirochetal diseases, SLE, RA, EBV, HIV, etc.; false- due to early abx therapy or w/in 6 wk of infxn. IgM response first, then declines. IgG+ after ~1 mo. Confirm ELISA results w/Western blot Se 20%-30% in first weeks (IgM) but >80% after 6 wk; Sp > 95%
- CSF if suspected neuro disease: Intrathecal Ab if (IgGCSF/IgGserum)/(albCSF/albserum) >1 (Compare CSF and serum specific Abs, correcting for total IgG concentration in both compartments).
- If only PNS involvement, there is no reason to expect CSF Ab to be positive

- Active CNS infection—CSF pleocytosis ± increased prt, should improve w/Abx.

| Other Laboratory Dx of Lyme Dz | | |
|---|---|---|
| | **Comments Sensitivity/Specificity** | |
| Western blot | Confirmatory, usu not helpful if seroneg; IgG blot + if 5/10 bands present; IgM blot + if 2/3 bands present | CDC recs: "Two tier" test w/ELISA & Western blot 56%-100% Se, 100% 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 +; 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) | |

**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 able to give 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** |
| Parenchymal CNS Lyme (e/o infxn crossing blood-brain barrier[a]) | IV ceftriaxone (first line)<br>IV cefotaxime IV PCN G | 2 g/day × 2-4 wk. 2 g/day q8h 18-24 MU/day q4h | Rash, n/v/d, pseudomemb. colitis, ↑ LFTs<br>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<br>Oral amoxicillin (children <8 yr & pregnant F) | 200 mg/day × 14-21 days<br>500 mg tid × 14-21 days | Photosensitivity rash in sun, pseudomembranous colitis<br>Rash, diarrhea, pseudomembranous colitis, hemolytic anemia |
| CNS Lyme w/e/o infxn crossing blood-brain barrier[a] | IV ceftriaxone (first line)<br>IV cefotaxime<br>IV PCN G | 2 g/day × 2-4 wk 6 g/day<br>18-24 MU/day div q4h | Rash, n/v/d, pseudomemb. colitis, ↑ LFTs.<br>Rash, n/v/d, HA, pseudomembranous colitis<br>GI upset, n/v/d, black or hairy tongue |
| 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.)<br><br>Oral Abx are probably effective for meningitis and other neuro involvement, w/the exception of parenchymal CNS infection | | | |



## 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 (early L:<1 yr post-infxn, late L: >1 yr post-infxn) | Seroreactivity w/o other e/o dz | Infectious only via 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 yr after exposure); Gummatous dz (15%, 1-46 yr); General paresis (~5%, 2-30 yr): chronic dementia w/prominent behavioral ↓, delusions; Tabes dorsalis (~5%, 3-50 yr): 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 dark-field 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% (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 up to 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.

**When to do an 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.

**Syphilis Treatment** (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 days 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 days or procaine PCN3 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 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

## Epidemiology

- Leptospirosis transmitted by urine of infected animal
- Rats, mice moles, most common vector

**General:** Neurologic manifestations in 10%-15% of cases. Consider in pts w/acute hepatorenal 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. May cause meningitis ± encephalitis

**Dx:** *Imaging*: nl or may show diffuse cerebral edema. *CSF*: ↑ lymphs common (<500 cells/mm3). Can detect serum & CSF antibodies. organism can be found in blood & CSF for first 7-10 days. After 7-10 days can be found in urine. Confirm w/ELISA and PCR. Gold standard for dx: MAT (microscopic agglutination test).

**Rx:** Options: PCN G, ampicillin, & doxycycline for less severe cases.

**Prognosis:** Significantly altered MS & ↑ ↑ CSF protein are poor prognostic findings.

# 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

**Presentation**: 20%-60% HIV pts—Distal, symmetric, polyneuropathy, affects small ± large sensory fibers. Si/Sx: Combination of pos neuropathic sx (paresthesia, pain) and neg neuropathic sx (numbness, imbalance); usually no motor sx. Neuropathic pain 50%-90% of patients. Neuropathy does not correlate w/viral load or CD4 count. Also ↑ risk for entrapment neuropathy (e.g., carpal tunnel). DM, INH exposure, malnutrition ↑ risk. Older dideoxynucleotide antiretroviral agents: didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) sensory polyneuropathy clinically indistinguishable from HIV-induced neuropathy. **Less common presentations**: AIDP, CIDP, mononeuritis multiplex w/and w/out concurrent CMV infxn

***Exam*:** ↓ sensation (can be all modalities, esp pain & temp; JPS often ok); ↓ ankle reflexes; strength typically preserved. ***Diagnosis*:** Exclude other causes/mimics of axonal sensory polyneuropathy (DM, B12 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. 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.

***Treatment*:** Supportive. Symptomatic Rx: TCAs, gabapentin, pregabalin, lamotrigine, duloxetine. Identify & treat confounding factors such as DM.

**Acute neuromyopathy mitochondrial toxicity:** Resemble GBS, associated w/several NRTIs, particularly w/d4T, also zidovudine (AZT), ddI, and lamivudine (3TC), either alone or in combination. Lactic acidosis suggests acute mitochondrial toxicity possibly 2/2 metabolic effects of the nucleoside analogs. Acute cauda equina syndrome: Rapidly developing painful paraparesis w/bladder and bowel involvement; characteristic of CMV polyradiculitis in advanced immunodeficiency.

**HIV-associated myopathy: (1) *Zidovudine myopathy*:** Fatigue, prox muscle weakness & atrophy, myalgias. More common after cumulative dose >200 g. Ragged red fibers seen on electron microscopy. Ddx: preserved DTR and sensation unlike CIDP or other neuropathy. CK usu ↑. Rx: d/c zidovudine; CK and muscle pain dec first, later return of muscle strength. **(2) *Pyomyositis*:** Rare. Indurated, tender muscle mass. Dx: nl-high CPK. Ultrasound, CT scan, & MRI helpful. Aspirate & culture. Rx: IV abx & surgical drainage as needed. **(3) *Nemaline rod myopathy*:** Subacute development of weakness & atrophy. ↑ CPK. Nemaline rods on bx w/variable muscle necrosis & inflammation. Rx: steroids, ?IVIg. **(4) *HIV wasting illness*:** Prox weakness & atrophy w/diarrhea, fever, cachexia. CPK usu wnl. **(5) *Diffuse infiltrative lymphocytosis***



***syndrome*:** B/l salivary gland enlargement or xerostomia. CD8 polyclonal lymphocytic infiltrate on bx of minor salivary gland. May initially p/w myositis, neuropathy, or mononeuritis multiplex. Rx: steroids. **(6) *Opportunistic infxn or tumor infiltration of muscle***.

**HIV-associated myelopathy ("vacuolar myelopathy"):** Pathologic diagnosis. Characteristic pathology at autopsy in ~55% of patients dying from AIDS. Clinical myelopathy is less common. ↓ incidence due to ART; ~5%-10% untreated pts affected; CD4 usu <350/mm$^3$.

***Presentation***: Gradual onset weeks-months leg weakness, spasticity, gait ataxia 2/2 ↓ proprioception; urinary incontinence less common. Typically painless & mimics subacute combined degeneration of B12 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 clinically. B12 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$^3$.<br>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/mm3. Often in conjunction w/TB meningitis. |
| **Other:** Vitamin B12 deficiency, idiopathic transverse myelitis, multiple sclerosis, lymphoma. |
| HAND, HIV-associated neurocognitive disorders.<br><br>References: *Neurol Clin* 2008;26:799; *Lancet Neurol* 2005;9:543. |

## Three conditions w/in the spectrum of HAND: Asymptomatic neurocognitive impairment (ANI); mild neurocognitive disorder (MND); HIV-associated dementia (HAD).

**Epidemiology:** Overall incidence ↓ w/widespread ART of HAD. Milder cognitive dysfxn, still common (20%-

69%) in HIV+ pts. **Presentation:** Progressive cognitive, behavioral, & motor dysfxn, similar to a subcortical dementia. ↓ memory, attention; psychomotor slowing. Depressive sx, 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, may precede HAD. Sx may wax and wane.

**Risk factors:** Low CD4 count, older age at seroconversion, anemia, ↑ age, duration of dz, 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), toxoplasmosis, 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) & decrease in *N*-acetylaspartate (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). Ineffective Rx: Memantine (*AIDS 2007;*21(14):1877), transdermal selegiline (*Neurology 2007;*69:1314) minocycline (*Neurology 2013;*80:196)

**Prognosis:** Both HAD & HAND predict ↓'d survival regardless of whether on ART.

## INTRACRANIAL OPPORTUNISTIC INFECTIONS

*Toxoplasma gondii* *Cryptococcus neoformans*
Cytomegalovirus (CMV) Fungal Encephalitis
Progressive Multifocal Leukoencephalopathy (PML) Herpes Varicella-Zoster Virus (VZV)

**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*. |

## 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. Incidence ↓ ↓ in era of ART & toxoplasma/pneumocystis prophylaxis. 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).

***Risk factors*:** CD4 count <200 cells/mm3, not on ART or toxoplasmosis prophylaxis. **Presentation:** Symptomatic in ˜10% cases: mononucleosis-like illness w/prominent lymphadenopathy 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. *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 (12%-70%). *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).

*Imaging*: CT: Single or multiple contrast-enhancing lesions, often w/ring or nodular enhancement; common in cortex and deep gray matter (e.g., basal ganglia, thalamus. cerebellum and brainstem less commonly affected. MRI more sensitive.

**Ddx:** CNS lymphoma, fungal abscess, mycobacterial or CMV infxn.

**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 count sustained at 100-200 cells/mm3. (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/mm3. (2) Seroneg pts advised to avoid undercooked meat & cat feces.

## 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/mm3. *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/mm3), ↑ 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/d) w/**flucytosine** (100 mg/kg/d) × 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 H2O remove CSF to ↓ CP by 50% (usu ~20-30 mL 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 Rx-only 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—IRIS

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.

## 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).

## IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

**Epidemiology:** ~25% develop some form of IRIS, <1% have neuro si/sx. Risk factors: ART naive, 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 yr). 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.

## MENINGITIS IN HIV PATIENTS

*Main causes*: *Syphilis, cryptococcosis, HIV, & tuberculosis (see CNS syphilis, cryptococcosis, tuberculosis)*

### 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.



# ENCEPHALITIS IN HIV PATIENTS

## CMV ENCEPHALITIS

**General:** CMV (Herpes family) is the 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 DUE TO CNS ESCAPE

Rare subacute encephalitis w/progressive cognitive decline despite well-controlled serum HIV load and immune reconstitution by cART. MRI: Multifocal WM hyperintensities and CSF: mononuclear pleocytosis. Presence of HIV by PCR in CSF w/serum level in undetectable or CSF HIV load much higher than serum is diagnostic. Modification of cART based on CNS penetration or genotyping of CSF HIV may → marked reversal of encephalopathy.

## 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 intxns w/ART. Newer AEDS (e.g., LEV, TPM, GPN, LTG) may be safer, although risks of older AEDs, e.g., PHT, CBZ (effect on p450 system), or VPA (previous in vitro studies showing it may induce HIV replication) likely minimal (*Seizure* 2008;17:27).

# FOCAL LESIONS IN HIV

Ddx depends on degree of immunosuppression: CD4 >500/μL, benign and malignant brain tumors and metastases predominate, as in immunocompetent hosts. CD4 cell counts 200-500/μL, HIV-associated cognitive and motor disorders are common, but usually do not present w/focal lesions. CNS mass lesions most common in severely immunosuppressed CD4 cell counts <200/μL. Most likely dx: Opportunistic infxns (Toxo, PML) and AIDS-associated tumors, i.e., primary CNS lymphoma (PCNSL).

**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; 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.



## 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: HIV + PCNSL. Survival ~3 mo; <10% >1y (*Eur J Cancer* 2001;37:1296).

## CNS TUBERCULOSIS

**Epidemiology:** In 2012, 8.6 mil new TB cases, 1.3 mil deaths (WHO 2013). ~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*: Droplet Inhalation. Seeds 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—encases arteries & cranial nerves primarily in basal meninges. HIV-associated CNS TB 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:** Bacterial, viral, 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 four large volume (20-45 mL) 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<br>Thoracic & lumbar cord most commonly affected by radiculomyelitis<br>P/w: Back pain, paresthesias, weakness, & bowel/bladder dysfxn.<br>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 |

## 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 mo): Donor-to-recipient, common bacterial, or nosocomial infxns Middle (1-6 mo): Opportunistic viral, fungal, or atypical bacterial infxns 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 posttransplant. *Dx*: CSF PCR. *Rx*: Acyclovir (10 |

mg/kg) × 14-21 days. Recheck CSF to ensure clearance of (+)PCR before starting maintenance oral Rx.

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**EBV:** Rarely p/w meningoencephalitis; usu as mass lesion a/w systemic or CNS lymphoma or PTLD. Usu occurs middle to late in course posttransplant. *Dx*: Bx & CSF PCR. *Rx*: Stop immunosuppression → resection, XRT, chemo. Antiviral Rx not effective. Prognosis poor.

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**JC Virus (PML):** P/w cognitive impairment, visual loss, weakness, gait disturbance, & poor coordination, usu late in course posttransplant. *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.

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**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.

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Adapted from *Continuum: Lifelong Learning in Neurology* 2006;12:95; *Neurol Clin* 2003;21:193.



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**Neurologic Fungal, Bacterial, & Protozoan Infections in Transplant Patients**

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**Focal CNS Lesions**

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**Aspergillus** (incl *A. fumigatus*, *flavus*, *terreus*, & *niger*): Most common cause of focal CNS lesion in transplant pts. Can occur anytime in the posttransplant period. Often accompanied by concurrent pulmonary dz. Angioinvasive, can cause strokes, commonly ICH w/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 immunosupp.
- 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):**

Most commonly seen in patients with poorly controlled diabetes

- Typically present as mass lesion
- Angioinvasive & thus complicated by cerebral infarcts
- Direct invasion vs. hematogenous spread
- Rx: Resection, high-dose amphotericin B (1.5 mg/kg/d) or liposomal amphotericin (5-7.5 mg/kg/d)
- 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 United States
- Histoplasma found in Ohio valley region of the Midwest
- Coccidioides found in Southwestern desert & Central California
- Blastomyces found in Mississippi Valley & North Central United States
- 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.

## PARASITIC NEUROLOGIC DZS

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| Parasitic CNS infections | | |
|---|---|---|
| **Disease (*Organism*)** | **Clinical Features** | **Radiographic Features** |
| **Cestodes (Tapeworms)** | | |

| | | |
|---|---|---|
| Cysticercosis (*Taenia solium)* | Sz w/mature lesions, hydrocephalus from obstructing cyst | Cyst w/solex; late calcification |
| Hydatid disease (*Echinococcus*) | Focal neurologic deficits,↑ ICP | Large fluid-filled cysts |
| **Nematodes (Roundworms)** | | |
| Trichinosis | Skin lesions, severe myositis, CNS lesions, eosinophilia, meningitis, encephalitis (rare) | Granuloma |
| Strongyloidiasis (*Strongyloides stercoralis*) | Encephalitis, myelitis, seizures | |
| **Trematodes (Flukes)** | | |
| Schistosomiasis (*Schistosoma japonicum, S. mansoni, S. haematobium*) | Myelopathy, seizures, tumor symptoms, swimmer's itch | Solitary granuloma |
| Paragonimiasis | Seizures, meningoencephalitis, pulmonary lesions | Solitary granuloma |

## NEUROCYSTICERCOSIS

**General:** Infxn of nervous system w/larval stage of cestode, *Taenia solium*. Most common CNS helminthic infxn. Most common preventable cause of acquired epilepsy worldwide.

**Epidemiology:** 2.5 million people worldwide carry the tapeworm; many more infected w/the larvae, cysticerci. Accounts for up to 30% of epilepsy in endemic areas.

**Pathogenesis:** Infxn due to accidental ingestion of *Taenia solium* (pork tapeworm) eggs, usually due to contamination of food (fecal→oral) by people w/taeniasis. Humans: Definitive hosts carrying the intestinal tapeworm, pigs: Normal intermediate hosts harboring the larvae or cysticerci.

### Presentation

CNS Locations involved: Parenchymal >>> intraventricular > subarachnoid > spinal

- Parenchymal dz: Most commonly p/w epilepsy. Szs can be GTC or SPS.
- Intraventricular/subarachnoid space: ↑ ICP from inflammation of larvae/cysts, may cause: Hydrocephalus, HA, vomiting, AMS, stroke.

**Imaging:** (Intraparenchymal disease) **(1) Viable cysts:** *CT*: Hypodense, well-demarcated nonenhancing lesions w/thin cyst wall. *MRI*: Hypointense on T1, hyperintense on T2. May see scolex on FLAIR or DWI. **(2) Degenerating cysts:** *CT*: Iso- to hyperdense + enhancement & edema. **(3) Calcified cysts:** *CT*: Punctate hyperdense lesion. *MRI*: Areas of ↓ signal; not well visualized 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. CSF *not* necessary for dx of parenchymal dz. Serum and CSF Ag, best for subarachnoid dz. (*Expert Rev of Anti-Infective Therapy, 2011.*)

**Rx:** Varies depending on #, location, size, & stage of cysts (see table below). **(1)** All pts should have precautionary *funduscopic exam* to r/o ocular cysts, retinal detachment & avoid visual loss 2/2 antiparasitic Rx. **(2)** ↑ ICP should be treated immediately; may preclude antiparasitic Rx. **(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 most common finding on imaging. Episodic perilesional edema at time of sz recurr. Utility of steroids & ppx AEDs 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 or high cyst burden | Albendazole + steroids. Initial tx seems to exacerbate neurologic sx, but pt will improve and cysts will ↓ in number and size<br>Albendazole + praziquantel may increase parasiticidal effect (*Lancet Infect Dis* 2014) |
| Calcifications | Antiparasitics not indicated; AEDs for recurrent szs |
| Encephalitis (massive parasite burden, ↑ ICP) | Antiparasitic agents contraindicated; treat w/steroids & hyperosmolar Rx |
| Subarachnoid disease | Prolonged albendazole for >1 mo + steroids; for giant cysts consider resection |
| Intraventricular cysts | Neuroendoscopic removal vs. surgery; shunt placement PRN; antiparasitic agent w/steroids ↓ shunt failure |
| Spinal cord intramedullary cysts | Resection; antiparasitic agents controversial; if used, highdose steroids must be used before, during, & after |
| Intraocular cysts | Resection |
| Taeniasis (tapeworm) infxn | Niclosamide, single 2-g dose |

| Antiparasitic Agents for Treatment of Neurocysticercosis & Taeniasis |
| --- |
| **Albendazole**, 5 mg/kg tid for 15-30 days: Destroys 85% cysts. Good CSF penetration, useful against ventricular & subarachnoid cysts. Steroids ↑ levels.<br>**Praziquantel**, 50 mg/kg/d div tid × 7-15 days. Effective also against taeniasis. Steroids ↓ levels. Destroys 70% of cysts.<br>**Dexamethasone** 12-32 mg/day in divided doses. Used at onset, esp important if large lesion is causing mass effect<br>**Niclosamide**, single dose (2 g for adults) for Rx of taeniasis (tapeworm infxn) |

## CEREBRAL ECHINOCOCCUS

**General:** Clinically relevant species: *E. granulosus* & *E. multilocularis*—cause **cystic echinococcosis** & **alveolar echinococcosis**, respectively. Usual sources of infection are water and vegetables contaminated by canine feces. Incubation period mo-yr.

**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% of cases. Sx: HA, n/v, szs, CN palsies, other focal deficits. Typical lesion is a large fluid-filled cyst w/parasite visible on imaging, but a solid nodular brain lesion, a "chitinoma," also known to occur. Tx: Mebendazole is recommended when surgery is not feasible.

## 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). Chronic si/sx: Autonomic neuropathy (GI dysmotility most commonly) and cardiac disease develop over 10-30 yr. Parasite can be detected in peripheral nerves, but peripheral neuropathy not observed.

**Dx:** Definitive: Detect 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: Benznidazole & 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 or alternating intermittent delta wave bursts (*Ann Neurol* 2008;64:116). *Card agglutination* a good screening test. *Definitive dx*: identification of trypanosome in serum, CSF, or biopsied tissue. **Ddx** includes malaria, some pts may be coinfected.

**Rx & prognosis:** W/o appropriate Rx, case fatality rate 100%. Follow CSF q6mo × 2 yr after Rx. Selection of agent depends on early vs. 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:** Found in tropical areas: Caribbean, S. America, Africa, Middle 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.

**Imaging:** Suspect in any pt w/focal cerebral lesion or e/o myeloradiculopathy/conus-cauda equina syndrome 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:** Detection of parasitic antigens by ELISA (from blood sample): highly effective screening method. May also detect 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 Med 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 mcg/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 *Plasmodium* genus; cerebral malaria caused by *Plasmodium falciparum*.

**Epidemiology:** ~500 million cases of malaria annually w/~3 million deaths. Cerebral malaria in 2% of falciparum malaria cases

**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 ↑ risk for more severe dz. Sx: HA, seizures, coma w/diffuse cerebral edema. Rarely focal features, hemiplegia, aphasia, cerebellar ataxia.

**Dx:** Requires high index of suspicion; malaria should be included in ddx in any pt w/*febrile illness & encephalopathy from or returning from area w/endemic malaria*. In endemic areas, three neg blood smears 8-12 h apart required to r/o dx. *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. *Imaging*: CT may show brain swelling, which, in combination w/hypodensities in basal ganglia & cerebellum, suggests 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. Corticosteroids ineffective.

**Prognosis:** *Neurologic sequelae*: Up to 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, Acanthamoeba* spp, *Balamuthia mandrillaris*, & *Sappinia diploidea*.

***N. fowleri*:** Causes **1° amebic meningoencephalitis**, an acute fulminant infxn, 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.

***Acanthamoeba* 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. *Acanthamoebae* 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 & immunofluorescence 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.

# OTHER VIRAL 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 1 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, & GI distress. **(2) "Dengue hemorrhagic fever"** in pts w/prior infxn—bleeding diathesis, thrombocytopenia, & vascular permeability; can → "dengue shock syndrome." **(3) Neuro 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.

**Presentation:** Mild influenza-like illness w/HA, cough, GI 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).

# INFECTIOUS NEUROPATHIES

## HERPES ZOSTER

**Definition & Etiology:** Herpes zoster = shingles: acute, unilateral, painful dermatomal skin eruption.

- VZV reactivation in peripheral nerve distribution from latency in dorsal root ganglion

**Risk factors for VZV reactivation:** Age >50, immunosuppression (from Rx) or immunocompromised states, HIV, organ tranplt, trauma, psychological stress

### Clinical manifestations

- Sensory Sx: Itching, paresthesia, dysesthesia, allodynia, and hyperesthesia, neuropathic pain in dermatomal distribution (60%-90%) of patients. Then eruption of dermatomal rash w grouped vesicular lesions.
- Consecutive dermatomes may be seen in all Pts; more widespread in immunosupp.
- Lesions in V1 distribution of facial nerve require urgent ophthalmologic evaluation.
- Postherpetic neuralgia (PHN) = severe pain lasting >90 days after episode; may last mos-yrs, more frequent w/inc age and w/delay of antiviral Rx.
- **Rx:** recommended w/in first 72 h of skin lesions in normal host or at any time dx in immunosupp. oral acyclovir (800 mg 5 × days × 7-10 days), valacyclovir (1,000 mg tid × 7 days), or famciclovir (500 mg tid × 7 days) shortens the duration of both rash and sensory symptoms. Acyclovir 10 mg/kg IV q8h if disseminated or high-risk pt (medically ill, immunosupp., V1 zoster w/any ophthalmic s/s, etc.). Antiviral therapy does not affect progression to PHN.
- **Prevention:** Vaccine for pts >60 yr (↓ lifetime risk 20% to 10%, also (↓ PHN).

## HIV: *SEE HIV-ASSOCIATED NEUROPATHY*

LYME: *SEE ABOVE*

**Hepatitis C:** (RNA virus; accounts for 10%-30% of acute viral hepatitis; *Lancet* 2008;372:321).



- Transmission: Blood > sexual; peripheral neuropathy develops in ~10% of HCV patients, 26%-86% w/concurrent mixed cryoglobulinemia.
- Most patients develop length-dependent sensory or sensorimotor axonal polyneuropathy. Mononeuropathies, mononeuropathy multiplex, &, rarely, demyelinating inflammatory neuropathies also reported.
- Majority of pts w/HCV assoc peripheral neuropathy have cryoglobulinemia (mixed cryoglobulinemia aka type II). Cryoglobulins: Proteins that precipitate on exposure to the cold induce inflammation by activating complement. Extraneurologic manifestations: Palpable purpura, arthralgias, and membranous glomerulonephritis.

- Tx: HCV DMT w INF-α and ribavirin shown to improve PNS si/sx in both mixed and nonmixed cryoglobulinemia-assoc peripheral neuropathy.

**West Nile Virus:** Single-stranded RNA virus typically a/w encephalitis.

- **Presentation**: Flaccid paralysis due to motor neuron dz—20% of pts w/CNS infx. Rarely (5%) present w/isolated motor paralysis w/o si of meningoencephalitis. Progressive weakness w/in 3-7 days post infxn. Motor neuropathy begins asymmetrically, then usu generalizes.
- **Exam**: Proximal > distal weakness, reduced or absent reflexes.
- **Studies**: NCS: diffuse low-amplitude CAMPs and normal amplitude SNAPS; EMG: widespread active denervation w/reduced motor unit recruitment. EMG/NCS may be normal at time of acute presentation. May take up to 2 wk to see Δs.
- **Tx**: Supportive weakness may involve respiratory muscles requiring mechanical ventilation.

**Botulism:** Caused by toxin produced by anaerobic gram + bacteria, *Clostridium botulinum*. Most often transmitted by consumption of honey in children <1 yr, home-canned foods, wound botulism in IV drug users. Binds to presynaptic nerve terminal, irreversibly blocking acetylcholine release in NMJ—results in flaccid paralysis and autonomic dysfunction incubation period of toxin after ingestion or inhalation 12-36 h, can be delayed up to 7-10 days depending on botulinum strain.

- **Presentation**: Prodromal syn: Nausea, abd pain, diarrhea w/in hrs of exposure. Weakness in descending pattern. Ocular/bulbar muscles first—>ptosis, diplopia, dysarthria, dysphasia. May progress to proximal muscle weakness, respiratory failure requiring mechanical ventilation.
- **Studies**: NCS: Reduced amplitude CAMPs and normal amplitude SNAPS; EMG: Widespread fibrillation potentials as muscle is functionally denervated.
- **Dx**: Based on clinical hx, physical exam, EMG/NCS, and detection of toxin.
- **TX**: Antitoxin (human botulinum immunoglobulin) and supportive care.

## RABIES

**Presentation** (*Travel Med Infec Dis* 2011;1-15): Incubation period wks-1 yr (usu 1-2 mo). ***Encephalitic***: Predilection to brainstem, diencephalon, and hippocampi. 2/3 cases respiratory and autonomic dysfunction. Pharyngeal spasms, hydrophobia, aerophobia, dysphasia, hyperactivity, hallucinations progressive encephalopathy, paralysis → coma → death. ***Paralytic*:** 1/3 cases rapid-onset quadriparesis, w/few cerebral manifestations early on, similar to motor-predominant GBS, 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, w/in 6-10 days of onset w/out ICU support and w/in 30 days w/ICU support (only one 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.

## 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. Pain/temp sensory loss, localized to skin lesions in tuberculoid disease, but extends beyond skin lesions in lepromatous disease, affects widespread cooler regions of the body (i.e., ears, hands, feet, etc.). Spares reflexes, position, and vibratory sense.

**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 + rifampin 600 mg qmo × 6 mo. **(2) *MB*:** Dapsone 100 mg qd + rifampin 600 mg qmo + 300 mg clofazimine qmo + 50 mg clofazimine qd × 12 mo.

*Corticosteroids*: If leprosy reaction during Rx.

## BELL PALSY

**Definition & Etiology**: Acute, idiopathic, unilateral facial nerve palsy (peripheral CN VII). Thought to be due to reactivation of HSV-1 in cranial nerve VII.

**Clinical manifestations**: Unilateral facial muscle weakness, LMN pattern invol, hyperacusis, decreased taste/lacrimation/salivation.

**Dx:** Dx of exclusion: R/o brainstem lesion, Lyme, zoster (incl sine herpete), HIV/AIDS, sarcoid.

**Rx:** (*NEJM* 2007;357:1598; *JAMA* 2009;302:985). ~80% recover spontaneously by 9 mo (much lower rate in diabetics). Corticosteroids (prednisolone 25 mg PO bid × 10 days) started early (w/in 72 h of sx onset) improve odds of recovery (note: No conclusive data for diabetics, immunosuppressed). No conclusive data to support the use of acyclovir or valacyclovir.

# Headache

Rene A. Colorado

Graham Huesmann

David W. Chen

## EVALUATION OF HEADACHE

**History:** Points to Consider

**Description:** Acuity, freq, duration, location, severity, onset pattern, 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, alcohol, food, environment.

*PMH & ROS*: Stroke, vasc dz/risk factors, connective tissue d/o, autoimmune d/o, infxns, travel, rashes, trauma.

Family history.

**Physical exam:** Palpation of head; auscultate neck, chest; fundus exam; MS, CNs, motor, sensory, coord, gait, DTRs.

**Workup:** Depends on presentation, consider: Vitals, O2 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; MRI head/neck; angiogram if suspect aneurysm/AVM/vasculitis/dissection. Whether to use IV contrast depends on specific clinical suspicion.

**Indications for neuroimaging:** Focal finding on exam; HA on exertion or Valsalva; acute-onset severe HA; HA awakens pt; change in well-established HA pattern; newonset HA in pt >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/FHx; begin early-late teens around puberty, decline in severity & frequency w/age, especially postmenopause; may present w/variety of sx as aura, but acephalgic migraine a dx of exclusion (r/o stroke, TIA, sz). When evaluating for migraine, 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,

menstrual relationship common.

**Migraine w/aura**: Fully reversible visual, sensory, speech/language, motor, brainstem, or retinal disturbance; sx spreads gradually ≥5 min; lasts 5-60 min; HA or migraine sx follow w/in 60 min (*Cephalalgia* 2013;33(9):629.)

**Rx:** Nonpharmacological; relaxation techniques, biofeedback, etc.; 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 treatment of attack (see specific meds in table below):***

*Mild-moderate*: NSAIDs, antiemetics, simple analgesics, or their combination; consider triptans if prior poor response to the above.

*Mod-severe*: **Triptans** preferred**,** can combine w/NSAID and/or antiemetics; consider DHE. Consider corticosteroids for status migrainosus, severe & resistant or refractory migraines, higher baseline disability, & previous history of recurrent headaches; do not use >6×/yr (*Curr Pain Headache Rep* 2014;18:464). Give maximal recommended dose of triptan when possible. Avoid opiods; use seldom & only as last resort (initial use is assoc. w/longer length of stay, early return to ED, & progression to chronic migraine) (*Cephalalgia* 2014;pii:0333102414557703).

***Considerations*:** Early intervention = maximum benefit; 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; consider parenteral route for possible malabsorption; 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 500 mg); concurrent use w/serotonergic meds should be monitored for serotonin syndrome; concurrent use w/MAO inhibitors is contraindicated, except w/naratriptan & frovatriptan, both have longer half-lives; migraine w/aura is not a contraindication to triptan use. Coronary & vascular disease is a contraindication.

***Common possible side effects of triptans*:** Lethargy, paresthesias, & muscle tightness & stiffness, especially neck & chest—explain to pts, 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 | Moderate statistical & clinical benefit |
|---|---|
| Naratriptan po | APAP + codeine po |
| Rizatriptan po | Butalbital, ASA, caffeine + codeine po |
| Sumatriptan po | Butorphanol IM |
| Zolmitriptan po | Chlorpromazine IM, IV |
| Dihydroergotamine (DHE) SC, IM, IV, in | Diclofenac po |
| DHE IV+ antiemetic | Ergotamine + caffeine + pentobarbital + bellafoline po |
| acetaminophen (APAP), aspirin (ASA) + caffeine po | Flurbiprofen po |
| ASA po | Isometheptene po |
| Butorphanol in | Ketorolac IM |

| | |
|---|---|
| Ibuprofen po<br>Naproxen po | Meperidine IM, IV<br>Methadone IM<br>Naproxen po<br>Prochlorperazine IM, pr |
| **Equivocal or inconsistent evidence** | **Ineffective failed vs. placebo** |
| Butalbital ASA + caffeine po<br>Metoclopramide IM or pr<br>Ergotamine + caffeine po<br>Metoclopramide IM or pr | APAP po<br>Chlorpromazine IM<br>Granisetron IV<br>Lidocaine IV |

Adapted from *Neurology* 2000;55:754.

**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; pt preference (*Headache* 2005;45(Suppl 1):S34).

**Commonly Accepted Rx for Migraine Prophylaxis**

| Med | Typical dosage | Main adverse effects |
|---|---|---|
| Amitriptyline | 10-150 mg/day | Weight gain, dry mouth, sedation, arrhythmias, blurred vision, urinary retention |
| Nortriptyline | 10-100 mg/day, in 3-4 doses | |
| Doxepin | 25-150 mg qd | Hepatotoxicity, nausea, weight gain, somnolence, tremor, teratogenicity, rash, abdominal pain |
| Depakote | 250-500 mg bid | |
| Depakote ER | 500-1,000 mg qd | |
| Propranolol | 40-240 mg/day, in 3-4 doses | Fatigue, exercise intolerance, asthma/COPD exacerbation, cold hands, bradycardia |
| Inderal LA | 80-240 mg qd | |
| 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.

**Chronic Migraine:** Headache on ≥15 days/mo > 3 mo, which has features of migraine at least 8 days/mo. R/o other HA d/o including medication overuse HA, hemicrania continua, chronic tension HA. **Rx:** Treatment of comorbid psychiatric illness & nonpharmacological mgt is essential. Topiramate & botox injections shown beneficial in RCTs but other conventional prevention meds may also work (*Nat Rev Neurol* 2012;8:162).

## 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°g IV push over 1°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.

### Estrogen-related migraine

Women of childbearing age. Usually occur right before & during menstruation or w/withdrawal of estrogen. **Rx**: Acute treatment, as for nonmenstrual migraines. *Prevention*: Extended duration OCP if already on OCP or if indication for OCP exist or prophylaxis as above. Short-term prevention: Long-acting triptan or NSAID 2-3°days before & continue during menses. Women w/migraine w/aura have increase risk of stroke (see Migraine and Stroke Risk below); use of OCP should be avoided or carefully considered.

### Migraine with brainstem aura

Aura of visual, sensory, or speech/language sx associated w/dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, or decreased consciousness; aura of 5-60 min, usually unilateral, followed by HA w/in 60 min, similar to vertebrobasilar stroke presentation; should prompt stroke w/u w/vessel imaging. If vascular w/u is neg, **Rx** is per migraine algorithm.

### Hemiplegic migraine

Aura of typically uni/l motor weakness & visual, sensory, and/or speech/language sx; there are familial forms; it is rare & stroke should be r/o. **Rx** is per migraine algorithm except that triptans & DHE should be avoided (controversial); additional meds to consider include acetozolamide & lamotrigine (*Lancet Neurol* 2011;10:457).

### Retinal migraine

Recurrent migraine associated w/monocular visual disturbance, including scintillations, scotoma, or blindness. Extremely rare. Resembles retinal artery occlusive d/os. W/u w/ophthalmologic & stroke evaluation. ESR, CRP if > age 50 to eval for giant cell arteritis.

### Migraine and Stroke Risk

Migraine w/aura is associated w/twofold increased in risk of ischemic stroke, particularly among women, & is higher in those < age 45, smoker, & women on OCP (*BMJ* 2009;339:b3914).

### Migrainous infarction

One or more aura symptoms associated w/an infarct in the appropriate aura territory demonstrated by neuroimaing. Most common in the posterior circulation & in younger women (*Cephalalgia* 2013;33:629). Admit for stroke management & w/u.

### Persistent aura without infarction

Aura symptoms for ≥1 wk w/out evidence of infarction on neuroimaging; occurs rarely; often visual & bi/l; may last for months or years; consider PRES.

**Imaging & migraine:** Commonly, pts 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.

**PFO:** There is an association of PFO in pts w/migraine w/aura (but not w/o aura); closure has not been shown to be beneficial & evaluation/closure for PFO is not recommended (*Curr Neurol Neurosci Rep* 2014;14:426).

**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 pts 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 "buildup," 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.

## HEADACHE AND PREGNANCY (SEE *CHAPTER PREGNANCY NEUROLOGY*)

### TENSION HEADACHES

**Sx:** No age/sex difference; last 30 min-7 days; often bi/l, described as a "tight band" around the head; not worse w/activity; no n/v, photo/phonophobia, or other associated sx.

**Rx (nonmed):** Stress management, biofeedback, 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. Avoid opiods & barbiturates.

**Preventative medications:** Tricyclics, dosing as for migraines; muscle relaxants.

## TRIGEMINAL AUTONOMIC CEPHALGIAS (TACS)

**Autonomic Symptoms of TACS and Other Primary Headaches**

| 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 w/sexual activity |
| Cluster-tic syndrome | Hypnic headache |

*SUNCT* = short-lasting unilateral neuralgiform headache attacks w/conjunctival injection and tearing (*Brain* 1997;120:194). *SUNA* = short-lasting unilateral neuralgiform headache attacks w/cranial autonomic features.

**Features of TACs:** Attacks of mod-severe uni/l pain typically orbital/periorbital or temporal or a combination associated w/autonomic features including ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead & facial sweating, miosis, ptosis, and/or eyelid edema; often associated w/restlessness and/or agitation; age of onset is usu 20-40s

| | Cluster Headache | Paroxysmal Hemicrania | Hemicrania Continua | SUNA/SUNCT |
|---|---|---|---|---|
| **Duration of attacks** | 15-180 min | 2-30 min | Constant w/fluctuations | 1-600 s |
| **Frequency of attacks** | qod to 8×/day | 1-40/day | Months-years | 1-200×/day |
| **Pain intensity** | Extremely high | High | Moderate | Mod-high |
| **Prevalence** | 0.9% | 0.02% | Rare | Very rare |
| **Other** | Circadian rhythmicity; alcohol trigger | Responds to indomethacin | Responds to indomethacin | ↑↑ lacrimation & eye redness; touch trigger |

Adapted from *Headache* 2013;53:1470.

**Cluster headache:** Attacks are clustered over a few mos, then abate for mos to yrs.

**Clinical findings:** Must have at least one autonomic disturbance; onset fast, often reaching peak w/in few min; debilitatingly severe & should be taken very seriously (people have committed suicide to avoid pain). Attacks occur in two or more clusters over days-months; can be episodic or chronic (chronic is fewer than 10-20% of cases) (*Cephalalgia* 2007;27:824).

**Rx:** Sumatriptan SC, zolmitriptan IN, & high-flow oxygen have best evidence for effective rx.



**Abortive Therapies for Cluster Headaches**

| | | |
|---|---|---|
| Sumatriptan SC | 6 mg SC | Best Rx |
| Zolmitriptan IN | 5 mg one nostril × 1; repeat in 2 h max 10 mg/24 h | Best Rx |
| Sumatriptan IN | 5-20 mg one nostril × 1; repeat in 2 h. Max 40 mg/24 h | Acceptable |
| Zolmitriptan PO | 5 mg × 1; repeat in 2 h max 10 mg/24 h | Acceptable |
| 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 |
| Octreotide SC | 100 µg × 1 | Alternative to triptans |
| Corticosteroids PO | 1 mg/kg PO; max 60 mg/24 h, 5 days then taper 10 mg q3d | Tendency for rebound; start w/prophylactic med |

Adapted from *Neurology* 2010;75:463.

| Prophylactic Meds | | |
|---|---|---|
| Verapamil PO | 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. |
| Suboccipital steroid injection | Steroid + lidocaine 1%-2% | Various steroids and formulations have shown efficacy. |
| Lithium PO | 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. |
| Melatonin PO | 10 mg qhs | |

Adapted from *Neurology* 2010;75:463; *Lancet Neurol* 2011;10:891; *Cephalalgia* 2012;32(8):630.

**Surgical interventions:** Trigeminal nerve ablation, occipital nerve stimulators, & deep brain stimulators remain investigational.

**Paroxysmal hemicrania**

**Clinical findings:** Similar to cluster but attacks are shorter & more closely spaced; absolutely responsive to indomethacin.

**Rx:** Indomethacin 25-50 mg/day, divided bid-tid; max 200 mg/24 h. Any suspected cluster HA should have trial to r/o this.

### HEMICRANIA CONTINUA

**Clinical findings:** Attacks are persistent, strictly uni/l; occasional exacerbations; present for months; ipsi autonomic features; responds to indomethacin. Can have migrainous sx such as photo/phonophobia.

**Rx:** Indomethacin 25-50 mg/day, divided bid-tid; max 200 mg/24 h.

## SUNA/SUNCT

**Clinical findings:** Attacks are shorter & more freq than paroxysmal 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. **SUNCT** requires ipsi conjunctival injection & tearing. **SUNA** requires ipsi conjunctival injection or lacrimation, but *not both*.

**Rx:** Limited evidence. Acute attacks may respond to IV lidocaine (1-4 mg/kg/h). *Prevention*: Lamotrigine (up to 300 mg/day), topiramate (up to 300 mg/day) or gabapentin (up to 2,700 mg/day) (*Headache* 2013;53:1401).

### OTHER CAUSES OF PRIMARY HEADACHE

**Nummular HA:** Mild-moderate highly variable duration HA in small circumscribed rounded area of the scalp (commonly parietal) in absence of structural damage. Previously known as coin-shaped HA. **Rx**: Reassurance, simple analgesics.

**Hypnic HA:** Average onset 63 yr, female predom; lasts ~1 h; a/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.

**Primary exercise HA:** W/exercise/exertion; b/l, pulsating/throbbing; 5 min to 48 h; ave age of onset, 24; exclude SAH, dissection on first occurrence. **Rx:** Indomethacin (25-150 mg) prior to exercise.

**Primary 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.

**Primary stabbing HA:** Transient, localized stabs occurring spontaneously in absence of structural damage; stabs usu last ≤3 s; attack frequency usu low; location may move ipsi/contralaterally; more common in migraineurs. **Rx:** Indomethacin, melatonin.

**New daily persistent HA (NDPH):** Unremitting daily headache of clear abrupt onset, varying intensity; migraine-like, tension-like, or a combination; pts typically lack HA hx. **Rx:** Limited evidence; treat based on phenotype (i.e., migraine vs. tension); often refractory to treatment.

## SECONDARY HEADACHE DISORDERS

### HEADACHES SECONDARY TO TRAUMA

HA most common w/in 2 wk; present in mild > severe TBI; most resolve w/in 3 mo; most often tension type HA but can present as migrainous, cluster, neuralgias, & other HA/pain syndromes (*Curr Pain Headache Rep* 2010;14:292). Trauma/surgery can also trigger neuralgias & related pain syndromes. **Rx**: Depends on HA phenotype; consider trigger point injections, especially for neuralgias, & nonpharmacological treatments.

### 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, pre-eclampsia, & 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 posttrauma; 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.

***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 *Vascular Neurology*.

### Venous sinus thrombosis

**Risk factors:** OCPs, dehydration, hypercoagulable, hyperviscous, or hypoproteinemic states, malignancy, extrinsic venous compression (i.e., meningioma or abscess), pregnancy & postpartum, 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 *Vascular Neurology*.

### Hypertensive urgency/emergency

Hypertensive HA occurs typically when SBP ≥200 mm Hg; resolves w/Rx of HTN.

### Giant cell arteritis

**Clinical findings:** M > F > 50 yo; incidence ↑ w/age, peaks at 70-80; giant cell arteritis w/inflamm & 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.

## HEADACHES SECONDARY 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.

**Workup:** 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/neuroophtho 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 Hypoparathyroidism COPD Right heart failure w/pulmonary HTN Sleep apnea Renal failure Severe iron deficiency anemia Obstruction to venous drainage Cerebral venous sinus thrombosis Jugular vein thrombosis | Tetracycline & related compounds Vitamin A & related compounds Anabolic steroids Corticosteroid withdrawal Growth hormone Chlordecone Nalidixic acid Lithium Norplant levonorgestrel implant system 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 overdrainage 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 pts, causes increased risk of SDH.

**Workup**: If fluid can be collected, send for beta-trace protein to confirm 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 Meningitis, Encephalitis, and Brain Abscesses):*** 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

**Medication overuse headache (MOH):** Chronic HA induced by overuse of any headache medication; can be tension/migraine in quality; most common primary HA is migraine; prev 0.7%-1.7%. **Rx:** Abrupt w/d favored except if on mod-high doses of opiods, barbiturates, or benzodiazepines, which should be tapered. Start prevention & acute treatment for primary HA. Consider long-acting NSAID (naproxen) as bridge therapy during w/d period.

**Prevention:** Limit use of abortive treatment (triptans or ergotamine) to <10x/mo & simple/combination analgesics < 5×/mo.

**Drug withdrawal headaches:** Often due to caffeine or opiate; HA itself is not dangerous; w/d danger depends on med/drug.

## NEURALGIAS

**Trigeminal neuralgia (TN):** Recurrent uni/l brief electrical shock-like pains involving one or more divisions of CN V (V2 & V3 most common); may result in face grimace (*tic douloureux*); can be triggered by brushing teeth, chewing, talking, & light contact w/the skin; more common in F > age 50. Classified as classic TN (idiopathic or due to microvasc compression) or painful trigeminal neuropathy (~15% of cases) when secondary to another disorder such as herpes zoster, trauma, MS plaque, mass lesion. If young age, bi/l involvement, trigeminal sensory loss, or abnormal trigeminal reflexes, suspect secondary cause (*Neurology* 2008;71:1183).

**Workup:** MRI brain to r/o MS/mass lesion

**Rx:** Responds well to meds (see table below); b/c condition is episodic, meds should be weaned after pain subsides; carbamazepine & oxcarbazepine are first line; the rest can be used as add-on therapy.

**Procedures for trigeminal neuralgia**: Lidocaine or botox injections. Percutaneous procedures, such as

rhizotomy, stereotactic radiosurgery (gamma knife), surgical microvascular decompression.

**Occipital neuralgia:** Similar to trigeminal neuralgia but affects C2 on occiput.

**Workup**: MRI of the brain w/CISS or FIESTA sequence (thin cuts thru pontine cistern) & MRI C-spine to evaluate for vasc compression, tumor, demyelinating lesions.

**Rx:** For mild-mod: Warm/cold compresses, massage, PT to reduce secondary muscle tension; meds in above table & TCAs. Mod-severe: Occipital nerve block (diagnostic & therapeutic). Consider for refractory cases: Pulsed radiofrequency, occipital nerve stimulation, & botox injections (*Curr Pain Headache Rep* 2014;18:2014).



| Meds | Doses | Precaution | Side Effects |
|---|---|---|---|
| Carbamazepine | 300-2,000 mg/day | Check CBC, lytes, & ECG. | Sedation, hyponatremia, leukopenia |
| Oxcarbazepine | 600-1,800 mg/day | Check lytes. | Headache, dizziness, diplopia |
| 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, dizziness |
| Pregabalin | 600-1,200 mg/day | Check renal function. | Sedation, dizziness, peripheral edema |
| Clonazepam | 1.5-8 mg/day | None | Sedation |

# Central Nervous System Vasculitis

Amanda L. Piquet

Tracey Cho

Often considered in ddx of subacute encephalopathy & typically has an insidious, progressive course. 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/vasculitides in the "Neurorheumatology" 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 (leptomeningeal/cortical arteries & arterioles > medium-size arteries > veins/venules >> large intracranial arteries).

**Etiology:** Idiopathic. **Epidemiology:** M = F, commonly 30-50 yo. **Ddx:** Reversible cerebral vasoconstriction syndrome (RCVS), infxn, intravascular lymphoma, 2° CNS vasculitis (CTD, malignancy, other systemic vasculitides, drugs).

**Clinical manifestations** (*Ann Neurol* 2007;62:442): *HA* + *encephalopathy* + *strokes*. Subacute (sx develop over *weeks-months*). Si/sx: HA (63%), encephalopathy (50%), focal deficit/stroke (40%), sz (16%), ICH (8%), myelopathy. **Workup:** CBC w/diff, BUN/Cr & UA, & LFTs. *ESR can be normal*. Consider EMG, nerve/muscle bx for subclinical dz if systemic involvement suspected and/or evidence of peripheral neuropathy.



| **Minimally Invasive Testing** | |
|---|---|
| **Serology** | R/o underlying processes. ANA, RF, anti-Ro/La, anti-Sm, anti-RNP, anti-dsDNA, APLS antibodies, ANCA, C3 & C4, cryoglobulins, SPEP/UPEP, quantitative IgG, ACE, infectious serol. (HIV, TP-EIA, Hep B/C at minimum). |
| **LP** | 80%-90% abnormal. ↑ or nl OP, ↑ TP, ↑ WBC (lymph), ↑ IgG, ± OCB, micro neg Additionally send VZV IgG & IgM, CMV PCR (if pt is immunocompromised) & VDRL (if serum TP-EIA positive), & others as indicated |
| **MRI** | Most sensitive Dx test (>90% abnl). Multifocal, bilateral T2/DWI abnormalities ± enhancement involving G/W matter. Stroke >> ICH. Rare tumor-like mass lesion (about 4%). |
| ***Combination of neg MRI* & *LP has high neg predictive value*** | |
| **Invasive Testing** | |
| **Conventional Angiography** | Suspicion + consistent CSF or MRI → consider conventional angio. **Nonspecific** pattern of beading, aneurysm, circumferential/eccentric irregularities, multiple occlusions. |

| | |
|---|---|
| | Sensitivity 40%-90%, specificity 30% (CTA/MRA less sensitive compared to conventional angiography).<br>Path confirmed cases have shown normal angio (vascular abnormalities can occur in arteries smaller than resolution of angio). |
| **Pathology** | Gold standard. Clinical suspicion + prior w/u inconclusive or to confirm dx prior to Rx. Sample leptomeninges + cortex in an affected region if possible (vs. random sampling of non-dominate hemisphere if imaging negative). Segmental inflammation = false neg 25% vs. autopsy (*J Neurol* 2001;248:451). Targeted biopsies diagnostic 78% (*Am J Surg Pathol* 2009;33:35-43).<br>Histopathology: Granulomatous (most common, associated w/***β***-amyloid deposition), lymphocytic, or necrotizing pattern (least common, associated w/ICH). |

## VASCULOPATHY VS. VASCULITIS

Vasculitis = inflammation of blood vessel wall leading to destruction. Vasculopathy = thrombus, compromising blood flow; nonimmunologic injury to sm vessels → important to distinguish since Rx is very different!

**Radiographic mimics** (*Curr Opin Rheumatol* 2008;20:29; *Ann Intern Med* 2007;146:34; *Lancet* 2012;380:767-77).

**RCVS.** Most important: Severe, acute "thunderclap" HA, sometimes recurrent HA + w/(multi)focal deficits (21%).

| **Characteristics of PACNS vs. RCVS** | | |
|---|---|---|
| | **RCVS** | **PACNS** |
| **Demographics** | 2:1 female | 1:1 |
| **Acuity** | Acute (usually severe thunderclap HA) | Subacute |
| **Clinical setting** | Defined setting (esp drug exposure, postpartum) | No clear setting |
| **Reversibility** | Days-weeks | Months or longer |
| **CSF findings** | Normal to near normal | Abnormal (leukocytosis + elevated TP) |
| **MRI** | Normal in 70% but can have evidence of localized SAH & less frequently ischemic or hemorrhagic stroke | Abnormal in >90% of patients |
| **Angiography** | Always abnormal, reversible in 6-12 wk | Possibly normal, diffuse abnormalities indistinguishable from RCVS |

| | | |
|---|---|---|
| **Treatment** | Supportive +/- nimodipine | Steroids +/- cyclophosphamide |

**Atherosclerosis:** Intracranial vasculopathy. Assess pt risk factors for atherosclerotic dz (HTN, DM, smoking, etc.).

**Intravascular lymphoma:** Occlusion of sm vessels. Immunohistochemistry on B-& T-cell makers on bx helps differentiate. Presence of vasculitic changes on bx does not exclude dx. **Bacterial endocarditis:** Septic embolic can produce occlusions & a vasculitis pattern on angio.

Also consider other vasculopathies: Fibromuscular dysplasia (FMD), post-XRT, CADASIL, hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS).

## SECONDARY ANGIITIS OF THE CNS

**Definition:** Systemic vasculitis w/CNS involvement *or* extravascular process resulting in CNS vasculitis (e.g., meningitis w/secondary involvement of vessels). Heterogeneous group of d/os that includes infxn, systemic vasculitis, connective tissue disorders, etc. Typically, the systemic vasculitides involve the PNS (mononeuropathy multiplex) > CNS.



| Systemic Vasculitides | |
|---|---|
| **Behcet disease** | Vasculitis of all sized arteries & veins; oral aphthae, ocular dz; CNS involvement 10%-20% |
| **PAN** | Systemic sx & neuropathy; PNS >> 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** | Meningovascular form of neurosyphilis, inflammation, & fibrosis of sm arteries. Favors basilar a. & distal territories MCA. Most infarcts in lenticulostriate region +serum FTA-ABS or TP-EIA & CSF VRDL, CSF w/↑ TP, ↑ WBC↑ & usually ↑ IgG, ± OCB |
| **TB** | Gelatinous exudates 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<br>Detection of VZV IgG in CSF to diagnose (VZV DNA often negative). For CMV, detection of CMV PCR diagnostic in CSF |
| **Hep B & C** | PAN & cryoglobulinemia |
| **HIV** | Vasculopathy ± vasculitis. CNS vascular dz 2/2 HIV or opportunistic infection or lymphoproliferative disease of CNS |
| **Fungi, *Bartonella*, rickettsial** | Extremely rare Fungal—aspergillosis, mucormycosis, coccido, candidosis |
| **Leptospirosis** | Hepatitis & aseptic meningitis → SAH & ICH from inflamed blood vessels |
| **Parasitic** | Schistosomiasis, cerebral malaria, SA cysticercosis |
| **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 angioendotheliomatosis, premalignant lymphomatoid granulomatosis |
| **Paraneoplastic** | PNS; assoc w/SCLCA & lymphoma ± anti-Hu |
| **Drugs** | More likely RCVS rather than true vasculitis. Cocaine, amphetamines, phenylpropanolamine, high-potency cannabinoids (K-2, “spice”), opioids<br>Secondary hypersensitivity rxn such as SJS & leukocytoclastic vasculitis (rare PNS >> CNS involvement) |
| **Cogan syndrome** | ↓ vision (interstitial keratitis) & cochleovestibular dysfxn assoc w/↑systemic vasculitis |

| | |
|---|---|
| **Susac syndrome** | Retinopathy, BRAO, hearing loss, encephalopathy. Vasculopathy → microinfarcts |
| **Inflammatory** | Antiphospholipid antibodies syndrome; neurosarcoidosis; inflammatory bowel disease; graft-versus-host disease |

# TREATMENT OF CNS VASCULITIS

**Therapy, monitoring, & follow-up for CNS vasculitis:** Pts will generally be on high-dose steroids & cyclophosphamide (CYC)—each w/specific complications as part of remission induction therapy. If a pt does not respond promptly to steroids, then CYC should be initiated. Generally, induction therapy w/CYC is continued for 6 mo to 1 yr followed by remission maintenance therapy w/azathioprine, methotrexate, or mycophenolate mofetil.

Close neurological f/u for management of complications of Rx or dz & med adjustments. Repeat imaging (typically MRI/MRA) q3mo during medication changes or PRN w/changes in sx. Longer intervals w/serial imaging appropriate when on stable therapy. F/u testing & prophylactic meds for expected complications of each Rx discussed below.

## STEROIDS

Recommend high-dose glucocorticoids as an important part of remission induction therapy. There is no "validated" schedule; however, it is reasonable to start w/Solu-Medrol 1 g qd × 3 days, then a SLOW taper. The initial high dose should be maintained for 1 mo & should not be reduced to less than 15 mg/day for the first 3 mo of Rx (*Ann Rheum Dis* 2009;68(3):310-317).



**SLOW steroid taper:** 1 mg/kg qd × 4 wk, 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* (serial MRI/MRA q3mo during 1st year of Rx). As steroids tapered off, watch for adrenal insufficiency.

**Prophylactic medications while on steroids:** 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 80 mg TMP PO qd or 160 mg TMP 3 times/wk for PJP ppx; consider PPI for GI ppx if symptomatic.

**Close PCP involvement:** Monitoring labs, side effects (e.g., HTN, DM, weight gain).

## CYCLOPHOSPHAMIDE

**General considerations:** Usually reserved for cases that fail steroids or w/rapidly progressive course & biopsy support or thorough negative w/u for other etiologies. Usually given as scheduled IV infusions (better tolerated & reduced risk for sterility & cystitis compared to daily oral).

**Expected duration/schedule of CYC therapy:** Initial dose often given in hospital, subsequent doses in outpatient infusion center. Dosing of CYC based on EULAR recommendations for small-& medium-vessel vasculitis (*Ann Rheum Dis* 2009;68(3):310-317).

**Initial dosing of CYC for induction therapy:** 15 mg/kg (max 1.2 g; severe leukopenia & renal impairment may necessitate dose adjustments) IV q2wk × 3 doses then q3wk × 3-6 doses then reassess & continue Rx until remission.

**Maintenance therapy:** Continue CYC × 6 mo from time of clinical improvement/stability then switch to azathioprine (1-2 mg/kg daily) or mycophenolate mofetil (1-2 g daily) or methotrexate (20-25 mg/wk) for 2-3 yr

total for maintenance of remission, then try tapering those.

Adjunctive Rx (antiemetics, IVF/mesna for renal protection, etc.)—see protocol below

**Dose adjustments:** Necessary dose adjustments may be required based on two factors: (1) Renal impairment & (2) leukopenia (see below for CBC monitoring).

**Laboratory while on CYC** (Sem Neurol 2014;34(4): 467-478):

*CBC w/differential* (*& ANC*): (1) Just prior (<24 h) to initial dose & each maintenance booster. (2) Check on days 7, 10, 14, 27-28 after IV dose.

*Urinalysis:* Before each Rx & continue every 3-6 mo even once CYC discontinued (lifelong surveillance for bladder cancer is recommended). Additionally, can consider cystoscopy q1-2 yr.

*BUN/Cr:* (1) Prior to dosing; adjust for renal insufficiency if needed. (2) Monitor every 2 wk.

| **Suggested Protocol for CYC 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 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 CYC & total at least 2 L over 24 h. |
| *Dosing & schedule*: Antiemetics: Ondansetron 8 mg IV 1 h prior to CYC, then metoclopramide or ondansetron PRN. Steroids: Continue at same dose as before starting CYC. Consider: ASA, MVI, thiamine, folate. DVT ppx if bedridden (e.g., LMWH). |
| *Mesna:* To prevent hemorrhagic cystitis; dose: 60%-140% of CYC dose total if given IV.<br>PO mesna is ~50% bioavailable. If given orally, doses must be adjusted accordingly: Give 1/3 of entire dose 30-60 min before IV CYC, 1/3 dose 4 h after start of CYC (or immediately after 4 h infusion runs in), 1/3 dose 8 h after start of CYC.<br>*Example dosing schedule*: 11 am, IV mesna 333 mg/12 pm, IV CYC 1,000 mg; 4 pm, IV mesna 333 mg; 8 pm, IV mesna 333 mg. |
| *CYC rate*: May vary depending on inpatient & outpatient protocols. Protocol should be based on best practice at specific center. For example, infusion duration over 60 min, may infuse subsequent CYC infusions over 30 min if no adverse rxn. |

**Rituximab:** May be used as 2nd-line tx if intolerant to CYC; however, limited data based on case reports (*Neurology* 2014;8:1287-1288).

# Paim

Khaled Moussawi

Brian J. Wainger

## PHYSIOLOGY

**Characterization:** Location, duration, radiation, quality, continuous vs. episodic, intensity (visual or numerical scale); evoked vs. spontaneous, triggering/mitigating factors, associated features (n/v, spasm), effect on quality of life.

**Physiology:** 1° pain neurons, nociceptors consist of A-β & δ-fibers. Transmit location & intensity of pain from DRG neurons → STL tract → thalamus → sensory cortex, & affective pain component via spinoparabrachial tract → periaqueductal gray region (PAG) & limbic areas.

### Sensory Nerve fiber types

- A-β fibers: Rapid conduction (40-50 m/s). Thickly myelinated: Vibration, proprioception, touch.
- A-δ fibers: Slow (10-30 m/s), thinly myelinated: Initial fast pain & temperature sensation.
- C-fibers: Very slow (0.7-2.3 m/s), unmyelinated: Delayed pain & temperature. Peptidergic (CGRP, SP) & nonpeptidergic types.

**Pain Types: (1) Nociceptive:** Pain 2/2 ongoing high-threshold noxious stimulus (injury, trauma, surgery). **(2) Inflammatory:** Physiologic or pathologic pain 2/2 inflammation (release of "inflammatory soup" following nerve injury). **(3) Neuropathic:** Pathological pain 2/2 lesion in PNS/CNS; pain often present despite absence of continued stimulus (spontaneous pain). Quality may be burning, gnawing, aching (C-fibers, spontaneous), vs. shooting, lancinating (A fibers upon touch). Includes trigeminal neuralgia, postherpetic neuralgia, neuropathy, trauma, neuromas, root irritation, SC injury, thalamic pain syndrome. See detailed syndromes below. **(4) Dysfunctional:** Maladaptive/pathological pain; no known CNS/PNS lesion. Related to abnormal processing (i.e., depression, somatization, fibromyalgia). Pain can be primary as well as amplified by or manifestation of psychiatric disease (i.e., depression) (*J Clin Inv* 2010;120(11):3742-3744).

**Abnormal sensory responses:** *Hyperalgesia* (↑ pain sensation to noxious stimulus), *dysesthesias* (unpleasant paresthesia), *allodynia* (pain elicited by nonnoxious stimulus, e.g., wind, light touch, clothing). *Spontaneous pain*—stimulus independent. **Sensitization: A-Peripheral**: Tissue injury → release of inflam. mediators & influx of inflam. cells → posttranslational modifications of nociceptor receptors & channels → lower activation threshold & increased pain responses. **B-Central:** 1-Nonnociceptive afferents (Aβ) become able to mediate pain → invasion of superficial dorsal horn: explains allodynia. 2-Posttranslational modifications of AMPA & NMDA receptors → enhance Ca influx → activates kinases → plasticity in different areas of CNS → prolonged response (up to hrs) to brief stimulations: explains hyperalgesia. 3-Peripheral nerve injury → activation of CNS microglia & astrocytes → CNS inflam. → hypersensitivity. 4-Death of inhibitory interneurons in SC → cross-talk from nonnociceptive inputs via (Aβ) → activate central pain tracts in response to nonnoxious stim. (touch) → allodynia (*Cell* 2009;139:267-284) (*Nat Neur* 2014;17(2):183-191) (*Nat Med* 2010;16(11):1267-1276). Central sensitization major determinant in chronic pain.

**Pain perception:** Variable threshold to activate pain fibers. Lowered by inflam. → hyperalgesia, allodynia. Increased by other mechanisms: Placebo, acupuncture, distraction, positive mood → lower pain perception.

**Endogenous Modulation of Nociception:** 1-Activation of nonnociceptive afferents → inhibit pain transmission via inhibitory interneurons in dorsal horn → raise pain threshold (gate control theory). 2-Descending NT systems:

Opioid, serotonergic, adrenergic systems → inhibit nociceptive transmission but become facilitatory as part of central sensitization.

## PRINCIPLES OF CHRONIC PAIN MANAGEMENT

- Start w/first-line agent → try different agents within same drug class or try second drug class → resort to opiates as last resort (risk of tolerance, addiction, serious side effects).
- Elderly: Favor acetaminophen, morphine immediate release, Lidoderm patch.
- Role for nonpharmacologic rx: PT, rehabilitation, CBT, biofeedback, acupuncture, interventional pain mgmt., psychological support, hydrotherapy, meditation, electrical stimulation.

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**Commonly used meds in different pain conditions:**

**Acetaminophen:** Counsel re: Toxicity (<3.25 g/day, <2 g/day if liver disease).

**NSAIDS:** If one NSAID fails, try another class (ibuprofen 200-800 mg tid; naproxen 25-500 mg bid, celecoxib 100-200 mg bid, diclofenac 50-75 mg bid, ketorolac 10 mg PO qid × 5d or 30-60 mg IV/IM q6h, indomethacin 25-50 mg tid, nabumetone 1,000-1500 mg qd, meloxicam 7.5-15 mg qd). SE: GI bleeding (consider PPI if high risk), renal dysfunction w/prolonged use.

**Tricyclic antidepressants (TCAs):** Nortriptyline, amitriptyline. Avoid in elderly, pts w/risk of delirium, pts w/heart disease. Effect expected in 7-14 days. SE: Anticholinesterase effects—dry mouth, urinary retention, constipation, orthostatic hypotension, sedation, glaucoma, arrhythmias, conduction disorders. Major risk: Cardiac tox, risk of death w/OD. Consider EKG (QRS/QT) if > 40 yo. Uptitrate q4-7d to minimize SE. Nortriptyline better tolerated 2/2 secondary amine structure; less SE than amitriptyline (↑ antichol SE) (tertiary amine).

**Selective serotonin & norepinephrine reuptake inhibitors (SSNRI):** Duloxetine, venlafaxine. Common SEs: Nausea (~20%-30%), drowsiness (10%-20%), loss of appetite (8%). Venlafaxine may cause HA (30%), HTN (3%-10%), constipation (8%-15%). Less sexual SEs than TCAs. Minimize venlafaxine SE by slow uptitration (75 mg q4d).

**Carbamazepine:** Generally well tolerated. Blocks Na channels. SE: Stevens-Johnson's (test for HLA-B*1502 for at-risk population—Asian descent), dizziness (44%), nausea (29%), vomiting (18%), bone marrow suppression, hypoNa (4%-21%), pruritus (8%), ataxia (15%), hepatic dysfunction, interaction w/other rx.

**Oxcarbazepine:** Similar to carbamazepine but better tolerated.

**Valproic acid:** Avoid in young females 2/2 teratogenicity, weight gain (4%-9%), hair loss (6%-24%). SE: hyperammonemia, tremor (9%-57%), sedation (17%-30%), nausea (22%-48%), other GI toxicity, bone marrow suppression (dose dependent) (1%-27%).

**Gabapentin:** Generally well tolerated. Acts on voltage-gated Ca channels → reduces release of glut & subs P. SE: Somnolence (4%-21%), dizziness (10%-28%), ataxia (3%-12%), suicidal ideations. Minimize SE by slow uptitration (100 mg q3d). Renal dosing if AKI/CKD. Potential for abuse at high doses. To d/c, slow taper.

**Pregabalin:** Similar to gabapentin; negligible hepatic metabolism (use in liver patients). SE: Sedation (10%-35%), dizziness (9%-40%), dry mouth (2%-11%), peripheral edema (5%-12%), blurry vision or diplopia (3%-10%), suicidal ideations.

**Topiramate:** SE: Memory problems (3%-12%), word finding difficulty, confusion (3%-11%), sedation (6%-29%), dizziness (4%-25%), nephrolithiasis (1%-3%), GI upset, weight loss (4%-21%), hyperammonemia (26%).

**Lidocaine patch:** 5%, apply 12 h/day. Useful for postherpetic neuralgia & myofascial pain especially in elderly

(no systemic SE). 5% ointment alternative.

| 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 |
| Topiramate | 25 mg qd | 100-200 bid | 400 mg/day |
| Carbamazepine | 100 mg bid | 200-400 mg bid | 1600 mg/day |
| Baclofen | 5 mg qd-bid | 10-20 mg tid | 80 mg/day |
| Oxcarbazepine | 300 mg bid | 600 mg bid | 2400 mg/day |

Modified from *Pain* 2007;122:237.

**Opioids**

- Act via μ, δ, κ, & orphan receptor-like opioid receptors.
- Major effects: Analgesia, resp depression, n/v, cough suppression, miosis, ↓ GI secretions & mobility, ↓ sympathetic CV output.
- **High risk of death with prescription opioids** (*NEJM* 2014;370:22): Epidemic of prescription-opioid overdose deaths in the United States; 82% of deaths from unintentional overdoses especially w/long-acting opioids. Related to substance use disorder.



| Opioid Equianalgesic Dose Conversion Table | | | | |
|---|---|---|---|---|
| **Drug** | **PO/PR (mg)** | **Onset/peak (min)** | **SQ/IV/IM (mg)** | **Onset/Peak (min)** |
| Morphine | 30 | 15-60/90-120 | 10 | 5-10/10-30 |
| Oxycodone | 20-30 | 15-30/30-60 | n/a | |

| | | | | |
|---|---|---|---|---|
| Hydrocodone | 20-30 | | n/a | |
| Hydromorphone | 7.5 | 15-30/90-120 | 1.5 | 5-10/15-30 |
| Fentanyl patch | | | 15 mcg/h | 12 h |
| Fentanyl | n/a | | 0.1 | <1/5-7 |
| Oxymorphone | 10 | | 1 | |
| Meperidine | 300 | | 75 | |
| Methadone | 2.5-7.5 | 30-60/90-120 | n/a | |
| Codeine | 200 | | 120 | |

***Opioid Conversion***

1. Using table above, calculate "equianalgesic" 24-h dose of the desired opioid.
2. Reduce calculated 24-h dose by 25%-50% 2/2 incomplete cross-tolerance.
3. Divide calculated dose by number of doses/day.
4. Order liberal "rescue" dose (10%-15% of 24 hrs starting dose) & titrate.
5. Monitor response closely.
6. After 12-24 h, recalculate scheduled dose (total 24-h dose/doses per day).

Modified from Ballantyne J, ed. *The Massachusetts General Hospital Handbook of Pain Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

Starting opioids: Opioid-naive patients → 5 mg oxycodone (2.5 mg in elderly) or 2-5 mg IV morphine (0.5-1 mg in elderly); not opioid naïve → 10%-20% of total daily opioid in short-acting form. Repeat or increase dose to decrease pain score >50%. **In opiatenaïve** patients, continue to use short-acting opiates. May consider long-acting opiates in palliative care patients (if switching to fentanyl patch, bridge with shortacting opioid for first 12 h).

- Morphine: 90% renal clearance; most renally cleared opiate; avoid in renal failure.
- Use lower opioid doses for hepatic & renal impairment.

Weaning Opioids: Drop dose by 50% over first 2 days → reduce dose by 25% every 2 days until total dose is equivalent to *30 mg morphine/day* → d/c drug after 2 days at 30 mg/day (oral morphine equivalents).

Methadone: Metabolism varies between individuals → variable t1/2 → risk of respiratory depression. Slow β-elimination phase w/t1/2 = 15-60 h (t1/2 increases at higher doses). 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. Rough guideline: Start at 10:1 (morphine to methadone) conversion.

Responses to medications: *1-Opioid-induced hyperalgesia*—reduced pain threshold. *2-Tolerance*—need to ↑

dose to maintain analgesia; *physical dependence*—w/d sxs upon abrupt cessation. *3-Addiction*—dependence → preoccupation w/obtaining drug, compulsive use despite adverse consequences, loss of control; *pseudoaddiction*—drugseeking behavior 2/2 inadequate rx.

SE mgmt: Resp depression/apnea → naloxone bolus 0.4 mg, repeat q2-3min. Sedation → reduce dose (tolerance develops); consider CNS stimulant (methylphenidate 2.5-5 mg qd). Constipation → bowel regimen. Delirium → reduce dose, switch. Treat w/antipsychotics if refractory. N/V → antiemetics for few days (tolerance develops). Pruritus → switch opioid. Myoclonic jerks → lower dose, switch opioid, low-dose BZD. Allergy: very rare → switch class.

**INTERVENTIONAL PAIN MGMT:** Several interventions currently used for pain including epidural or paravertebral (facets, sacroiliac joint) local anesthetic & steroid nerve blocks for back pain, radiofrequency ablation of medial branch to facet joints, Gasserian ganglion block for trigeminal neuralgia (TN), greater occipital nerve block for TN, suprascapular nerve block for shoulder pain, IV regional block or cervical or lumbar sympathetic block for complex regional pain syndrome (CRPS). Other interventions include intrathecal drug administration, spinal cord stimulation of DC, & neurosurgical interventions (disc decompression, spinothalamic tractotomy, nerve section) used in cases of severe & refractory pain. Evidence currently best supports the following interventions: 1-Epidural injections (steroid + lidocaine) for radiculopathy → transient pain improvement w/o affecting outcome; 2-Spinal cord stimulation for CRPS type 1 & after failed back surgery (*Pain* 2013;154:2249-2261).



## PAIN SYNDROMES

### Bone pain

- NSAIDs.
- Bisphosphonates: May reduce osteolytic pain. Prior to initiation, check & replete vit D (risk of severe hypocalcemia). Check GFR before each dose (for both dosing & toxicity).
- Zoledronate 4 mg IV over 15 min q3-4wk.
- Pamidronate 90 mg IV over 2 h q3-4wk.
- Other: Interventional pain management, radiation therapy, or surgery.

### Cancer pain

Pain Ladder per WHO (American Pain Society: Principles of Analgesic Use in Acute/Cancer 2008).

- Step 1 (mild-to-moderate pain): Acetaminophen or an NSAID +/- adjuvant agent.
- Step 2 (pain uncontrolled by step 1): Short-acting PRN opioid + Step 1.
- Step 3 (moderate-to-severe or uncontrolled pain): Long-acting opioid or continuous infusion + Step 2.

### Complex regional pain syndrome

**Definition:** Severe continuing pain disproportionate to inciting event (usually injury, but can be immobilization or DVT). Clinical dx. Mean age 36-46 yr, F > M. Caused by injury-like fracture, strain, surgery, or contusion.

**Si/Sx:** Sensory (hyperesthesia, allodynia), exquisite sensitivity to touch (clothes, air), vasomotor (temp/color asymmetry), sudomotor (sweating changes), edema, motor (wkns, tremor, dystonia, myoclonus), dystrophic (nail or skin thickness Δs, shiny, scaly, discolored skin devoid of hair).

2 types: *Type I* (*reflex sympathetic dystrophy*)—w/o major evident nerve damage; *type II* (*causalgia*)—with major

evident nerve damage.

Mechanism: Possibly adrenergic hypersensitivity 2/2 overexpression of adrenergic receptors.

**Rx** (*Cochrane review* 2013;30:(4):CD009416): Low-quality evidence for benefit from bisphosphonates, calcitonin, or IV ketamine. Low-quality evidence for PT/OT. TCAs & AEDs widely used but no clear supportive evidence. Sympathetic blockade used w/o strong evidence.

### Cramps

First line: Vitamin B complex, diltiazem, naftidrofuryl (AAN guideline 2010). Quinine: Most effective drug (level A) but not FDA approved due to serious SE including risk of death (93 cases). AAN guidelines recommend avoiding routine quinine use & limiting its use to disabling cramps.

### Diabetic neuropathy pain

**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).

**Rx** (*Neurology* 2011;76(20):1758-1765):

- First line: Pregabalin (level A).
- Second line: Gabapentin, TCAs (amitriptyline, nortriptyline), SNRIs (duloxetine, venlafaxine) (level B). Lidocaine patch (level C). Venlafaxine may be added to gabapentin for better response.
- Third line: Opioids (morphine, oxycodone, dextromethorphan, tramadol), valproic acid, capsaicin (level B). All potentially effective but concern for side effects.
- Lacosamide, oxcarbazepine, lamotrigine probably not effective.

### Dynias

(*Sem Neurol* 1996;16:63.)

**Definition:** Poorly understood focal, often chronic pain syndromes. Usually treated w/neuropathic pain meds, esp TCAs.

**Glossodynia:** Painful tongue, synonymous w/"burning mouth syndrome." Must r/o: Reactions to dental materials/implants, vit. def (B12, other B vitamins, Fe, folate, & 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 necessary component of rx.



**Orchidynia:** Testicular dynia, orchialgia; 1° or 2/2 infection, tumor, 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 infections, 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 disease of anus or rectum, or referred from urogenital tract or lower spine. Includes *proctalgia fugax*, sudden brief spasms of pain.

**Headaches: separate chapter**

Glossopharyngeal neuralgia

Similar to TN but affects CN IX, causing paroxysmal pain in throat, in tonsillar fossa. Pain may localize or radiate to ear. Provoked by talking, swallowing, chewing. May be a/w bradycardia, syncope (cardioinhibitory reflex by vagus nerve). Rx like TN.

**Neuropathic pain**

Includes several different entities (TN, diabetic neuropathy, postherpetic neuralgia, etc.). See detailed syndromes in this section. General empiric treatment approach (*Am J Med* 2009;122(10 suppl):S22-32) (*Mayo Clin Proc.* 2010;85(3)(suppl):S3-S14):

- First line: TCAs (nortriptyline, amitriptyline), SSNRI (duloxetine, venlafaxine), gabapentin, pregabalin, topical lidocaine (for localized pain; used alone or in combination w/other agents). If one drug fails, switch to another first-line agent before trying second line.
- Second line: Opioids & tramadol: Similar efficacy to TCAs, but higher risk of abuse & worse SE profile.
- Third line: Other AEDs: Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid.
- Consider tramadol only if acute rescue therapy is needed.

**Low back pain**

**Epidemiology:** Fifth most common complaint. 90% of acute episodes (duration < 3 mo) recover; less likely to recover after 3 months. Return to work rate after 6 months off <50%; after 2 yr close to 0%. *Red flags*: Si/sx conus medullaris or cauda equina compression—bowel or bladder retention or incontinence, groin paresthesias, progressive wkns, worsening pain. Urinary retention is 90% sens for cauda equina syndrome (w/o this, probability of cauda equina ~ 1:10,000).

**Common causes/Approach:** Distinguish between muscle strain, lumbar disc herniation/radiculopathy, lumbar facet joint syndrome, sacroiliac joint syndrome, spinal stenosis:

1. Muscle strain: H/o acute injury, exam w/paraspinal tenderness or spasm. Rx: NSAIDs, muscle relaxants, PT.
2. Lumbar disc herniation/radiculopathy: Shooting, stabbing pain, radiating in distribution of affected root (mostly L5 or S1). Exam w/+ straight leg raise. Paraspinal tenderness or spasm. Possible reduced sensation in affected dermatome (especially L5) & mild weakness (L5 → tibialis anterior, S1 → peroneus longus & brevis). Positive straight leg raise is 91% sens for disc herniation 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, & ↓ pinprick most discriminating tests (*PLoS Med* 2009;6:e1000047).
3. Rx: NSAIDs, muscle relaxants, PT. If no improvement → epidural steroid injection (*Pain* 2013;154:2249-2261). Surgery if sx do not improve after 3 months or severe pain or weakness.
4. Lumbar facet joint syndrome: A/w arthritis. Pain may radiate to anterior or posterior thigh. Exam w/paraspinal tenderness. Pain worse w/back extension and/or lateral rotation to painful side. Straight leg raise is negative. Rx: NSAIDs, intrajoint steroid injection. If no improvement → nerve block.

5. Sacroiliac joint syndrome: A/w arthritis. Pain may radiate to hip & medial thigh. Pain worse w/going up the stairs. Exam w/hip joint tenderness & severe pain on hip external rotation (Patrick/FABER test) or single leg standing. Rx: NSAIDs, intrajoint steroid injection.
6. Spinal stenosis: 2/2 degenerative spondylolisthesis, disc herniation, osteophytes. Neurogenic claudication. Pain radiates to LE, is worse w/standing or walking, & is



better w/sitting. Pts walk w/hunched back. Exam noncharacteristic (minimal paraspinal tenderness, leg raise can be normal). Rx: NSAIDs; epidural lidocaine possibly beneficial but no evidence for epidural steroid compared to steroid + lidocaine (*NEJM* 2014;371(1):11-21). If no improvement → surgery, opiates.

**Occipital neuralgia**

Paroxysmal pain isolated to sensory fields of greater or lesser occipital nerves (suboccipital, occipital, post. parietal). Usually deep, burning pain, hyperalgesia 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, C1-C2, or C2-3 facet joints. R/o postfossa tumor, Arnold-Chiari malformation, abnl vasc. structure (e.g., AVM/dural fistula) or injury (e.g., vert dissection).

**Rx:** 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; if diagnostic blocks of cervical nerve or medial branch (which innervates the facet joints) are positive, radiofrequency ablation can provide longer relief (*J Am Osteopath Assoc* 2005;105:S16).

**Otalgia:**

Pain in external ear. May be incipient sx of Bell palsy. Idiopathic vs. secondary to nasopharyngeal tumor, vertebral a. aneurysm, prezoster eruption, low-cluster HA, glossopharyngeal neuralgia, or migraine.

**Phantom limb pain:**

Distinct from phantom limb awareness, phantom sensations, & 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 & ↓ pain (*Nat Rev Neurosci* 2006;7:873).

**Postherpetic neuralgia (zoster pain)**

**Key features:** Painful prodrome in up to 75%; dermatomal distribution of grouped vesicles or papules; history of prior rash in same location suggests herpes *simplex*, not zoster; pain & allodynia in area of rash; frequency increases w/age. Pain as burning w/superimposed stabbing waves. Cranial variants: 1-HZ ophthalmicus (CN V1): Rash appears 4-5 days after pain onset, 2-HZ auricularis (Ramsay-Hunt syndrome): Rash in external ear ww/o palate, occipital area; ww/o hearing loss, tinnitus, vertigo, combined w/CN VII paralysis.

**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 > 90 days (mostly in elderly).

**Rx:** (*NEJM* 2014;371(16):1526-1533)

- First line: Topical lidocaine 5%.
- Second line: TCAs (amitriptyline, nortriptyline), gabapentin, pregabalin.
- Third line: Opioids.

Acute treatment w/antivirals within 72 h: ↓ length of rash & acute pain but no effect on risk of postherpetic neuralgia (*Cochrane* 2014;(2):CD006866).

### Poststroke pain (dejerine-roussy syndrome)

**General:** Usually 2/2 thalamic stroke but also 2/2 lesions throughout spinothalamocortical pathway; pain develops usu 1-2 mo after ischemic stroke/ICH. Can be spont or evoked.

**Rx:** Amitriptyline & lamotrigine first line. Alternatives: Mexiletine, fluvoxamine, gabapentin (*Anesth Analg* 2009;108:1645).

### Sodium channel mutations

Rare pain syndromes a/w mutations in voltage-gated sodium channel NaV 1.7 (*Adv Genet* 2008;63:85).

- Erythromyalgia: Prominent features: Erythema, swelling, burning pain, predom of distal extrem. 1° & 2° forms exist. 1° form: Most of the characterized mutations lower threshold for channel activation. Secondary causes include PN, mushroom or mercury poisoning, hypercholesterolemia, myeloproliferative disease, & autoimmune conditions.
- Paroxysmal extreme pain disorder (familial rectal pain syndrome): Pain in theocular, mandibular, & rectal areas. Associated mutations impair channel inactivation.



### Spasticity

From MS, SC injury, stroke, TBI, etc.

**Rx:** First line: PT/OT. Baclofen (start at 5 mg tid, titrate 5-10 mg/week): Common dose 15-80 mg/day divided tid (high doses limited to severe conditions like SC injury). Adjust dose if renal failure. Taper by 15 mg/week.

Second line: Tizanidine: Start at 2 mg qhs, increase by 2 mg qwk; max dose 36 mg/day divided tid. Max single dose 16 mg. SE: Somnolence (48%-92%), dry mouth (49%-88%). Cannabinoids improve reported outcome but not objective measures. Also consider botulinum injections for focal spasticity & intrathecal baclofen pumps for treatment-resistant spasticity.

### Spinal cord injury pain

86% of pts w/SC injury report pain at level of injury or below at 6 months. 27% w/debilitating pain. Pain burning, sharp, or shooting. Not a/w magnitude or location of lesion.

**Rx:** Similar to neuropathic pain.

### Trigeminal neuralgia

**Definition:** Unilateral lancinating brief (few sec < 1 s) 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 & third CN V2, V3; rare in V1. Precipitated by light mechanical stimulation to small areas of face/oral mucosa (trigger zones): Light touch, wind, eating, chewing, drinking, or speaking. Spatial & temporal summation from subtle stim. → trigger attack. May cause ipsi. muscle spasm (**tic douloureux**). Two types: (1) Classic/idiopathic TN (idiopathic or 2/2 vascular compression of CN V): Clinical sensory exam is normal; pts are asymptomatic between attacks. (2) Symptomatic TN: Sensory loss; identifiable structural lesion (e.g., MS, basilar artery aneurysm, cerebellopontine angle tumor [schwannoma, meningioma, epidermoid]) compressing CN V5 root. Imaging (MRI) indicated for symptomatic or bilateral TN.

**Rx:** AAN guideline 2008.

**Pharmacological:** Most pts respond well to medical rx. First line: Carbamazepine (level A); best studied; 70%-80% response but half become tolerant after several years. Second line: Oxcarbazepine (level B): Better side effect profile than carbamazepine. Third line: Lamotrigine, baclofen (level C). No clear evidence for other medications used to treat other neuropathic conditions (pregabalin, gabapentin, phenytoin, valproic acid).

**Surgical:** After failure of medical therapy but insufficient evidence what constitutes rx failure. Some experts refer pts to surgery after failure of first-line agent. 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.

## PAIN HYPOSENSITIVITY SYNDROMES

- **Congenital insensitivity to pain:** Universal analgesia. Extremely rare condition in which nociception is impaired but other sensory modalities are preserved. Pts often suffer damage to oral cavity & limbs due to absent pain sensation. Caused by lack of pain neurons in DRG or nonsense mutation of sodium channels Nav1.7 → loss of function of Nav1.7 channel.
- **Hereditary sensory & autonomic neuropathy (HSAN):** Reduced pain sensation a/w peripheral neuropathy. 5 types: 1-HSAN1: “Hereditary sensory neuropathy”; most common; sx start in adolescence; rare sensorineural hearing loss. SPTLC1 mutation. 2-HSAN2: “Congenital sensory neuropathy”; sx start in infancy. Mutations in WNK1 or FAM134B genes. 3-HSAN3: “Familial dysautonomia” (**Riley-Day syndrome).** Sx start in infancy: Hypotonia, feeding problems, poor growth, resp. infections, autonomic sx; mutation in the IKBKAP gene. 4-HSAN4: “Congenital insensitivity to pain w/anhidrosis”; loss of ability to sense any pain; self-mutilation. Mutation of neurotrophic tyrosine kinase receptor type 1 (NTRK1). 5-HSAN5: “Congenital insensitivity to pain w/partial anhidrosis,” a/w mutation of NGF β protein (lig & for NTRK1).
- **Asymbolia:** Pt aware of stimulus but cannot recognize its painful or hurtful nature; lacks emotional, motor, or verbal response. Form of agnosia to pain.

# Dizziness and Deafness

Taha Gholipour

Stephen W. Parker

**Vestibular system:** Otolith organ cilia are floating w/in endolymph (viscous fluid). Mvmt of head causes endolymph to move in opp direction. 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 → vibrates basilar membrane of organ of Corti thru TM → middle ear ossicles → fluid wave of endolymph in cochlea.→ Hair cells signal transmitted thru cochlear/auditory nerve to dorsal + ventral cochlear nuclei → superior olivary n. → inferior colliculus. → medical geniculate n. → auditory cortex (transverse temporal gyri of Heschl).

## APPROACH TO DIAGNOSIS OF DIZZINESS

Must be cautious interpreting history as per nature of the condition; pt's description & word selection might not be helpful in localizing the abnormality. Exam findings in central lesions can sometime mimic peripheral etiologies & misleading if not interpreted in context.

**History:** *Key questions*: meaning of "dizzy," (room spinning, light-headedness, giddiness, imbalance), pace of sx very useful (acute, subacute, chronic, episodic), positional vs. constant, assoc sxs (visual changes, hearing loss, weakness), previous h/o similar sxs, **meds** (Δs or new additions). Pt's PMH, FH, or risk factors for cerebrovascular disease, malignancy, or inflammatory or infectious causes can guide exam & imaging.

**Elements of History: Central vs. Peripheral Features**[a]

| | Central | Peripheral |
|---|---|---|
| Nausea | Variable | Variable |
| Positional | Rare | Common |
| Diplopia, dysarthria, dysphagia | Common | Rare |
| Imbalance | Variable, often severe | Variable, often mild/moderate |
| Hearing loss, tinnitus | Rare | Common |
| Oscillopsia | Severe | Mild |
| Other neurologic sx | Common | Rare |
| Recovery | Months | Days-weeks |

| | | |
|---|---|---|
| Recurrence | Rare | Variable |

[a]Classic features—central lesions can mimic peripheral features.

| Sxs | Mechanism |
|---|---|
| Disequilibrium: Imbalance or unsteadiness while standing or walking | Multiple: loss of vestibulospinal, proprioception, visual, motor fxn, joint pain/instability, & psych factors |
| Light-headedness 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 continuous 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 head induced: 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 system |

**Physical examination:** *Key elements*: Orthostatic vital signs, general exam, visual acuity, eye movements (spontaneous, pursuit, saccades), looking for long tract sensorimotor deficits or signs (weakness, Horner's, loss of pinprick OR touch sensation, Babinski's), vestibular-ocular reflex testing, position testing, axial & appendicular coordination (e.g., finger mirroring and heel-to-shin for appendicular), stance & gait (never defer).



| Exam findings: Central vs. Peripheral features[a] | | |
|---|---|---|
| | **Central** | **Peripheral** |
| Neurologic signs: CNs, weakness, sensory Δ, dysmetria, ataxia | Common | Rare |

| | | |
|---|---|---|
| Nystagmus[b] | 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 |
| Head impulse, thrust[b] | Maintains fixation | Impaired fixation w/catch-up saccade |
| Alternate cover test[b] | Skew deviation, **vertical** ocular misalignment apparent in alternate fixation | No vertical jump w/alternate refixation |
| Caloric test | Poor fixation suppression | Canal paresis |

[a]Classic features—central lesions can mimic peripheral features.

[b]Three-step exam of head impulse, nystagmus, Test of Skew (w/the mnemonic HINTS) is shown to be sensitive & specific for detecting central causes of acute vestibular syndrome such as stroke from peripheral causes (see *Stroke* 2009;40:3504-3510).

| **Vestibular-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 three or more lines above static visual acuity indicates a vestibular defect. |
| Head thrust | Pts fixate on a 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 impaired VOR. |
| Head-shaking nystagmus | Pitch the pt's head down 30 degrees & oscillate the head horizontally 20×. | Elicitation of jerk nystagmus after head shaking indicates a vestibular imbalance. |

**Imaging:** CT/MRI: Stroke/ICH, mass.

**Neurophysiology:** Electronystagmography or videonystagmography, computerized rotational vestibular testing—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 junction disorders, psych.

**Stroke: (see *stroke* chapter)** common sx in postcirculation, often risk factor, arrhythmia, other neuro finding help decide on intervention, vessel imaging, MRI. Dysmetria and/or gait ataxia in isolated cerebellar strokes, suspect in high-risk pt who can't walk. If ordering MRI, include coronal DWI + ADC.

| Cerebrovascular D/os | |
|---|---|
| Vertebrobasilar insufficiency/TIA | Episodic, concurrent diplopia, dysarthria, drop attacks, ataxia, transient tinnitus, visual changes<br>Consider subclavian steal syndrome. |
| PICA stroke | Lateral medullary (Wallenberg) syndrome |
| AICA stroke | Cerebellar ± brainstem stroke or direct infarction of inner ear (peripheral) |
| SCA stroke | Ipsilateral dysmetria<br>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 w/or preceding HA, pt in migraine demographic; treat HA. If basilar migraine suspected triptans contraindicated 2/2 risk stroke. *Migrainous vertigo*: Migrainous 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 difficult to differentiate from BPPV w/o imaging or specialized vestib testing.

**Multiple sclerosis:** Can mimic peripheral dz if lesion in root entry zone of vestibular nerve; middle cerebellar peduncle common site; look for INO, pendular nystagmus, dysmetria, scanning speech.

**Epilepsy:** Rare. Vertiginous epilepsy: Recurrent vestibular sx alone or w/other sz/sx.

| 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 | Second most common CPA tumor CN V, VII, VIII equally likely to be affected |

| | |
|---|---|
| meningioma | |
| 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/postinfectious/postvaccination | Generally age <6<br>Parainfectious/postvaccine pathology is demyelination.<br>Bact & viral causes, incl VZV, HSV, Lyme Can be assoc w/cerebellar swelling in severe cases<br>Steroids ± EVD or suboccipital decompression may be indicated.<br>Recovery is the norm. |
| Alcohol related | Especially vermian |
| Others | Vitamin deficiencies (thiamine, vit E) Toxins (AEDs, chemotherapeutics) MF-GBS<br>GAD- or gliadin-assoc cerebellar ataxia |

**Hereditary ataxias:** SCA1-SCA28: Autosomal dominant; 6 are CAG repeat (SCA1-3, 6, 7, 17); Friedreich 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<br>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<br>Progressive dizziness or gait instability ± positional vertigo, tinnitus, hearing |

| | |
|---|---|
| | loss, lower CN signs, downbeating nystagmus<br>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 trigger psych sx; phobic postural vertigo; subjective sx gen w/o falls assoc w/spec stimuli/positions/social situations; examine gait. Normal testing.

## 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 parainfectious; 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 antiemetics & vestibular suppressants (meclizine, bz); vestib rehab.

**Meniere disease:** Caused by endolymphatic hydrops. Recurrent attacks of vertigo lasting >20 min w/horiz rotatory nystagmus; hearing loss (may remain between attacks); sense of fullness and/or tinnitus; vertigo often severe w/days of disequilibrium/N/V; often prog. to b/l; *TX*: No definite Tx, treat acute attacks antihistamines, symptomatic, role of steroids uncertain (pulse methylprednisolone or prednisone 1 mg/kg × 10-14 days; 2 -wk taper). Long-term low-Na diet useful, diuretics may be helpful; avoid EtOH/tobacco, possibly caffeine/chocolate useful; ENT referral if unsuccessful/severe to consider interventions.

**Benign paroxysmal positional vertigo:** Most common cause of vertigo; canalithiasis: debris trapped in canal causes abnl cupula stim w/head mvmt; brief (<1 min) spells provoked by Δs in position; central findings absent; BPPV 85%-95% in post canal, 5%-15% lateral BPPV (ant, multiple, b/l rare); dx w/Dix-Hallpike maneuver. Recovery often spont after weeks-months 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<br>Rotate head 45 degrees<br>Lie pt down quickly keeping head at 45 degrees lowering head off back of table ˜20 degrees below horiz<br>Observe eyes for 45 s. |
| Pos results | Latency: 2-10 s<br>Direction: Rotational-upbeat nystagmus toward affected ear (sx more severe w/affected side down)<br>Duration: 30-60 s<br>Reversal: Direction reverses when sitting up.<br>Fatigability: Effect diminishes w/repeated tests. |



| Rx BPPV |
|---|

| | |
|---|---|
| **Epley maneuver**<br>• Only effective for posterior canal dz<br>• Multiple studies demonstrate effectiveness. | Pt sitting upright w/legs extended<br>Rotate head 45 degrees toward affected side.<br>Lie down quickly w/head at 45 degrees, lowering head off back of table ~20 degrees below horiz (affected side ↓) & hold 30 s.<br>Turn head 90 degrees toward nonaffected side & hold 30 s.<br>Turn head & body an additional 90 degrees toward nonaffected side, & hold 30 s (pt now lying on side w/face pointed nearly ↓) & hold 30 s<br>Bring pt to upright sitting position.<br>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<br>Semont maneuver |
| **Brandt-Daroff exercises**<br>• Less effective than Epley<br>• Often used in conjunction | While sitting up, pt turns head 45 degrees to L.<br>Quickly lie to R w/head held in position (looking up), & hold 30 s or until dizziness subsides.<br>Return to upright position w/head neutral position & hold 30 s.<br>Turn head 45 degrees to R & quickly lie to L w/head held in position (looking ↑) & hold 30 s or until dizziness subsides.<br>Return to ↑ position w/head neutral position & hold 30 s.<br>Repeat 5× for 1 set; repeat 3 sets/day. |
| **Medications** | Not recommended except in hyperacute phase, antiemetics, meclizine, BZs, scopolamine |
| **Surgery** | Posterior semicircular canal occl. & singular neurectomy are rarely considered<br>Reported effective only in unblinded, retrospective studies |

## APPROACH TO DIAGNOSIS OF HEARING LOSS

**History:** Tempo, trauma, occupational exposure, infxn (otitis externa/media, measles, mumps, CMV, syphilis, Lyme), dizziness, recent HEENT surg, meds (aminoglycosides, quinine, salicylates, cisplatin, loop diuretics, e.g., furosemide).

**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 | Any abnl pattern w/poor speech discrimination | Autoimmune hearing loss |
| Sudden uni/l hearing loss, tinnitus, vertigo, head trauma, straining | Nl TM; vertigo & nystagmus | Any uni/l abnl pattern | Perilymph fistula |
| Sudden, fluctuating, uni/l hearing loss, tinnitus, episodic vertigo | Nl TM | Uni/l lowfrequency 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.

| Stance | | |
|---|---|---|
| **Maneuver** | **Description** | **D/o** |
| Romberg | Stand w/feet together + 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 backward or falls backward. | PSP, PD |

| **Bedside Positional Maneuvers** | | |
|---|---|---|
| **Maneuver** | **Description** | **D/o** |
| Dix-Hallpike | See above under “BPPV” for details. | BPPV, central positional nystagmus, central positional vertigo |
| 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 | Superior canal dehiscence, perilymphatic fistula |

# Multiple Sclerosis and Other CNS Inflammatory Demyelinating Diseases

Marcelo Matiello

Taha Gholipour

Rene A. Colorado

Riley M. Bove

Group of diseases of the CNS (see table below) in which destruction of myelin is a prominent feature along w/infiltration of inflammatory cells, particularly in a perivascular distribution. Lesions are primarily in white matter but variable degrees of neuronal and axonal degeneration may be seen, and in some diseases (e.g., NMO), tissue necrosis including vessels and axons is also possible.



| CNS Inflammatory diseases | | |
|---|---|---|
| | **Acute** | **Relapsing/Progressive** |
| **Idiopathic/Autoimmune** | | |
| Primary and idiopathic | MS (CIS, Marburg, tumefactive), isolated ON, ADEM, TM, cerebellitis | MS (RRMS, SPMS, PPMS), relapsing ON, NMO |
| Paraneoplastic | Paraneoplastic syndromes | |
| Connective tissue dz | SLE, Behcet disease, RA, Sjögren syndrome, antiphospholipid antibody syndrome (APLAS) | |
| Granulomatous | Wegener granulomatosis, sarcoidosis, lymphoid granulomatosis | |
| Vasculitis | CNS and systemic vasculitides | |
| **Other Etiologies** | | |
| Infectious | PML | HIV (→ CIDP), Lyme, neurosyphilis, HTLV1, SSPE, tropical spastic paraparesis/HTLV-1-ass. myelopathy |
| Congenital | | Adrenoleukodystrophy, Alexander dz, Canavan dz, Krabbe dz, metachromatic leukodystrophy<br>Adrenoleukodystrophy<br>Adrenomyeloneuropathy |

| | | |
|---|---|---|
| Toxic metabolic, radiation | Central pontine myelinolysis (CPM), toxic leukoencephalopathy CO poisoning | Subacute combined degeneration (B12 & IF deficiency), NO poisoning, Marchiafava-Bignami dz<br>Radiation-induced necrosis |
| Vascular, hypoxic | PRES, delayed hypoxic cerebral demyelination | Progressive subcortical ischemic demyelination |

## MULTIPLE SCLEROSIS (MS)

**Definition:** Most common autoimmune inflammatory demyelinating CNS disease, characterized by dissemination in time (multiple attacks) and space (different sites in the CNS). While there are no clinical features that are unique to MS, some are highly typical of the disease including sensory symptoms in limbs or face, visual loss, acute or subacute motor weakness, diplopia, gait and balance problems, Lhermitte sign, acute transverse myelitis, and pain. Typically presents in young adults w/two or more clinically distinct episodes of CNS dysfn w/at least partial resolution.

**Pathophysiology:** Complex genetic-environment interactions are suspected to increase susceptibility to disease. The roles of humoral and cellular immunity are not fully understood; however, it is known that activated T cells interact w/endothelial molecules and migration across the BBB is increased by proteinases. CD4+ T cells are reactivated after unknown antigen presented by the MHC class II; cytokines and chemokines lead to chemoattraction of B cells (intra-CNS production of Abs—oligoclonal bands seen on CSF analysis), monocytes, and CD8+; inflammatory cascade results in demyelination and axonal injury mediated by cytotoxic CD8+ and macrophages.

**Epidemiology:** Estimated prev: 400,000 US; 2.3 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, EBV antigen, HLA DRB1, low vitamin D/poor sunlight exposure, high BMI in childhood/adolescence, melanocortin receptor. More severe in African Americans.

**Clinical Scenarios:**

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 contrastenhancing 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):** Typical MRI but w/o clinical sx; repeat imaging at 3 mo, 6 mo; if new lesions, may initiate Rx. In 5-yr FU clinical events identified in 34% (~10 of these fulfilled criteria for PPMS). Age <37 yr, male sex, and spinal cord involvement are predictors of symptom onset (*PLoS One* 2014;9(3):e90509).
3. **RRMS:** Relapsing remitting MS—85%-90% of initial course. Short-term relapse risk correlates w/enhancing lesions on baseline MRI & w/relapses over prior 2 yr.
4. **PPMS:** Primary progressive MS (older pts, African Americans).
5. **SPMS:** Secondary progressive MS (RRMS initially than becomes progressive after decades).
6. **"Benign MS":** Low dz burden over >20 yr course; first few years are predictive. Female sex, early onset, and

presentation w/optic neuritis and sensory symptoms are a/w favorable courses. Label “benign MS” is often temporary; disease may become disabling.

New classifications have been proposed based more simply on whether MS is active (new clinical attacks, new lesions, or enhancing lesions) and/or progressive (worsening on clinical evaluation) (*Neurology* 2014;83:278-286).

**MS attack:** Symptomatic inflammatory demyelinating event lasting >24 h w/objective clinical findings, >30 days from prior attack.



## WORKUP FOR MS

DDx broad, MUST r/o MS mimics. Institute w/u early; goal: start appropriate Rx to prevent further attacks and possibly alter the disease course.

**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 tests (depending on presenting syndrome):** NMO Ab (more likely to be positive in LETM (longitudinal extensive transverse myelitis), severe or bilateral ON), Lyme (if in endemic region), RPR, $B_{12}$, HIV, ESR, ANA, ACE, HTLV-1 (in progressive myelopathies) to r/o other etiologies.

**CSF:** WBC <50; **IgG index** = (CSF IgG/CSF albumin)/(serum IgG/serum albumin); nl range 0.34-0.66; elevated in MS (also elevated in *ddx:* SSPE, viral encephalitis, CADASIL, HIV, SLE, NMO, ADEM, ALD) **Oligoclonal bands** (OCB): shows bands exclusive to CSF, (may also be present in: SLE, APLAS, Sjögren, sarcoidosis). For both tests, a serum sample should be send at the same time as CSF.

**MRI:** T1 axial w/gadolinium, T2/FLAIR axial & sagittal. *Brain:* Multifocal WM lesions, usually >3 mm. Corpus callosum involvement is quite specific. **Acute plaques** = fade after 4-6 wk. T2 hyperintense lesions (**T2H**): Stable, shrink, or grow. **Dawson fingers:** Periventricular ovoid lesions w/long axis perpendicular to ventricles. T1 hypointensities **“Black holes”:** Old plaques; may persist × years; represent axonal loss. ***Spinal cord*:** Lesions in up to 80% pts, usually cervical, <1 cord segment, peripheral; may be asx.

## 2010 MCDONALD DIAGNOSTIC CRITERIA FOR MS (*ANN NEUROL* 2011;69(S):292-302)

In the past, as a rule, a dx of MS was not determined unless there was clinical hx of two or more relapses and evidence on examination of more than one discrete lesions of the CNS (dissemination in time and space). Currently, MRI aids capacity to identify clinically silent lesions, of different ages, as key part of dx criteria. Current diagnostic criteria are shown in the table.



| Clinical Scenarios | Additional Data Needed |
|---|---|
| 2 or more attacks (relapses)<br>2 or more objective clinical lesions | None; clinical evidence will suffice (additional evidence desirable but must be consistent w/MS) |
| | |

| | |
|---|---|
| 2 or more attacks<br>1 objective clinical lesion | Dissemination in time, demonstrated by simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing w/reference to a baseline scan; or await a second clinical attack |
| 1 attack<br>2 or more objective clinical lesions | Dissemination in space and time, demonstrated by:<br>DIS: 1 T2 lesion in at least 2 of 4 MS typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or await a second clinical attack implicating a different CNS site; and<br>DIT: Simultaneous presence of asymptomatic gadoliniumenhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing w/reference to a baseline scan; or await a second clinical attack |
| 1 attack<br>1 objective clinical lesion (clinically isolated syndrome) | Dissemination in space and time, demonstrated by:<br>For DIS: 1 T2 lesion in at least 2 of 4 MS typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord);<br>or await a second clinical attack implicating a different CNS site; and<br>For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing w/reference to a baseline scan; or await a second clinical attack |
| Insidious neurological progression suggestive of MS (primary progressive MS) | 1 yr of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria:<br>1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS characteristic (periventricular, juxtacortical, or infratentorial) regions<br>2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord<br>3. Positive CSF (oligoclonal bands and/or elevated IgG index) |

**Red flags suggestive of possible alternative dx** (*Neurology* 2007;13:13). **(1)** Hearing loss, especially b/l, **(2)** onset <10 yo 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:** Extensive 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, toxic; 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: idiopathic; 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 syndrome, vit E deficiency).

**Spinal cord sx:** Transverse myelitis (TM) (***ddx***: ***Acute*:** NMO (LETM), 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 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 (e.g., secondary migraine; ddx broad); **(5)** back pain; **(6)** dysesthetic limb(s); **(7)** brief painful focal szs.

**Cognitive changes:** Initial deficits include attention and processing speed. 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 ACUTE MS ATTACKS

**Ddx attack: Pseudorelapse (recrudescence of previous syndrome 2/2 infection or fatigue).** Bladder infxn > tooth infxn > URI; also, r/o other common neurologic causes, e.g., disk herniation; **routine w/u (minimal):** U/A, ESR, CBC, CXR (looking for infectious trigger). **Uhthoff phenomenon** (worsening of neurologic symptoms when body gets overheated—hot weather, exercise, fever, saunas, etc.). Sx and symptoms disappear or improve w/cold shower and air-conditioning.

**For most attacks, IV methylprednisolone (Solu-Medrol) 1 g/day ×** 3 days typically; 5 days if ongoing evolution of symptoms at day 3 or severe attack **(or 1,250 mg PO prednisone)**. 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. ± **10-14 days PO prednisone taper (rarely done).**

**Plasmapheresis:** 5-7 courses of 1-1.5 plasma volume exchanges. Used in fulminant cases that are refractory to steroids. *Neurology* 46(6):878-886.

### Disease-modifying therapies (DMTs) in CIS and RRMS

Utility: Decrease severity & number of relapses, steroid courses, & hospital stays, may 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, increase dose or switch DMT. (4) Check MRI 6 M & 12 M after starting DMT, may need to change dose



or Rx. (5) Limited data on safety w/pregnancy & breast-feeding; usually d/c DMTs & trial of steroids or IVIg for relapses.

## Injectables

**Beta Interferons (IFNs):**

*MOA:* Enhance suppressor T cells, decrease release of metalloproteinases & proinflamm cytokines, prevent helper T cell adhesion to BBB, down-regulate antigen presentation.

*SE/AE/monitoring:* Overall good safety profile. Injection site inflamm, HA; **Flulike sx**, rhinitis, fatigue. Rare: Depression/suicide, szs, thyroid abnls, decrease plts, lymphopenia, elevated LFTs, symptomatic hepatitis. Check CBC & LFTs @ baseline, 1 mo, 3 mo, 6 mo; then q6mo. TFTs q6mo. Think developing neutralizing antibody (Nab) if more relapses/new T2 lesions. Consider switch to alternate class of DMT if pos. If Nab neg, no further testing.

*Dosage and key clinical trials:* Beta IFN-1a 30 µg IM qwk (**Avonex**). Trials: CIS CHAMPS and 22 or 44 µg SC

3×/wk (**Rebif**) titrate over 4 wk. Pivotal trial for RRMS: PRISMS (*Lancet* 1998;352(9139):1498); for CIS: ETOMS (*Lancet* 2001:357(9268):1576-1582).

Beta IFN-1b 8 MIU (0.25 mg) SC qod (**Betaseron** and newer **Extavia**) titrate over 6 wk. Trials for RRMS IFNB MS Study (*Neurology* 1993;43(4):655-666); for CIS BENEFIT (*Neurology* 67(7):1242-1249).

Pegylated interferon beta-1a (**Plegridy**) formed by attaching a polyethylene glycol (PEG) group to the N-terminus of IFN beta. Has prolonged half-life and consequently a reduced dosing. Approved for RRMS, ADVANCE trial (*Lancet Neurol* 2014;13(7):657-665).

### Glatiramer acetate (GA, Copaxone)

*MOA:* Synthetic polypeptides; may bind to MHCs as decoy for myelin proteins causing shifting immune response from TH1 to TH2.

*Dosage and key trials*: 20 mg SC daily and new 40 mg SC dosing 3×/wk. Copolymer 1 Multiple Sclerosis Study Group trial (*Neurology* 1995;45(7):1268)

*SE:* Very good safety profile. Flushing, **local injection site rxn**. Localized lipoatrophy.

## Oral

### Dimethyl fumarate (DMF, Tecfidera)

*MOA:* Unclear neuroprotective and immunomodulatory properties.

*Dosing:* Starting dose 120 mg PO bid; increased to 240 mg PO bid after 7 days.

*Key trials:* DEFINE: DMF vs. placebo (*NEJM* 2012;367(12):1098-1107), and COMFIRM DMF vs. GA vs. placebo.

*SE:* Flushing and gastrointestinal symptoms, including diarrhea, nausea, and abdominal upset. May decrease lymphocyte counts, CBC should be in first 6 mo and then yearly. Should be discontinued if lymphocytopenia develops. Isolated cases of PML have been reported.

### Fingolimod (Gilenya)

*MOA:* Modulates the sphingosine-1-phosphate receptor and impairs lymphocyte migration, resulting in sequestration in the lymph nodes.

*Key trials:* FREEDOMS (*NEJM* 2010;362:387-401)—fingolimod vs. placebo; TRANSFORMS (N Engl J Med 2010;362:402-415)—fingolimod vs. IFN beta 30 mcg IM weekly—two deaths in the high-dose fingolimod group (disseminated VZV infection and HSV encephalitis).

*SE/AE:* Headache, diarrhea, **elevated LFTs**, fatigue, cough, **HTN**. Less common but potentially serious are **bradyarrhythmia** and AV block (usually first dose effect), macular edema (reversible), skin cancers, VZV infections, and paradoxical worsening of MS disease activity w/severe MS relapses. Isolated cases of PML have been reported. Contraindicated for pts w/active ischemic or conductive heart dz (unless treated w/a pacemaker) or Rx w/antiarrhythmic drugs. Considered second-line Rx.

*Dosage:* 0.5 mg PO qd. **Before start:** check CBC, LFT, EKG, perform ophthalmologic exam, skin exam for precancerous skin lesions, VZV serology and vaccination if Ab titers neg/low at least 1 mo before fingolimod. 1st dose should be given w/q1h BP and HR for 6 h where symptomatic bradycardia can be managed; w/EKG obtained at the end of the 6-h observation. Ophthalmologic exam should be repeated in 3-4 mo after starting fingolimod and routinely in pts w/diabetes mellitus or a history of uveitis. Consider shingles vaccine in anyone approaching the age of 60, <1 mo prior to start.

**Teriflunomide (Aubagio)**

*MOA:* Inhibits de novo pyrimidine synthesis needed for the proliferation of activated lymphocytes.



*Dosing and key trials:* 7 or 14 mg once a day; TEMSO trial compared to placebo (*NEJM* 2011;365:1293-1303); TEMSO II.

*SE/AE/monitoring:* Diarrhea, nausea, hair thinning, and elevated ALT. Teriflunomide is pregnancy category X. Pts w/known liver disease may not be treated w/teriflunomide. Obtain baseline LFTs; screen for latent TB, pregnancy test. Monitor ALT levels monthly for 6 mo; discontinue if drug-induced liver injury is suspected and for women who are pregnant, also men and women who are planning to conceive. Pregnancy should be avoided until the serum concentration of teriflunomide is <0.02 mg/L. Manufacturer recommends an "accelerated washout protocol" if need to decrease levels fast.

## INFUSION

**Natalizumab (Tysabri)**

*MOA:* Monoclonal Ab against α-4-integrin on lymphocytes, preventing migration to CNS. *Dosing:* 300-mg infusion IV q4wk. Contraindicated in pregnancy.

*Key trials:* AFFIRM trial (*NEJM* 2006;354:899-910) as monotherapy and in SENTINEL (*NEJM* 2006;354:911-923) in combination w/IFN SC showed strong anti-inflammatory effect in preventing new relapses and new MRI lesions.

*SE/AE:* Increased risk of infections including herpes, infusion reactions, HA, fatigue, pruritus, arthralgias, cholelithiasis. Development of neutralizing antibodies to natalizumab possible. Antibodies to natalizumab: check if no clinical response to Rx or if ongoing active lesions; if Abs present, discontinue natalizumab.

**Rare:** Progressive multifocal leukoencephalopathy (PML) in pts exposed to JC virus. Serum serology for JCV-Ab commercially available and encouraged to test prior to discussing Rx w pt. risk of seroconversion, check every 6 M while on natalizumab. The length of Rx, JCV titer, and prior immunosuppression increase risk. Testing CSF for JCV DNA also recommended after 2 yr or if symptoms/imaging concerning for PML. Other opportun infections observed. Rare cases of melanoma have been reported but association not yet proven.

MRI brain w contrast q6mo for PML surveillance recommended. Dermatologic and ophthalmologic exam at baseline, w/follow-up during Rx as needed; check baseline LFT then q6mo. Stopping natalizumab can be a/w rebound severe increased inflammatory activity and in some cases immune reconstitution inflammatory syndrome (IRIS); some centers use glucocorticoids as a bridge to other Rxs if discontinuation needed.

**Alemtuzumab (Lemtrada)**

*MOA:* Humanized monoclonal Ab leads to depletion of CD52-expressing T cells, NK cells, and monocytes.

*Key trials:* CARE-MS compared alemtuzumab to IFN (44 μg SC 3x per wk); CARE-MS II alemtuzumab vs. IFN or GA.

*Dosage:* IV 12 mg daily for 5 consecutive days (total 60 mg) at the start of Rx; then 12 mg daily for 3 days (total 36 mg) 12 mo later.

*SE/AE/monitoring:* Infusion reactions (90% of pts) HA, rash, nausea, fever. Herpes infections (16%-18%)—need prophylactic acyclovir (during alemtuzumab infusion and for 28 days after w/acyclovir 200 mg PO bid) and prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) (e.g., trimethoprim-sulfamethoxazole 80-160 mg daily) during Rx and for several weeks after Rx. Thyroid autoimmunity (16%-30%) seen at longer follow-up. Due to

frequent SE, reserved for pts w/RRMS who have an inadequate response to two or more first-line Rx. In the United States, requires special registration through a restricted distribution program. Surveillance for bone marrow suppression, infections, and autoimmune disorders is necessary.

## OTHER TREATMENTS

Vitamin D: Blood levels of "25-hydroxyvitamin D" should be obtained, w/current goal levels in MS, in the middle range of normal. Otherwise, usual dose is 1,000 IU for levels between 20 and 35 ng/mL and 2,000 IU daily for levels below 20 ng/mL. Vitamin D3 supplements are preferable (more active biologically, raises blood levels more effectively, and is more stable on the shelf than D2).

**Glucocorticoids**—IV glucocorticoid bolus, typically 1,000 mg of methylprednisolone, is used at many institutions for the Rx of primary or secondary progressive MS alone (e.g., monthly) or in combination w/other immunomodulatory or immunosuppressive medications. RCT data are limited and conflicting. Some providers use during periods of staying off Rx due to pregnancy or to prevent relapses in periods of increased risk of relapses.

**Rituximab (Rituxan)**—Rituximab (and similar newer agent ocrelizumab) is an anti-CD20 monoclonal Ab on B lymphocytes that causes B-cell depletion. Initial trials



encouraging in terms of effectiveness and ongoing. Suggested dosage 1,000 mg IV q2wk × 2 doses; check CD19, CD20 count. Redose at 12 M or earlier, at 6-9 mo if either marker rises above 0. Infusion reactions, thrombocytopenia, leucopenia, and increased infections common. Contraindicated in pregnancy.

**Mitoxantrone (Novantrone)**—Approved for use in both RRMS and SPMS. AAN recommended that, because of cardiac toxicity and the limited evidence of benefit, mitoxantrone should be reserved for pts w/rapidly advancing disease who have failed other therapies. Risk of developing leukemia increased. Should be considered as last option.

**Azathioprine, mycophenolate mofetil, and methotrexate**—oral immunosuppressing agents used off-label and small clinical trials suggested some benefit in RRMS and SPMS. Availability of newer agents described above place these lower in list. Sometimes used when comorbidities w/other immune/rheum disorders, or as add-on to IFN or GA.

**Cyclophosphamide**—Limited observational evidence supports the use of pulse (e.g., monthly) intravenous (IV) cyclophosphamide for RRMS alongside steroid. There is a greater experience w/pulse cyclophosphamide for progressive forms of MS, but data are conflicting regarding benefit.

**Use of second-line treatments:** In setting of rapid progression ("malignant MS") or refractory disease—disease activity (relapses, new MRI lesions or progression) that is refractory to initial disease-modifying therapy w/IFN or GA and to oral agent, more aggressive Rx plans should be considered, such as adding methylprednisolone (see Glucocorticoids above), switching to natalizumab or alemtuzumab, or use of other immunosuppressant or cyclophosphamide.

## MONITORING MS COURSE

**MRI:** Ongoing debate as whether to change DMT at any new lesion. Despite stable lesions, may see new fxnal disability, esp w/advanced MS.

**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 yr; 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.

## MANAGEMENT OF CLINICAL MANIFESTATIONS OF MS

### General guidelines

- Careful history & exam
- Tackle one problem & one intervention at a time to avoid polypharmacy
- Emphasize pt control over individual sx & overall mind-set
- Encourage social support groups; refer to MS Society website (http://www.nationalmssociety. org).

**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:* Worse 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.

**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).



| Spasticity Rx | | |
|---|---|---|
| **Agent** | **Dosing** | **Side effects; other** |
| Baclofen ($GABA_B$ 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, propranolol, 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 longterm mgt (limits urethral damage & leakage); Meds: Anticholinergics: LA (Detrol) 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 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*: NeuroPsych 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.

### 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 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 United States; 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. **MRI:** Same as adults.

**Course:** 98% RRMS; relapse rate higher but better attack recovery; disability accumulation may be slower, but significant dz burden accumulates earlier. More cognitive than physical disability in childhood compared to adult MS.

**Ddx:** Infectious (viral, Lyme, West Nile virus), genetic/metabolic d/os, ADEM, NMO, small-vessel CNS vasculitis, endocrinopathies, vasculopathies, inflammatory d/os, genetic/metabolic disorders, i.e., mitochondrial d/os and leukodystrophies, nutritional deficiencies, neoplasms (*Neurology* 2007;68:S13).

**Management:** Attend to cognitive, developmental, psychosocial consequences, & familial coping. **Rx: (1)** Attacks: Methylprednisolone 30 mg/kg/d (maximum 1 g) for 3-5 days, then ± prednisone 1 mg/kg/d & taper over approximately 4 wk. **(2)** DMTs—no RCTs; consider interferon or copaxone. Refer to center w/pediatric MS expertise.

## 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 the United States. F > M (2:1); ages 20-50; Like MS: higher latitudes, Western Europe & Northern United States, far from equator. HLA-DR15; HLA-DQA-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 retroorbital; 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

**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, Farnsworth-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 (anterior ischemic optic neuropathy). 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 (retinal nerve fiber layer). Other findings: Perivenous sheathing or periphlebitis retinae (12%); uveitis, pars planitis.

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**MRI brain & orbits w/& w/o 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.

**Fluorescein 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, 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 & postinfectious. **(2)** Adults: >50 yo **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:** *Neuroretinitis* (*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,

paraneoplastic. **(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 yr, 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 × 11 days 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 × 14 days 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. ***Acute*:** IV Solu-Medrol 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-C5 → 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** (*Sem Neurol* 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 postcord 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, anti-la; $B_{12}$, 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 immunosuppressive (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 Solu-Medrol 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 Autoimmune TM | | |
|---|---|---|
| **Clinical** | **MRI spine/brain w/gado** | **CSF** |
| **Multiple sclerosis:** Sx asymmetric. Common syndromes: Sensory useless hand syndrome (↓ JPS in UE); Brown-Séquard | Spine: Lesions short (<2 vertebral segments), usually peripheral. Brain: WM lesions, enhance if acute | OCBs+ in 90% ↑ IgG index 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 3 mo. 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 | Spine: Lesions variable. Brain: No | Inflammatory. ± ↑ |

| cause identified | lesions | IgG index & OCBs |
|---|---|---|

From *Sem Neurol* 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, $\alpha_2$-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; immunocompromised; 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 SPECTRUM DISORDERS

**Epidemiology:** Estimated prevalence of 5 per 100,000; similar worldwide. F:M 2:1; among relapsing pts, 80% female; compared to MS, relatively more common in non-Caucasians (Asian, African, and Latinos); in tropical countries, may account to up to 20% of pts seen in demyelinating disease clinics.

**Clinical manifestations: (1) Course:** Relapsing (85%), or fulminant monophasic. **(2) TM:** LETM: (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, but do not look like MS; encephalopathy; ataxia, szs, intractable vomiting, hiccups, endocrinopathies, PRES. **(5) Associated d/os:** ***Adults*:** 1/3 w/associated collagen vascular dz; SLE, Sjögren's, thyroid & other autoimmune dzs. Small series of association w/infection (e.g., TB). Paraneoplastic NMO is very rare. ***Children*:** 42% w/concurrent autoimmune d/os (SLE, Sjögren's, juvenile RA, Graves', autoimmune hepatitis).

**Diagnostic testing: Serum:** + serum NMO IgG (anti-aquaporin-4 ab) (73% Se, 91% Sp for NMO (*Lancet* 2004;364:2106); higher sens w/cell-based assay; if serum (-) but strong suspicion, check CSF NMO IgG. Some seropositive pts have systemic autoimmune dz (SLE or Sjögren's).

**CSF:** Usu pleocytosis (eos, PMNs). No OCBs in >80%. IgG index nl or transiently ↑. **MRI** ± gado: *Spine*: LETM, spans >3 vert segments; *brain*: often periventricular—brainstem, supra-& infratentorial white matter, cerebellum, thalamus, hypothalamus, periaqueductal.

### *NMO diagnostic criteria*

Optic neuritis

Acute myelitis

At least two of three supportive criteria:

1. Contiguous spinal cord MRI lesions extending over ≥3 segments
2. Brain MRI not meeting diagnostic criteria for MS
3. NMO-IgG seropositive status



### *NMO spectrum disorder*

Pts who are NMO-IgG positive and have one of the conditions listed below likely have similar clinical course and response to therapy as do pts meeting criteria for NMO.

1. Limited (or inaugural) forms of NMO:
   a. Idiopathic single or recurrent events of LETM
   b. Isolated, recurrent, or simultaneous bilateral ON
2. ON or LETM a/w systemic autoimmune disease
3. ON or myelitis a/w brain lesions typical of NMO (hypothalamic, corpus callosum, brainstem)

**Treatment:** ***Attacks*:** IV methylprednisolone × 5-7 days. If sx progress despite steroids, plasmapheresis (seven exchanges over 2 wk).

***Recurrent sx*:** No RCTs & no FDA-approved Rxs. Aim for humoral suppression w/immunosuppressive Rx to prevent disability. Immunomodulatory therapies used in MS not effective and may worsen NMO course.

*Commonly used*:

Azathioprine (2.5 mg/kg/d) w/oral corticosteroids (prednisone beginning at 60 mg daily or every other day for 6-9 mo, subsequently decreasing to lowest possible maintenance dose or discontinuation).

Mycophenolate mofetil (2 g/day) w/oral corticosteroids is another effective option that may be used as initial or alternative Rx in pts w/difficulties w/azathioprine.

For refractory cases, rituximab (1,000 mg intravenously twice separated by 2 wk, repeated every 6-9 mo) is the most extensively studied alternative Rx.

**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.

**Monitoring Rx:** Insufficient evidence that NMO-IgG antibody titers correlate with disease activity, and therefore, monitoring titer is not currently advisable in reaching Rx decisions, such as intensifying or terminating immunosuppressive Rx. If a pt develops a severe relapse while on full dose of the medication, a second-line drug should be started.

## ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

**Definition:** Acute monophasic multifocal demyelination in brain &/or spinal cord w/white and gray matter involvement. Neurologic sx multifocal & often include encephalopathy. Usually postinfectious/postvaccination.

**Epidemiology:** Usually in children & adolescents (average age 5-8 yr). Pediatric studies estimated 0.4/100,000/yr and variable incidence after different vaccinations.

**Pathophysiology:** Immunologic dysregulation in genetically susceptible individuals triggered by environmental stimulus, probably through molecular mimicry.

**Etiology: Immune-mediated, different from encephalitis. *Postinfectious***: ~75%; *Viral*: Enterovirus, EBV, CMV, HIV, HSV, VZV, HAV, influenza, coronavirus, coxsackie virus, mumps, measles, dengue; less often *Bacterial*: Lyme, *Chlamydia*, *Mycoplasma*, beta-hemolytic Strep, *Rickettsia*, *Leptospira*, rarely 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 vaccines*: 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 4-7 days). **(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: somnolencecoma). **(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. **(2)** Rarely: Single large lesion (may see hemorrhagic demyelinating lesions in hyperacute ADEM variants *see below*). **(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 partially to completely, as opposed to MS lesions).

**Diagnostic testing: LP:** R/o viral & bacterial meningitis or encephalitis. Send CSF for GS & bacterial Cx, EBV, HSV, CMV, VZV, mycoplasma, rubella, other relevant infx w/u, oligoclonal bands (OCBs, **non-specific**). CSF can be nl. May see pleocytosis (if WBC >50, NOT MS) &/or increased protein; ± OCBs. **Serum:** CBC (leukocytosis in 2/3; often lymphocytic); ±↑ ESR & CRP. **Micro:** Studies negative by definition. Get blood, CSF for bacterial & viral Cx; nasopharynx & stool viral cultures. Check HSV, VZV, CMV, EBV, Mycoplasma, rubella. **EEG:** Background slow wave activity c/w encephalopathy. **MRI w/T2/FLAIR lesions, gad enhancement.** *See above for characteristics*. Repeat imaging in 6 mo to follow resolution and to detect multiphasic ADEM or MS (esp in adults).

**Differential diagnosis: (1) Infectious:** Viral/bacterial meningitis or encephalitis. **(2) Inflammatory demyelinating d/os:** MS (encephalopathy required for ADEM 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 may require brain bx). **(4) Malignancy**—CNS lymphoma or glioma; CSF cytology w/atypical cells; dx may require brain bx. **(5) Mitochondrial dz**—w/intercurrent infxn. MRI w/typical symmetric T2 signal in basal ganglia or parieto-occipital regions; ↑ serum & CSF lactate.

**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 1st week; 70% survivors w/residual deficits. May be improved w/aggressive corticosteroids, IVIg, cyclophosphamide, plasmapheresis.

**Leukodystrophies:** Rare WM involvement usu symmetric, unrelated to infx, variable progression, some have genetic tests.

**Treatment:** No controlled trials to date. **(1)** *Antibiotics*: Consider empiric acyclovir & antibiotics until infectious etiology excluded. **(2)** *Steroids:* Main Rx IV methylprednisolone pulse (i.e., 1 g qd for 3-5 days), then 3-6 wk oral prednisone taper. **(3)** *Steroid alternatives:* If steroids fail, fulminant course such as hemorrhagic cases, or steroid contraindicated: Plasmapheresis, IVIg (70% show complete recovery); mitoxantrone and cyclophosphamide have also been tried. **(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)—>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. Recrudescence of symptoms happens w/residual lesions.

**Prognosis:** *Overall good*: 50%-75% recover completely, 70%-90% w/min residual disability. 5% mortality. MRI

can show complete recovery (37%-75% of cases complete, partial in rest). 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).

## 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. burnetii*), Lyme, *Mycoplasma*, *Legionella*, *Salmonella typhi*. **(3) Parasitic:** Rickettsia, Malaria (*P. falciparum*). **(4) Postvaccination:** 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). **(4) Neoplastic:** Cerebellar/posterior fossa tumor (primary or secondary); neuroblastoma; paraneoplastic cerebellar degeneration; lymphoma. **(5) Drugs:** Thallium, lead, barbiturates, dilantin, piperazine, alcohol, solvents, antineoplastic drugs. **(6) 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 dz: Ceftriaxone 2 g IV bid × 2 wk; Q fever (*C. burnetii*): 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.

## SUSAC SYNDROME

**Definition:** Rare microangiopathy that affects mainly the brain and retina. Clinically manifests as a triad of encephalopathy, branch retinal artery occlusions (RAO), and sensorineural hearing loss. Most commonly presents between 2nd and 4th decades; 3:1 women-to-men ratio w/o racial or ethnic predilection. Microinfarction and lymphocytic infiltration of small vessels suggest an immune-mediated process and anti-endothelial cell Abs have been found in cases of SS.

**Clinical features: Monophasic form** is characterized by headaches, neuropsychiatric symptoms, long tract signs, seizures w/prominent encephalopathy. Pts w/a **recurrent course** have bilateral RAO and hearing loss at symptom onset w/very mild or no encephalopathy. The hearing loss is acute at onset and a/w tinnitus, and pts will have recurrent episodes of RAO w/progressive tunnel vision.

**Diagnostic testing: Retinal fluorescein angiography** shows occlusions of the middle segments of arterioles. Brain **MRI** shows multiple small white matter lesions involving periventricular and subcortical regions and linear defects involving the central fibers of the corpus callosum. Callosal involvement ranges from 79% to 100%. **CSF** is generally nonspecific, w/variable elevation in protein ranging from normal to 200 mg/dL, mild pleocytosis, and rarely oligoclonal bands.

**Management:** Based on expert opinion/anecdotal reports: IV and oral steroids, IV immunoglobulin (IVIg), azathioprine, cyclophosphamide, mycophenolate mofetil, and plasmapheresis. Treatment response is variable and should be tailored based on the severity of a pt's initial presentation. Also, pts w/SS should be started on antiplatelet therapy/aspirin as the first-line agent.



## MARCHIAFAVA-BIGNAMI DISEASE

**Definition:** Rare progressive dz characterized by demyelination & necrosis of the corpus callosum w/subsequent atrophy → stupor, coma, szs, & apraxia. Typically affects men >45 yo w/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; poor prognosis. ***Type B*:** *Partial or focal* corpus callosum; mental status nl or mildly impaired; better prognosis. **(2) 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. **(3) Associations:** Look for e/o chronic EtOH: Wernicke-Korsakoff (disconjugate eye movements, confusion), DTs, alcoholic neuropathy, truncal ataxia.

**Diagnostic testing: MRI:** T2 hyperintense and T1 hypointense signal changes mainly in central layers of CC and sparing dorsal and central layers (sandwich sign).

**Management:** No proven Rx. Manage szs & coma. Possibly helpful: Thiamine, folate, vitamin $B_{12}$ supplementation. Trial of IV corticosteroids (methylprednisolone 250 mg q6h) or amantadine (100 mg PO bid) theoretically warranted (e.g., some case reports of overlap w/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.

**T2 C-spine MRI w/typical MS lesion at C3/C4.**

**T2 and T1 post-gad cervical MRI of NMO pt showing LETM.**

**Brain MRI sagittal and axial w/multiple periventricular WM lesions in an MS pt.**

**Axial and coronal T1 post-gadolinium contrast in a pt w/R ON.**

# Spine and Spinal Cord Diseases

Pooja Raibagkar

Steve S. Han

## APPROACH TO BACK PAIN

Common problem w/broad differential. Majority of pts have musculoskeletal or mechanical causes that require only conservative management & most recover naturally. Goal: Identify causes that require further diagnostic workup & intervention.

| Warning Signs in History |
| --- |
| • Age >70 yr, history of cancer, unexplained weight loss, trauma |
| • Recent fever, immunosuppression, IV drug use, skin infxn, UTI |
| • Osteoporosis, prolonged corticosteroid use |
| • Pain >1 mo, nighttime pain, pain not relieved by lying down |
| • Pain increased w/coughing, sneezing, or Valsalva maneuver |
| • Unresponsiveness to previous therapies |
| • Straight leg/reverse straight leg raise signs |
| • Pain w/wkns/sensory loss & bowel/bladder dysfxn |



### Exam

*General exam*: Fever, rash, track marks, cachexia, new cardiac murmur (endocarditis), abdominal bruit (AAA), costovertebral tenderness (pyelonephritis, kidney stone), Grey-Turner or Cullen sign (retroperitoneal hemorrhage; pancreatitis), palpable abdominal mass, peripheral pulses (vascular 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 muscle 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: reproduces radicular pain, buttock through 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, sensory loss, saddle or perianal anesthesia, hyper- or hyporeflexia.

**Labs:** CBC, ESR, CRP (helpful when infxn or malignancy 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 musculoskeletal 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; preoperative planning.

*MRI*: Sensitive & specific for multiple causes of back pain: disc herniation, spinal stenosis, osteomyelitis, discitis, epidural abscess, metastases, arachnoiditis, & myelopathies. MRI w/gado necessary if suspected infxn/inflam/neoplastic 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; flexionextension views in surgical fusion procedures or in spondylolisthesis; hip & pelvis when osteoarthritis is presenting as LBP.

**EMG/NCS:** Help r/o radiculopathy mimics such as plexopathy & entrapment neuropathy. Help localize radiculopathy in potential surg candidates w/multilevel dz or poor correlation between sx, exam, & imaging. Useful in cases w/give-way wkns or when pain limits exam. Usually unnecessary in pts where exam correlates clearly w/lesion on MRI. Pain or sensory sx w/o wkns often has nl EMG/NCS.

**Differential Dx of Back Pain**

**Congenital**
- Spondylolysis & spondylolisthesis
- Spina bifida occulta
- Tethered cord

**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 syndrome)

**Neoplastic**
- Metastatic, hematologic, primary bone, neurofibromas

**Infectious/inflammatory**
- Transverse myelitis
- 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, ovarian ca or cyst
- Renal dz—pyelonephritis, nephrolithiasis, perinephric abscess
- GI—peptic ulcer dz, pancreatitis, cholecystitis
- Retroperitoneal mass or bleed—anticoagulation or various systemic processes

**Conservative Rx:** Indicated for most nonspecific causes of LBP. Key is early intervention. *General measures*: Early ambulation, resumption of nl physical activity w/o heavy lifting; discourage bed rest >2 days; avoid

activities that promote back pain. *Acute nonpharm Rx*: Heat wrap therapy. *Chronic Rx*: PT, cognitive-behavioral therapy, interdisciplinary rehab (*Ann Intern Med* 2007;147:505); possible role for massage, yoga, acupuncture, spinal manipulation. *Medications*: *First line*: Acetaminophen, NSAIDs.



*Second line*: Short-term opioid analgesics, tramadol, benzos. Systemic corticosteroids, topiramate, muscle relaxants use controversial; consider TCAs in chronic LBP (>4 wk) & gabapentin (for radiculopathy) (*Neuromodulation* 2014;17(Suppl 2):18-23). Epidural steroid injections may give short-term benefit for radiculopathy.

**Prognosis:** Most acute back pain resolves spontaneously; continuing poor function, unwillingness to remain active, psychiatric comorbidities, general poor health, & maladaptive coping strategies are predictors of chronicity.

**Spinal Cord Syndromes**

| Syndrome | Causes | Clinical Findings |
|---|---|---|
| Complete cord | Trauma Compression<br>Demyelination<br>Postinfectious | Bilat wkns (initially flaccid, then UMN) below lesion<br>Bilat loss of all sens modalities below level<br>Sens level: transverse over torso<br>Loss of bowel, bladder, sexual fxn<br>Hyporeflexia then hyperreflexia<br>Radiating pain; relieved w/sitting/standing w/malignancy |
| Hemicord (Brown-Séquard) | Trauma Demyelination<br>Compression Tumors | Ipsilateral UMN wkns (corticospinal), vibration & proprioception (dorsal column) below level of lesion<br>Contralateral pain & temperature (spinothalamic tract) 1-2 segmental levels below lesion |
| Central cord | Hyperextension<br>Syringomyelia<br>Tumors<br>Anterior spinal artery (ASA) ischemia<br>Demyelination<br>Hematomyelia | Wkns: arm > leg; distal > proximal<br>Loss of pain & temperature in cape-like distribution (shoulders, neck, upper trunk) or suspended sens level<br>Relative preservation of light touch, position, vibration<br>Sacral sensation may be spared |
| ASA | Decreased ASA flow<br>Vascular or thoracoabdominal surgery<br>Cardiac arrest<br>Hypotension | Loss of motor, sensory (pinprick, temperature), autonomic fxn below level<br>Preservation of vibration & proprioception (dissociated transverse sens loss)<br>Abrupt onset w/in min to hours; back & neck pain<br>Initial flaccid paraplegia, then spasticity & hyperreflexia<br>Vulnerable area is watershed zone at approximately T6 & region around artery of Adamkiewicz |
| Conus | Tumors | Onset sudden & bilat |

| | | |
|---|---|---|
| medullaris | Lipomas<br>Metastases<br>Disc herniation<br>Fractures | Early bowel/bladder incontinence<br>Impotence & loss of anal reflexes<br>Saddle anesthesia; ± sensory dissociation<br>Symmetric wkns, may be mild<br>Loss of Achilles but not patellar reflexes |
| Cauda equina | Ruptured disc<br>Spine fx<br>Hematoma (e.g., post-LP)<br>Tumor<br>Arachnoiditis | Severe lumbosacral radicular pain<br>Saddle anesthesia, may be asymmetric<br>Flaccid paraparesis<br>Late bowel/bladder incontinence; impotence<br>Loss of ankle jerks; possibly knee jerks |

# COMPRESSIVE MYELOPATHIES

## NEOPLASTIC SPINAL CORD COMPRESSION

Medical emergency; suspect in pt w/known or suspected cancer & back pain w/or w/o neurodeficits. W/neuro dysfxn, urgent w/u & rx necessary. First sign of malignancy in up to 20% of cases. Cancers commonly metastasize to spinal column leading to epidural compression. Adults: lung, prostate, myeloma, breast, renal cell, lymphoma. Children: sarcoma, neuroblastoma, germ cell, & lymphoma. Location: thoracic > lumbar > cervical, but thoracic most sx. Pain: often initial complaint; worse w/Valsalva,



recumbent position, mvmt; often nocturnal; local pain from stretching of periosteum; axial pain from fracture; radicular pain from root compression.

**Dx:** MRI entire spine w/gado. CT myelogram, if MRI not possible. CT for spinal stability, operative planning. Plain radiograph: To eval for fracture/collapse; not useful for screening. Metastatic w/u if primary unknown.

**Rx:** Palliative. Steroids: Standard rx in acute setting if not medically contraindicated, but optimal dose not clearly defined (*Int J Radiat Oncol Biol Phys* 2012;84:312). Highdose rx (dense paraparesis, grade 3 or worse): dexamethasone 100 mg load, then 24 mg q6h. Moderate-dose rx otherwise: dexamethasone 10 mg load, then 4 mg q6h, (*Neurology* 1989;39:1255). Decompression, reconstruction, stabilization surgery followed by RT may be superior to RT alone (*Lancet* 2005;366:643). Radiotherapy (RT): If expected survival <3 mo at dx, presence of a radiosensitive tumor (lymphoma, small cell lung ca, breast, prostate, multiple myeloma, seminoma, neuroblastoma, Ewing sarcoma), multiple areas of spinal cord compression, or total paraplegia for longer than 48 h, consider RT alone. Systemic chemotherapy in sensitive tumors.

**Prognosis:** Based on neurologic function before rx; median survival 3-6 mo. Early dx is key; single most important prognostic factor for regaining ambulation after treatment of is pretreatment neurologic status.

## CERVICAL SPONDYLOTIC MYELOPATHY

Most common cause of spinal cord disorder in adults > age 50. Initial disc degeneration & subsequent degenerative changes in vertebral bodies, hypertrophy of ligamentum flavum & laxity of facet joints causes narrowing of spinal canal, compression of roots, vascular disruption, apoptosis, neuroinflammation leading to a radiculomyelopathy.

**Exam:** Pain in the neck, subscapular region, shoulder, & radicular arm pain; Lhermitte sign. Sensory loss or paresthesias in dermatomal distribution; 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 dominant sign w/little wkns). Bladder dysfxn (urgency, frequency, retention).

**Dx:** MRI: Evaluate for canal narrowing, cord compression, or signal abnormalities 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 of motor weakness (ALS).

**Rx:** Indication for conservative management: Stable sx, no spinal instability, no T2 signal change in cord. Include physical therapy for gait training & neck immobilization w/firm collar, pain control. Indications for decompression: Acute/progressive deterioration in neuro fxn; disabling neuro deficits; consider in mild cases w/risk of deterioration (20%-60%). No role of pre-emptive decompression in asymptomatic cervical cord compression w/or w/o T2 signal change. (*Clin Neurol Neurosurg* 2014;124:114-118)

### LUMBAR SPINAL STENOSIS

Narrowing of lumbar spinal canal. Sx results from nerve root compression & ischemia or indirectly from ↑ intrathecal pressure from ↓ canal size. Standing erect narrows the lumbar canal; flexion opens up canal.

**Etiology & classification:** *Congenital*: Due to short pedicles, symptomatic onset 20-40s; cause idiopathic or due to skeletal changes (achondroplasia). *Acquired:* Degenerative: Disc degeneration, facet & ligamentum flavum hypertrophy; lateral recess stenosis; spondylolisthesis. Iatrogenic: Postlaminectomy/fusion; at adjacent level or at previously operated site. Spondylotic: Presents in 20s, a/w spondylolisthesis. Posttraumatic. Metabolic: Cushing synd, corticosteroid excess, Paget dz, acromegaly, hypoparathyroidism. Infectious: Osteomyelitis, discitis, Pott dz. Rheumatologic: Ankylosing spondylitis.

**Clinical manifestations:** Neurogenic claudication: asymm calf or buttock discomfort/radiating pain w/gradual onset of numbness & wkns of legs on prolonged standing or walking; often bilat & asymm; relieved w/sitting, lying, or positions that flex hips & knees (squatting, pushing shopping cart, bicycling). Also lumbosacral radiculopathy, conus medullaris, or cauda equina syndrome if acute disk herniation. Distinguish from peripheral neuropathy (hypoesthesia in stocking distribution, unrelated to posture, exertion), hip osteoarthritis (pain into groin provoked w/internal rotation of hip), trochanteric bursitis (tenderness of greater trochanter), & vascular claudication (worse walking uphill, not influenced by posture, relief of pain immediate w/activity cessation).

**Exam:** May be nl but often elicited on exertion; radicular motor & sensory sx; findings not specific; limited lumbar extension, sensory deficit, muscle wkns, pain w/straight leg raise (Lasegue sign), absent knee &/or ankle reflexes; 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 radiculopathy or neuropathy.

**Rx:** Conservative measures: For those w/o fixed or progressive neuro impairment; NSAIDs, epidural steroid injections, PT (abdominal strengthening, minimize activities w/lumbar extension), bicycling (lumbar flexion) better tolerated than walking, lumbar corset to 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; newer techniques w/o clear evidence of advantage (interspinous spacer; minimally invasive lumbar decompression). 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/stab wounds, sporting accidents, crushing industrial injuries, birth injuries. Predisposing conditions: Cervical spondylosis, osteoporosis, atlantoaxial instability, congenital conditions (e.g.,

tethered cord), spinal arthropathies. Diverse mechanisms but typically vertebral injury leads to spinal cord compression.

**Eval:** History: mechanism, LOC, sx (pain/numbness/wkns). Physical exam: motor, sensory, reflexes, autonomics, spinal palpation. Imaging: Helical CT, MRI if stable.

| ASIA Scale | |
|---|---|
| **A** | No motor or sensory fxn below level through the sacral segments S4-S5 |
| **B** | Sensory but not motor fxn preserved below level & includes S4-S5 |
| **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 & sensory fxn nl |

### Initial management

*ABCD*: Chin lift w/o neck extension; no jaw thrust. Nasotracheal intubation if breathing spontaneously. Avoid tracheostomy/cricothyroidotomy (may compromise later surgery). Goal MAP ≥90; dopamine as pressor of choice; avoid phenylephrine (possible bradycardia). Fluids w/caution for pulmonary edema. Immobilization (CPR takes precedence). Foley.

Glucocorticoid use is no longer considered standard of treatment (*Neurosurgery* 2013;72(Suppl 2):93-105) Surgery: Goal is to stabilize spine, reduction of dislocation, decompression of neural elements; no clear guideline for indication & timing (*Cochrane Database Syst Rev* 2008;(1):CD004725).

## COMPLICATIONS OF CHRONIC SPINAL CORD INJURY

**Pressure sores:** Turn q2h; wheelchair lifts for 5-10 s q15-30 min; daily skin exams; proper nutrition; wound care.

**DVTs:** Prophylaxis up to 3 mo post injury or until 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, chest pain, tachy/bradycardia in response to relatively benign stimuli below level of injury. Serious consequences: ICH/stroke, sz, pulmonary edema, MI, death. Mechanism: 2/2 injury above the major splanchnic outflow tracts (T5-T6); sensory nerves transmit signals up spinothalamic & dorsal columns → sympathetic neurons, intermediolateral gray matter → large sympathetic surge because of loss of inhibitory input from cerebral vasomotor centers → vasoconstriction & HTN; brainstem vasomotor reflexes → increased parasympathetic 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 apply 1 inch

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.

**Nutrition:** Enteral & parental feeding should be provided; PPI for 4 weeks to prevent GI stress ulcers.

# 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 weakness, ↓'d reflexes below lesion, bladder distension, ↓'d rectal tone, loss of temperature/light touch below lesion. Predictors of poor outcome: Proprioception loss, urinary dysfxn, gait disturbance at onset; lack of significant motor recovery in 24 h.

**Dx:** MRI w/DWI & T2; adjacent vertebral body infarction (confirmatory sign).

**Etiology:** Exercise, esp w/pre-existing spine dz; vascular compression: Local spinal column dz, aortic manipulation, endovascular procedures; hypoperfusion: Systemic hypotension, local atherosclerotic/arteriosclerotic lesions, radiation therapy; embolism: thromboembolic dz, iatrogenic, fibrocartilaginous; prothrombotic; meningitis, vasculitis, neoplasm.

**Rx:** Supportive: Keep MAP > 90; spinal cord perfusion pressure = MAP - intrathecal pressure; prophylactic or therapeutic lumbar drain [although limited evidence (*Eur J Vasc Endovasc Surg* 2008;35:46)]; 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, anesthesia after injection. Progressive 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 artery feeder to venous connection at the dural | Venous outflow obstruction causes arterialization of venous plexus leading to venous hypertension & |

| | |
|---|---|
| sleeve of root | 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 radiculopathy & myelopathy. Usually involves lower thoracic/lumbar region. Spinal AVM may have bruit. Coexisting vascular malformation of skin, Cobb synd.

**Spinal dural AVF:** Most common spinal vascular malformation.

**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 enhancement 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* & *Neurorheumatology*)

| MS | | NMO | ADEM |
|---|---|---|---|
| History | F:M = 2:1<br>Age: 20-50s | F:M = 9:1<br>Variable age of onset | F:M = 1:1<br>Children > adults<br>Antecedent infxn or vaccination |
| Clinical | Dissemination of lesions in time & space<br>Typical presentation: optic neuritis, INO, partial transverse myelitis | Acute myelitis (hours to days) ± H/o optic neuritis NMO Ab positive Relapsing course | Encephalopathy Monophasic Rarely relapsing |
| MRI spine | Gado enhancement of active lesions | Longitudinally extensive (>3 segments) | Variable length<br>May be >3 segments |

| | | | |
|---|---|---|---|
| | <2 segments<br>May see old T1 dark lesions<br>Cord expansion rarely | Gado enhancement of active lesions<br>Cord expansion | Often thoracic cord<br>Can see cord expansion<br>Variable enhancement |
| MRI brain | WM lesions, Dawson fingers, periventricular, juxtacortical, infratentorial lesions<br>Variable enhancement<br>May see old T1 dark lesions | NI or nonspecific subcortical lesions<br>May see atypical lesions in diencephalon, periaqueductal, dorsal medulla<br>± Optic nerve enhancement | Large subcortical or deep confluent white matter lesions<br>C-shaped lesions, open ring sign<br>Gray matter lesions in the basal ganglia & thalami<br>Uniform enhancement |
| Spinal fluid | Acellular or mild pleocytosis (<50 cells)<br>Lymph predominance<br>Increased IgG index<br>+OCB (85%) | Pleocytosis (50-1,000 WBC)<br>Neutrophil predominance<br>± Increased IgG index<br>+OCB (30%) | Pleocytosis (>50 WBC)<br>Lymph predominance<br>Variable IgG & OCB usually absent |
| Rx | IV steroids (1,000 mg methylprednisolone × 3-5 days) for acute exacerbation<br>Dz modifying tx | IV steroids ± plasma exchange<br>Immunosuppression to prevent relapse | IV steroids<br>IVIg or plasma exchange for steroid refractory cases |

## MYELOPATHY DUE TO NUTRITIONAL DEFICIENCIES

**Vitamin $B_{12}$ deficiency:** *Etiology*: Pernicious anemia, excessive antacid use, atrophic gastritis, HIV, gastric surgery, nitrous oxide abuse, nitrous oxide exposure during anesthesia, fish tapeworm infestation of the gut, inflammatory bowel dz. *Clinical manifestations*: Subacute combined degeneration (SCD); loss of vibration & proprioception, spastic paraparesis +/- painful paresthesias in hands progressing to lower limbs w/evidence of myelopathy, +/- optic neuropathy; + Romberg, + Lhermitte's; memory impairment, personality change w/prolonged def. *Dx*: ↓ serum $B_{12}$, ↑ methylmalonic acid & homocysteine, CBC w/macrocytic anemia & hypersegmented neutrophils; intrinsic factor Ab test + serum gastrin & pepsinogen when pernicious anemia suspected. MRI spine: Longitudinal T2 signal in post & lat columns of cervicothoracic cord; “inverted V” on axial image; not necessary for the dx of early myelopathy when it is most treatable. *Rx*: $B_{12}$ 1,000 µg IM daily × 5-7 days, then $B_{12}$ 1,000 µg IM weekly until improvement, then monthly indefinitely. High PO dose 1,000-2,000 µg daily as effective as monthly IM inj in absorption defect (not well studied in severe neurologic dz) (*Handb Clin Neurol* 2014;120:915-926).



**Folate deficiency:** *Etiology*: Drug-induced impairment of folate metabolism (trimethoprim, methotrexate, phenytoin, phenobarbital), alcoholism, inborn error of folate metabolism, dietary def, pregnancy. *Clinical manifestations*: Resembles SCD, neuropathy. *Dx*: ↓ serum folate & ↑ homocysteine, screen for $B_{12}$ def. *Rx*: Folate 1 mg PO tid × 4 mo, then 1 mg PO daily, monitor homocysteine levels.

**Copper deficiency:** *Etiology*: Gastric surgery, zinc toxicity (dental fixatives), TPN, copper chelators (clioquinol

& ethambutol). *Clinical manifestations*: Myelopathy resembles SCD w/sensory ataxia & spasticity; myeloneuropathy & peripheral neuropathy; rarely optic neuropathy. *Dx*: ↓ serum & urine copper levels, ↓ ceruloplasmin, check zinc; MRI w/↑ T2 signal in dorsal columns of cervical cord. *Rx*: Stop zinc. Mild-tomoderate def: Copper 8 mg PO daily × 1 wk, then 6 mg PO daily for 1 wk, then 4 mg PO daily × 1 wk, then 2 mg PO daily. Severe def: Copper 2-4 mg IV daily × 6 days.

**Vitamin E deficiency:** *Etiology*: Fat malabsorption. Acquired: gastrectomy, pancreatic insufficiency, biliary dz, cystic fibrosis, celiac dz. Genetic: Familial hypocholesterolemia, defect in alpha-tocopherol transfer protein. *Clinical manifestations*: Ataxia, dysarthria, nystagmus, signs of peripheral neuropathy, gaze palsies, retinitis pigmentosa, proximal muscle wkns, myopathy, action tremor. *Dx*: ↓ effective serum vitamin E level (calculate by dividing serum vitamin E by sum of serum cholesterol & triglycerides). Genetic studies when appropriate. MRI: ↑ T2 signal in dorsal column. *Rx*: Start w/low-dose vitamin E 200 mg PO daily, increase gradually based on clinical & lab response. High doses required in genetic dz; avoid excess fat in diet.

## TOXIC MYELOPATHIES

**Fluorosis (India):** *Etiology*: Overconsumption of fluoride in water → fluoride deposits in vertebra; myelopathy caused by compression of cord by extensive & hypertrophic changes in bony spine. *Sx*: Back pain, stiffness, cord compression, radiculopathy, spastic paraparesis, ↓ hearing 2/2 nerve compression. *Dx*: ↑ alkaline phosphatase & PTH, nl Ca & $PO_4$. Plain films: Osteosclerosis, calcification of ligaments, & interosseous membrane.

**Cassava toxicity (Africa):** Also called Konzo. *Etiology*: Insufficient processing of cassava root → cyanide poisoning. *Sx*: Abrupt onset of spastic paraparesis or slowly progressive ataxia, peripheral neuropathy, optic atrophy. *Dx*: Serum thiocyanate level.

**Lathyrism (India, Ethiopia, Bangladesh):** *Etiology*: Consumption of grass pea as a dietary staple. 2/2 toxin *β-N*-oxalylamino-L-alanine. *Sx*: Subacute paraparesis & autonomic dysfxn. *Prevention:* Mix w/cereal, detoxification.

**Organophosphate toxicity:** *Etiology*: Phosphorylation of neurotoxic esterase. *Sx*: Onset >1 after acute exposure; distal paresthesias & cramping muscle pain; progressive 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 & lateral columns.

**Radiation myelopathy:** *Etiology:* Spinal cord in field of radiation therapy. Early: Reversible myelopathy within 2-6 mo of spinal irradiation. *Sx*: Lhermitte sign. *Rx:* No active intervention, typically spontaneous resolution in a month to a year. Late: Irreversible chronic myelopathy by either demyelination or vascular damage. *Sx:* Paresis, numbness & sphincter dysfxn after 6-12 mo. *Dx:* Clinical. MRI spine: Initial MRI may be nl, later T1 hypointensity + T2 hyperintensity +/- enhancement w/contrast, eventually cord atrophy. *Rx:* No clear rx.

## INHERITED AND NEURODEGENERATIVE MYELOPATHIES

**Spinocerebellar ataxias:** *Sx*: Limb & trunk ataxia, peripheral neuropathy, loss of vibration, proprioception, & variable corticospinal sx in limbs. *SCA 1-37*: Dx by genetic testing, MRI w/cerebellar atrophy. *Friedreich ataxia*: Most common SCA; autosomal recessive, FXN 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 (autosomal dominant): SCA3 gene mutation. *Abetalipoproteinemia* (*Bassen-Kornzweig*): Lipoprotein electrophoresis. *Familial vitamin E def*: Low serum vitamin E.

**Leukodystrophies causing myelopathy:** *Sx*: Cognitive impairment, UMN signs, optic neuropathy, peripheral neuropathy, behavior changes, szs. *Adrenomyeloneuropathy*: Chronic, progressive spinal cord form of ALD seen in young/middle-aged men & rarely middle/older-aged women, X-linked, ABCD1 gene mutation, ↑ serum VLCFA.

*Metachromatic leukodystrophy*: Demyelinating peripheral neuropathy, deficiency of arylsulfatase A.

## PARANEOPLASTIC SPINAL CORD DISORDERS

**Myelitis:** Anti-Hu, anti-CRMP5/CV2, antiamphiphysin abs, usually w/lung cancer.

**Stiff person syndrome:** Antiamphiphysin ab, usually w/lung & breast cancer.

**Subacute motor neuronopathy:** Hodgkin & non-Hodgkin lymphoma; painless asymmetric LMN wkns.

**Subacute sensory neuronopathy:** Anti-Hu, anti-CV2 abs, w/SCLC, breast, prostate, colon, lymphoma, uterine sarcoma.

**Necrotizing myelopathy:** Lymphoma, lung, renal, breast, leukemia.

## 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:** Aspergillosis, blastomycosis, coccidioomycosis, cryptococcosis.

**Parasitic:** Toxoplasma, schistosomiasis, echinococcus, cysticercosis.

# Motor Neuron Disease

Richard C. Krolewski

Merit E. Cudkowicz

## 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) si/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 affect. Due to involvement of corticobulbar tracts, which exhibit supranuclear control over motor nuclei controlling speech, chewing, swallowing. Sx: Emotional lability or emotional incontinence w/spontaneous laughter or crying.
- ROS: Night sweats, fevers, weight loss, gynecomastia, impotence, rash, neck pain, sx suggestive of systemic dz (& possibly another etiology).
- Exposure to toxins/travel history/military history/family history (ask about dementia given ALS-FTD link); HIV risk factors; h/o malignancy, systemic dz.

**DDx:** See charts below for dzs affecting UMN, LMN, & both. Chronic motor peripheral neuropathies, Charcot-Marie-Tooth dz, cervical spondylosis or disc dz/cervical spine pathology, muscular dystrophies, myasthenia gravis, myopathies such as polymyositis, inclusion body myositis, pseudobulbar palsy secondary to vascular dz, chronic Lyme dz, spinal muscular atrophies, multifocal motor neuropathy w/conduction block.

**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/pelvis or PET scan to evaluate for malignancy; genetic testing, depending on clinical history. Send anti-GM1 antibody if lower motor neuron predominant, evidence of conduction slowing.

**Rx:** For many of these illnesses, no Rx to slow progression of dz. For amyotrophic lateral sclerosis (ALS), riluzole shown to prolong survival by months, & dextromethorphan/quinidine (Nuedexta) approved for emotional lability (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, early nutritional support (PEG), trach (if pt wishes), genetic counseling in appropriate cases, support groups. Agents for spasticity, medications to reduce drooling. Important to diagnose or exclude dzs w/available Rx.

| Summary Table of Motor Neuron Diseases | | |
|---|---|---|
| **UMN** | **LMN** | **UMN & LMN** |
| Primary lateral sclerosis | Multifocal motor neuropathy | ALS |

| | | |
|---|---|---|
| HTLV | Monomelic amyotrophy | ALS-FTD |
| Hereditary spastic paraparesis (HSP) | Spinal muscular atrophy (SMA) | ALS parkinsonian complex of Guam |
| Adrenomyeloneuropathy | Kennedy dz | Machado-Joseph dz |
| Lathyrism | Progressive muscular atrophy | Adult hexosaminidase def |
| Konzo | Paraneoplastic or neoplastic LMN disorder | Adult polyglucosan body dz |
| | Postradiation LMN syndrome | Paraneoplastic syndrome |
| | Polio/postpolio syndrome | |

## DISEASES AFFECTING PRIMARILY UPPER MOTOR NEURONS

### Primary lateral sclerosis (PLS)

*Clinical features*: 2%-4% cases of ALS; onset typically in 50s. Gradual spastic paraparesis spreading to UE, weakness, & unstable gait; may cause pseudobulbar affect, urinary urgency, subtle cognitive deficits. Tends to have slower progression (if it doesn't progress to ALS), dz duration average >7 yr.

*Dx/Rx*: 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. Supportive Rx, no proven benefit from riluzole (in contrast to ALS; see below).

### Human T-cell lymphotropic virus (HTLV)

*Clinical features*: HTLV-1 rarely may cause tropical spastic paraparesis in Caribbean or HTLV-1-associated myelopathy in Japan. HTLV-2: Similar to HTLV-1, may also cause myelopathy. Chronic, slowly progressive myelopathy beginning after age 30. Spastic paraparesis, paresthesias, painful sensory neuropathy, bladder dysfunction.

*Dx/Rx*: HTLV-1 & HTLV-2 serology in blood & CSF. Combination of PCR, HTLV-1 antibody, & oligoclonal bands (*Lancet* 2006;5:1068). Supportive Rx.

### Hereditary spastic paraparesis (HSP)

*Clinical features*: Clinically & genetically diverse disorder, which can be AD, AR, 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/Rx*: Family history; if no family history, then differential dx is same as PLS. 40% AD cases w/mutation in spastin on 2p22-21 (*Arch Neurol* 2009;66:509). Supportive Rx, especially baclofen, tizanidine, oxybutynin for urinary symptoms.

### Adrenomyeloneuropathy

*Clinical features*: X-linked recessive mutation in ABCD1 gene on Xq28 → very long chain fatty acid (VLCFA) accumulation; most common phenotype affects young boys 4-8 yr 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. EMG/NCS: Primarily axonal sensorimotor polyneuropathy w/lesser component of demyelination. Increased VLCFA levels in plasma, RBCs, or cultured skin fibroblasts. Sural nerve biopsy: Loss of both myelinated & unmyelinated axons w/onion bulb formation. EM: Lamellar inclusions in cytoplasm of Schwann cells (*J Neuropathol Exp Neurol* 1995;54:740).

*Rx:* Hematopoietic stem cell transplant (if evidence of cerebral involvement & depending on age & dz severity), dietary therapy/Lorenzo's oil; data is mixed (*J Mol Neurosci* 2007;33:105).

### Lathyrism

*Clinical features*: Caused by chronic ingestion of flour made from chickpea, *Lathyrus sativus*. Neurotoxin: BOAA or beta-*N*-oxalyl-amino-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/Rx*: Based on clinical history & exam. Supportive Rx, prevention by expanding public awareness. If eaten, steep in water & use metallic vessels rather than clay pots to reduce toxin burden (*J Neurol* 2012;259:1263).

### Konzo

*Clinical features*: Caused by chronic ingestion of cassava root; endemic in Tanzania, Zaire, Eastern Africa. Abrupt onset of nonprogressive spastic paraparesis; appears to target corticospinal tracts & motor cortex affecting LE.

*Dx/Rx*: Based on clinical history & exam (*Drug Metab Rev* 1999;31:561). Supportive Rx.

## DISEASES AFFECTING PRIMARILY LOWER MOTOR NEURONS

### Multifocal motor neuropathy (MMN)

*Clinical features*: Pure motor sx in association w/motor nerve demyelination. Cause unclear but believed to be autoimmune due to presence of anti-GM1 ganglioside ab. Ddx: ALS, progressive muscular atrophy (PMA), adult-onset SMA, benign focal amyotrophy, CIDP, MADSAM. Age of onset 20-75 & >2:1 M:F, dz progresses over many yrs. 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 loss 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-GM1 ab. CSF protein is usually normal but may be modestly elevated to <100 mg/dL.

*Rx*: IVIg 2 g/kg IV in divided doses over 2-5 days, followed by a maintenance dose of 0.4-0.6 g/kg once every 3-8 wk. Rituximab & high-dose cyclophosphamide also used, less supporting data. Check IgA level prior to administering IVIg (*Neurology* 2000;55:1256; *Brain* 2001;124:145, *Neuropsychiatr Dis Treat* 2014;10:567).

### Polio

*Clinical features*: Caused by poliovirus, an enterovirus; spread via fecal-oral route. Risk of paralytic dz increases w/age & level of virulence of virus. 3-6 days 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. Natural history is variable. Eradicated in many countries w/vaccination program.

*Ddx*: Acute paralytic dz caused by West Nile virus or other enteroviruses, GBS, AMAN, myasthenia gravis, neuralgic amyotrophy, acute intermittent porphyria, periodic paralysis, tick paralysis, & acute rhabdomyolysis.

*Dx*: EMG/NCS: Low-amplitude CMAPs, no demyelination or conduction block. SNAPs normal. EMG in acute phase may show positive sharp waves, fibrillation potentials, & fasciculations. CSF: Pleocytosis w/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% pts by 10th day of illness. ≥4-fold increase in serum poliovirus Ab titer.

## Postpolio syndrome

*Clinical features*: Also called progressive postpoliomyelitis muscular atrophy; cause unclear. Occurs in pts w/h/o polio usually at least 10 yr after their recovery. Stable course for many yrs 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 dzs w/similar sx. EMG/NCS: Provides evidence of remote poliomyelitis & may help exclude other dzs. NCS may show low-amplitude CMAP; EMG may show reduced number of motor units & chronic neurogenic motor unit potentials. Sensory NCS wnl (*Muscle Nerve* 2005;31:6).

*Rx:* Mainly supportive; lamotrigine may reduce pain & fatigue; IVIg w/equivocal results (*Cochrane Database Syst Rev* 2011;(2):CD007818).

## 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 begins in later teens but can present up to fourth decade.



Idiopathic, slowly progressive, painless weakness, & atrophy in one hand or forearm. Affects only a few myotomes in 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.

## Spinal muscular atrophy (SMA)

Clinically heterogenous group of progressive, hereditary dzs of anterior horn cells & select motor cranial nerve nuclei.

*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 hips/knees, scoliosis, & dislocations of hips. Small involuntary movements of fingers called minipolymyoclonus.

*SMA-3* (*juvenile SMA or Kugelberg-Welander*): Onset usually between 5 & 15 yr; present w/difficulty walking; waddling (Trendelenburg gait); lordosis, difficulty climbing stairs, fasciculations, slowly progressive limb-girdle weakness. If onset before age 2, often unable to walk by age 15. Most pts require wheelchair by mid-30s.

*SMA-4 (adult-onset SMA):* Rare & genotypically heterogenous disorder; onset mid-30s; AD in 30% cases. Slowly progressive limb-girdle weakness w/difficulty walking, ascending stairs, rising from chair. Normal life expectancy.

*Dx:* Molecular genetic analysis to identify mutations in SMN gene on chromosome 5q (*Cell* 1995;80:155-165, *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003;4:225-231). CK may be elevated. EMG/NCS: CMAPs may be reduced in amplitude; conduction velocities & sensory conduction studies normal. EMG may reveal acute denervation in form of fibrillation potentials & positive sharp waves, fasciculation potentials, & motor unit remodeling. There may be reduced recruitment of polyphasic motor units.

*Rx:* Supportive, trials ongoing for gene therapy, antisense oligonucleotides, & drugs that modify splicing.

## 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 CAG repeat in androgen receptor gene on X chromosome; CK levels may be elevated 10× normal; androgen levels are normal or decreased. EMG shows prominent chronic denervation changes in motor units, modest acute denervation changes. Sensory neuropathy, fasciculations in face & limbs (*Eur J Neurol* 2009;16:556).

## Progressive muscular atrophy

*Clinical features*: 8% of adult-onset motor neuron dzs; believed to be an ALS variant; however, often not included in clinical trials. 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 d/o of anterior horn cells. Muscle bx: Denervation atrophy but is usually unnecessary. Exclude other possible causes.

**West Nile virus-associated flaccid paralysis:** Acute flaccid paralysis may occur as a manifestation of West Nile virus due to involvement of anterior horn cells & motor axons. May be accompanied by fever, h/a, n/v, rash, meningismus, or occur in absence of systemic sx. Respiratory failure requiring intubation may occur. Dx: EMG/NCS c/w motor axonopathy or anterior horn cell process. + serum or CSF IgG &/or IgM ab or PCR for West Nile virus. CSF usually w/neutrophilic or lymphocytic predominance, elevated protein. Rx: Supportive (*Neurology* 2003;61:55-59; *Emerg Infect Dis* 2005;11:1021-1027; *N Engl J Med* 2002;347:1279-1280).



**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, dz may have a benign course. Rarely, dz may respond to Rx of underlying lymphoproliferative d/o.

**Postradiation LMN syndrome:** Result of radiation directed to lumbar paravertebral area for Rx of testicular cancer. EMG/NCS c/w disorder of cauda equina w/sparing of SNAPs. Dz usually progresses over first few yrs after sx onset but sx subsequently plateau.

# DISEASES AFFECTING BOTH UMN AND LMN

## Amyotrophic lateral sclerosis

*General*: Neurodegenerative dz 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. 68% FALS associated w/>35 different gene mutations including SOD1, FUS/TLS, VAPB, TDP-43, C9ORF72 (*Nature* 1993;362:59; *Science* 2009;323:1205; *Science* 2008;319:1668; *J Biol Chem* 2006;281:30223; *Nature Neurosci* 2014;17:17-23). C9ORF72 intronic repeat expansion associated w/large proportion (~40%) of FALS cases (*Neuron* 2011;72:257; *Neuron* 2011;72:245). TDP-43 aggregates have also been found in sporadic ALS (*Neurol Sci* 2011;32:9-16).

*Si/sx*: Weakness typically begins focally & spreads to surrounding muscles. Rarely, weakness may begin w/respiratory muscles. Some pts may present w/unilateral weakness (Mill's hemiplegic variant). 10% have bilateral UE wasting (flail arm variant). Bulbar (cranial nerve) onset is present in 20% of cases. 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, 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-GM1 Ab, ESR, SPEP or IFE, thyroid function studies, $B_{12}$, celiac testing. Acetylcholine receptor or voltage-gated calcium channel abs 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). Multidisciplinary clinic can extend life/quality, PT/OT/speech; nutritional care for dysphagia & aspiration risk. Consider early PEG prior to respiratory worsening. Survival & functional benefit w/hypercaloric enteral nutrition (125% of recommended calories) (*Lancet* 2014;383:2065). Respiratory support. Consider BiPAP or tracheostomy. Home/hospice care if pt wishes. Dextromethorphan/quinidine (Nuedexta) FDA approved to help w/pseudobulbar affect.

**ALS-FTD:** Cognitive impairment is 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). Genetic studies implicate a hexanucleotide repeat on chromosome 9 (C9ORF72) as a likely mechanistic link between ALS & FTD (present in 46% of FALS, 21% of sporadic ALS). Affected individuals have >30 repeats (*Neuron* 2011;72:245; *Neuron* 2011;72:257)

**ALS parkinsonian complex of Guam:** Disorder w/combination of ALS & parkinsonism. Most common cause of death for adults in native Chamorro population of Guam. Believed to due to toxin caused by 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 w/onset ranging from 4th to 7th decade. Sx: Cerebellar ataxia. Pts w/earlier onset may present w/spasticity & fasciculations of tongue & face. Other sx include extrapyramidal si/sx, dystonia, rigidity, protuberant eyes, & progressive external ophthalmoplegia. Due to CAG repeat on chromosome 14q32.1, which encodes for ataxin-3 gene.

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**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 dz.

**Adult polyglucosan body dz:** Rare, slowly progressive disorder characterized by UMN & LMN signs, cognitive decline, distal sensory loss, & loss of bowel & bladder function. MRI of the 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 dz:** 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

Michael P. Bowley

William S. David

## EVALUATION OF NEUROPATHY

**Obtain a careful history:** Ask about motor, sensory, & autonomic disturbances. Obtain time course & distribution of sx, h/o toxic or infectious exposures, family history, meds, vitamins, sx of systemic dzs. **Detailed physical exam:** Determine anatomic pattern & localization: Mononeuropathy, mononeuropathy multiplex, polyneuropathy (symmetric vs. asymmetric; length dependent vs. non-length dependent), predominant motor or sensory & to which modalities, autonomic sx. Evaluate for lymphadenopathy, organomegaly, musculoskeletal/joint abnormalities, rash. Examine hair, skin, & nails. Palpate peripheral nerves. Evaluate for pes cavus & hammertoes.

**EMG/NCS:** Helpful to confirm neuropathy pattern & localization. Distinguish between axonal and demyelinating neuropathy. **Autonomic fxn testing:** May be useful in small-fiber neuropathy & may narrow differential if autonomic involvement in somatic polyneuropathy. **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 nerve is useful when vasculitis is suspected as 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:** (1) Initial screening: Fasting glucose or HgbA1c (if normal, do 2-h glucose tolerance test), B12 w/metabolites (MMA, homocysteine), TSH, SPEP w/IFE (*Neurology* 2009;72:185). (2) Additional labs based on si/sx: Chem10, CBC, ESR, ANA, anti-Ro & La, HIV, Lyme, UPEP. (3) Genetic testing for cryptogenic polyneuropathy if appropriate si/sx/FHx.

## MONONEUROPATHIES

### ENTRAPMENT MONONEUROPATHIES: UPPER EXTREMITY

**Dorsal scapular nerve (C5): Compression site & risk factors:** Scalene muscles due to cervical hyperextension/flexion, trauma. **Si/sx:** Winging of scapula on arm abduction.

**Suprascapular nerve (C5-C6): Compression sites & risk factors:** Suprascapular notch, spinoglenoid notch due to repetitive forward traction or trauma. **Si/sx:** Atrophy of supraspinatus and/or infraspinatus muscles, aching posterior shoulder pain. **Dx:** History, exam, EMG/NCS. **Rx:** Most spontaneously improve over time. Steroid injection/surgery for refractory cases.

**Musculocutaneous nerve (C5-C6): Compression sites & risk factors:** Within belly of coracobrachialis, between biceps brachii & brachialis; weight lifting, shoulder dislocation, or surgery. **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; surgical decompression if persistent.

**Radial nerve (C5-C8): Compression sites & risk factors: (1)** Axilla: Crutches. **(2)** Spiral groove (Sat. night palsy; Honeymooner palsy): Compression/drunken sleep.



**(3)** Posterior interosseous nerve: RA, trauma, fracture, soft tissue mass, strenuous use of arm. **(4)** Superficial sensory branch (cheiralgia paresthetica): Wristbands, handcuffs. **Si/sx: (1)** Axilla: Weak triceps, brachioradialis,

supinator, wrist/finger extension; sensory loss over entire extensor surface of arm, forearm, & hand. **(2)** Spiral groove: Weak brachioradialis, wrist/finger extension; triceps spared; sensory loss in dorsolateral hand, thumb, dorsal aspect of proximal digits II-IV. **(3)** Posterior interosseous nerve: Weak wrist/finger extension, extensor carpi ulnaris; variable forearm pain but no sensory loss. **(4)** Superficial sensory branch: Sensory loss in dorsolateral hand, thumb, dorsal aspect of proximal digits II-IV. **Dx:** EMG/NCS; MRI at compression site. **Rx:** For compression at axilla, spiral groove & posterior interosseous nerve, conservative Rx w/modification of activities & wrist splint; usually improves after 6-8 wk. For superficial sensory branch, sx usually self-limited.

**Median nerve (C6-T1): Compression sites & risk factors:** (1) Wrist (carpal tunnel syndrome; CTS) due to tenosynovitis, arthritis, trauma, repetitive use, vibrating tools; a/w DM, pregnancy, thyroid dz, gout, amyloid. (2) Forearm due to trauma, casting, venipuncture; may involve only anterior interosseous nerve (AIN) or more proximal median nerve. **Si/sx:** (1) Wrist/CTS: Paresthesias & pain in lateral palm & digits I-IV, sx worse at night, thenar atrophy, weakness of thumb abduction, Phalen, Tinel, Flick signs (poor se & sp). (2) Forearm: AIN syndrome w/weakness of flexion of distal phalanx of thumb & index finger & forming "OK" sign, normal sensation. Proximal forearm w/forearm aching, Tinel, weakness of pronation, flexion digits II-III, thumb abduction & flexion, median distribution numbness. **Dx:** EMG/NCS. **Rx:** CTS: Wrist splints, anti-inflammatory medications, PT, surgery for refractory cases or if thenar atrophy, steroid injections (only limited short-term benefit). Forearm: Conservative Rx, surgery if fracture/trauma or refractory sx & suspected entrapment.

**Ulnar nerve (C8-T1): Compression sites & risk factors:** (1) Elbow: Retroepicondylar groove or cubital tunnel due to elbow leaning, chronic stretch, trauma; (2) wrist (Guyon canal) in mechanics, cyclists, RA or degenerative dz of wrist joints, wrist fractures. **Clinical features:** (1) Elbow: Numbness of medial hand (dorsal & palmar aspect.) & digits IV-V. Atrophy of intrinsic hand muscles, weakness of flexion of wrist & digits IV-V, claw hand. Tinel sign at elbow, Froment sign. (2) Wrist: Numbness of palmar medial hand & digits IV-V, 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

**Lateral femoral cutaneous/meralgia paresthetica (L2-L3): Compression site & risk factors:** Inguinal ligament due to tight clothing, obesity, DM, pregnancy, pelvic/abdominal mass. **Si/sx:** Sensory loss, burning, tingling in the anterior & lateral thigh from hip to knee. **Dx:** Hx & exam; NCS if unclear. **Rx:** Weight loss; rest; injection of local anesthetics or steroids; topical anesthetics, AEDs, tricyclics; rx underlying tumor if present.

**Obturator (L2-L4): Compression site & risk factors:** Obturator canal due to 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-L4): Compression site & risk factors:** Inguinal ligament due to lithotomy position, aortic or iliac aneurysms, retroperitoneal hematoma, trauma, pelvic/abdominal surgery. May be affected as forme fruste of lumbar radiculoplexus neuropathy due to diabetes or of idiopathic etiology. **Si/sx:** Weak hip flexion & knee extension, absent knee jerk. **Dx:** EMG/NCS. If suspect hematoma or unclear cause, CT abdomen/pelvis. **Rx:** Based on etiology. If due to lithotomy, trauma, position/stretch, then conservative Rx. If retroperitoneal hematoma, then surgical evacuation & discontinue anticoagulation/antiplatelet agents. If malignancy, then treat underlying tumor.

**Sciatic (L4-S3):** Divides into common fibular (peroneal) & tibial nerves. **Compression sites & risk factors:** (1) Gluteal region/sciatic notch due to immobilization, hemorrhage, iatrogenic injections. (2) Hip due to hip/femur fracture/dislocation or surgery. (3) Thigh due to immobilization, trauma, vasculitis, endometriosis. (4) Popliteal fossa due to Baker cyst. **Si/sx:** Pain down thigh, weakness of knee flexors & all muscles distal to knee; sensory loss of entire foot except over medial malleolus; absent ankle jerk; early si may mimic peroneal neuropathy as

these fibers are preferentially affected. **Dx:** EMG/NCS. **Rx:** Identify & treat underlying cause, conservative therapy (PT, orthotics, pain control).



**Common fibular (peroneal) nerve (L4-S1):** Divides into superficial (L5-S1) & deep peroneal (L4-S1) nerves. **Compression site & risk factors:** Fibular neck; due to leg crossing, squatting/trauma. **Si/sx: (1)** Common peroneal: Weakness of foot dorsiflexion & eversion, sensory loss in dorsum of foot. Variable Tinel at fibular head. **(2)** Superficial peroneal: Sensory loss of lateral part of leg & 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 & risk factors: (1)** Popliteal space due to Baker cysts, trauma, nerve tumors, entrapment. **(2)** Tarsal tunnel due to ankle fracture, tenosynovitis/RA, ill-fitting shoes, tumors. **(3)** Foot due to 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, or surgical decompression.

## MONONEUROPATHY MULTIPLEX

**Presentation:** Involvement of multiple separate peripheral nerves.

**Causes:** Primary vasculitides (microscopic polyangiitis, Churg-Strauss, Wegener granulomatosis, PAN), secondary vasculitides (RA, SLE, Sjögren syndrome), infection (leprosy, HIV, CMV, hepatitis B & C), DM, sarcoidosis, amyloidosis, hereditary neuropathy w/liability to pressure palsy (HNPP).

**Dx:** *Labs:* Chem10, 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-wks; pain in hips, thigh, & back; reduced vibratory & position sensation; reduced tendon reflexes (normal in 10%); facial diplegia often occurs (>50%), autonomic instability; paresthesias in toes & fingers; may be preceded by Campylobacter, EBV, CMV, Mycoplasma. **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 dz/myelopathy, necrotizing myelopathy, carcinomatous meningitis, poliomyelitis, brainstem dz, neuromuscular disorders such as myasthenia gravis or botulism, myopathy, critical illness polyneuropathy, porphyria, acute hypophosphatemia. **Dx:** Primarily a clinical diagnosis. *LP*: High protein, few cells (<10) = albuminocytological dissociation, present in ~50% of pts in 1st wk of sx & ~75% by 2 wk. If increased cell count (>50), consider GBS in setting of alternative dx such as Lyme dz, 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 due to SIADH. *Abs*: 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 4-

6 treatments qod; IVIg: 0.4 g/kg/d × 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: Si/Sx:** Slowly progressive, motor > sensory sx in both proximal & distal muscles. Weakness must be present >2 mo. Generalized hyporeflexia or areflexia, can have nerve root enlargement. May be a/w HIV, MGUS, plasma cell dyscrasias, hepatitis, inflammatory bowel dz, Hodgkin lymphoma. **Dx:** *Labs/x-ray*: Chem10, CBC, LFTs, ESR, HIV, SPEP, UPEP, immunofixation, skeletal bone survey for evaluation of underlying systemic disorder. *EMG/NCS*: Multifocal demyelination & partial conduction block. *CSF*: Albuminocytological dissociation (see GBS for same ddx if cell count is high). *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 dz 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). Plasmapheresis biweekly initially & then individualized (*Ann Neurol* 1994;36:838; *Ann Neurol* 2001;50:195).

**Multifocal motor neuropathy: Si/Sx:** Progressive, asymmetric, predominantly distal limb weakness (90% are in the distal upper extremity), muscle cramps, fasciculations, & atrophy over months-years. Depressed tendon reflexes. May be confused w/ALS but absent UMN sx. **Dx:** *EMG/NCS*: Persistent focal motor conduction block or other features of demyelination in motor responses. *CSF*: Protein usually normal but may be slightly increased. *Abs*: IgM anti-GM1 ab in ~20% to 80% of pts. **Rx:** IVIg per rx of CIDP (*Neurology* 2000;55:1256). Cyclophosphamide 1 g/m2 IV qmo × 6-8 mo may be of use in some nonresponders to IVIg. Unclear efficacy of rituximab. No benefit of steroids or plasma exchange.

**Acute sensory neuronopathy: Si/Sx:** Sensory ataxia, areflexia, numbness, variable pain. No weakness. May be GBS variant, or a/w cancer, HIV, Sjögren syndrome, pyridoxine toxicity, or idiopathic. **Dx:** CSF: Protein may be elevated. *EMG/NCS:* Absent/reduced sensory amplitudes w/normal motor studies. **Rx:** May treat w/IVIg as per GBS.

**Critical illness polyneuropathy (CIP): Si/Sx:** Acute or subacute neuropathy in the setting of sepsis/SIRS, steroids & paralytic use, multiorgan failure. 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: Primary axonal process w/early denervation. Normal CSF. **Rx:** Physical therapy.

## 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). AD inheritance. Si/sx include foot deformity (pes cavus, hammertoes); difficulties in running or walking; wasting in intrinsic foot, peroneal, & anterior tibial muscles; symmetric weakness; 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. AD but usually due to *de novo* mutations. Proximal weakness, global areflexia, enlarged peripheral nerves, & severe disability. (3) Type IV: Childhood onset of progressive weakness, inability to walk, AR. (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*: Approach should be graded based on motor CVs & pattern of inheritance. Most common identifiable subtypes include CMT1A,

CMT1X, HNPP, CMT2A & CMT1B (*Ann Neurol* 2011;69:22). **Rx:** Genetic counseling. Supportive care w/ankle-foot braces, orthopedic procedures for foot drop. Avoid neurotoxic agents.

**Hereditary neuropathy w/liability to pressure palsies (HNPP):** Recurrent episodes of isolated mononeuropathies typically affecting median, ulnar, radial, & common peroneal nerves. **Si/Sx:** Initial attack in 2nd or 3rd decade of life. Sudden onset, painless mononeuropathy, w/complete recovery w/in days or wks. **Dx:** *EMG/NCS*: Focal slowing distally & across sites of compression. *Sural nerve biopsy*: Tomacula, segmental demyelination, axonal loss. Biopsy often unnecessary. *Genetic testing*: PMP22 gene deletion on chromosome 17p11.2 in most pts. **Rx:** Activity modification to prevent nerve compression.

**Hereditary sensory & autonomic neuropathy:** Group of hereditary neuropathies in which sensory & autonomic symptoms predominate. Types I-V. **Si/S**x: Sensory loss, shooting pain, numbness in extremities & autonomic features, variable weakness. Dx: Genetic testing. **Rx:** Prevention of stress fractures, ulcers, good foot care.

**Metachromatic leukodystrophy:** AR deficiency of arylsulfatase A leading to sulfatide accumulation in brain & nerves causing progressive demyelination. Infantile, juvenile, & adult forms. **Si/Sx:** Gait disorder, hypotonia, lower limb areflexia, behavioral abnormalities, progressive dementia (more prominent in adult-onset form). **Dx:** *EMG/NCS*: Demyelination. *Nerve biopsy:* Demyelination. *MRI brain*: Confluent T2 hyperintensities in periventricular white matter. *Labs:* Increased urinary sulfatide excretion & abnormal arylsulfatase A assays in leukocytes or fibroblasts. **Rx:** Bone marrow transplantation may increase brain levels of arylsulfatase A.

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**Fabry disease:** X-linked lysosomal storage disorder causing a deficiency of α-galactosidase A leading to accumulation of ceramide trihexoside in tissue. Causes progressive vascular dz leading to renal failure, cardiac dz, strokes. **Si/Sx:** Angiokeratomas of trunk, buttocks. Distal paresthesias, lancinating pain worse w/heat, exertion, fever. Autonomic dysfunction. Women can be affected as well. **Dx:** *EMG/NCV*: 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; mutation on 14q31 causing deficiency of galactocerebroside β-galactosidase; results in extensive CNS & PNS demyelination. **Si/Sx:** Infantile form: Onset > age 1 w/rapidly progressive motor & intellectual deterioration, hypertonicity, opisthotonic posture, optic atrophy, & seizures. Adult form: Peripheral neuropathy, spasticity. **Dx:** *EMG/NCS*: Demyelination. *Sural nerve biopsy*: Segmental demyelination, tubular or crystalloid inclusions w/in Schwann cells, & multinucleated macrophages (globoid cells). **Rx:** Hematopoietic stem cell transplantation (*N Engl J Med* 1998;338:1119).

**Adrenomyeloneuropathy:** X-linked leukodystrophy causing defective β-oxidation of very long chain fatty acids (VLFCA) in peroxisomes & accumulation of VLFCA in tissues & serum. Causes adrenal insufficiency, progressive myelopathy, & peripheral neuropathy. **Si/Sx:** Presents in 2nd to 3rd decades w/progressive spastic paraparesis, distal muscle weakness, sensory loss, sphincter disturbances, spinocerebellar ataxia. Often misdiagnosed as MS. Female carriers can be symptomatic late. **Dx:** *Labs:* Elevated serum *VLCFA. EMG/NCS:* Distal axonopathy, 10% w/demyelination. *Sural nerve biopsy*: Loss of myelinated fibers; onion bulbs; lipid inclusions in Schwann cells. *MRI Brain*: White matter changes. *Genetic testing* (*Neurology* 1996;46:112). **Rx:** Dietary restriction of VLCFA w/administration of oleic & erucic acids (Lorenzo oil) though limited efficacy & side effects. Hematopoietic stem cell transplant in early dz; corticosteroids for adrenal insufficiency.

**Refsum disease (phytanic acid storage dz):** AR; defect in phytanoyl-CoA-hydroxylase causing phytanic acid accumulation in tissues. **Si/Sx:** Onset in childhood to 3rd decade of life w/night blindness or visual field constriction, ataxia/cerebellar signs, areflexia, distal sensory loss & paresthesias, distal weakness & atrophy,

enlarged nerves, pes cavus, overriding toes, short fourth metatarsals, sensorineural hearing loss, anosmia, cardiomyopathy, & ichthyosis. **Dx:** *Labs*: Elevated serum phytanic acid levels. *EMG/NCS:* Slow motor conduction velocities. Reduced or absent SNAPs. *CSF*: Protein increased from 100-700 mg/dL. *Sural nerve biopsy*: Hypertrophic neuropathy w/onion bulb formation. **Rx:** Dietary restriction of phytanic acid & its precursor phytol. Plasma exchange to lower serum phytanic acid levels in severe & rapidly worsening pts.

**Porphyric polyneuropathy:** Group of AD inherited disorders of heme biosynthesis: (1) acute intermittent porphyria, (2) hereditary coproporphyria, (3) variegate porphyria. Attacks precipitated by sulfonamides, griseofulvin, estrogens, barbiturates, phenytoin, & succinimide. **Si/Sx:** Severe, symmetric, rapidly ascending, motor > sensory neuropathy, proximal > distal, & may mimic GBS. Can also p/w autonomic dysfunction, fever, abdominal pain, psychosis. **Dx:** Increased porphobilinogen & delta-aminolevulinic acid in urine. **Rx:** IV glucose to suppress heme synthesis. Hematin 4 mg/kg qd for 3-14 days. Respiratory & cardiac support. Use of β-blockers for severe tachycardia. Vitamin B6/pyridoxine 100 mg bid. Avoid precipitants.

**Tangier disease:** Rare; AR; deficiency of HDL leads to cholesterol ester deposits in many tissues. **Si/sx:** Orange tonsils. Relapsing asymmetric multifocal mononeuropathies or symmetric polyneuropathy, or pseudosyringomyelia/bulbia. **Dx:** *Labs:* Low HDL & cholesterol; triglycerides elevated. *EMG/NCS*: Axonal degeneration & demyelination. *Sural nerve biopsy*: Segmental remyelination & loss of small axons. **Rx:** No known Rx.

**Abetalipoproteinemia (Bassen-Kornzweig syndrome):** AR; deficiency of abetalipoprotein-B causes fat malabsorption, hypocholesterolemia, & severe deficiency of vitamins A, E, & K. **Si/Sx**: Retinitis pigmentosa, spinocerebellar degeneration, steatorrhea. Progressive, large-fiber sensory neuropathy, gait ataxia, areflexia, impaired proprioception, & modest distal weakness. **Dx:** Abnormal spiky red cells (acanthocytes). **Rx:** Limit dietary fat & replete fat-soluble vitamins especially vitamin E (100 mg/kg/d).

**Familial vitamin E deficiency:** AR; mutation in the α-tocopherol transfer protein leads to low vitamin E levels. **Si/Sx:** Onset in first decade w/progressive ataxia, dysarthria, large-fiber sensory loss, pes cavus, scoliosis. **Rx:** Dietary fat restriction; vitamin E PO (100 mg/kg/d).

**Familial amyloid polyneuropathy:** Amyloid deposition in peripheral nerves due to deposition of transthyretin, apolipoprotein A1, or gelsolin. **Si/Sx:** Insidious onset in 3rd & 4th decade w/sensory impairment to temp, lancinating pains in LE,



paresthesias, autonomic dysfunction. **Dx:** *EMG/NCS*: Distal axonal neuropathy affecting sensory > motor fibers. *Sural nerve biopsy*: Amyloid deposition. *Genetic testing*.

**Neuropathy associated with mitochondrial diseases:** Myopathy a/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: **(1)** ATP synthase 6 syndromes including neuropathy, ataxia, & retinitis pigmentosa (NARP) or Leigh syndrome. **(2)** Mitochondrial neurogastrointestinal encephalopathy (MNGIE). **(3)** POLG1-related disorders including sensory ataxia neuropathy, dysarthria, ophthalmoplegia (SANDO), & CPEO.

## 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, & burning paresthesias in a stocking glove distribution. **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 & other platinum drugs, 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 (via vasculitis neuropathy). **Industrial toxins:** *N*-hexane, organophosphates, toluene. **Heavy metals:** Arsenic, lead, mercury, thallium.

**Systemic Si/Sx associated with 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.

## POLYNEUROPATHY ASSOCIATED WITH SYSTEM DISEASE

**Diabetic neuropathy:** Leading cause of peripheral polyneuropathy in developed countries. May present as (1) distal symmetric polyneuropathy (most common), (2) small-fiber polyneuropathy, (3) autonomic neuropathy, (4) lumbosacral radiculoplexopathy (diabetic amyotrophy), (5) thoracic radiculoneuropathy, (6) limb mononeuropathy, (7) multiple mononeuropathies, (8) cranial mononeuropathies; increased risk for entrapment neuropathies, such as CTS. **Dx:** Clinical history w/known or new dx of DM; 2-h GTT if fasting glucose & HgbA1c equivocal, 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, midodrine, pyridostigmine. For gastric emptying difficulties, metoclopramide. Diabetic diarrhea may be treated w/antidiarrheal agents or short courses of tetracycline or erythromycin. GU complications: urology evaluation. Frequent voiding schedule during the day.

**Uremic neuropathy:** Occurs in 60% of chronic hemodialysis pts. 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 dz or a/w underlying condition (i.e., cryoglobulinemia, vasculitic neuropathy, or AIDP a/w viral hepatitis; malabsorption syndromes in cholestatic liver dz).

**Hypothyroid neuropathy:** CTS or rarely distal symmetric polyneuropathy may occur. **Dx:** Thyroid function studies. **Rx:** Thyroid replacement.



**Neuropathy associated with 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 with 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):** Neuropathy a/w MGUS w/IgM > IgG > IgA. Onset typically in 6th decade w/subacute-chronic course. Male predominance. Most commonly a distal symmetric sensory > motor polyneuropathy. May mimic CIDP. **Si/Sx:** Distal sensory loss w/variable involvement of light touch, pinprick, vibration, & proprioception; gait ataxia, upper limb postural tremor (usually IgM cases w/demyelination), diminished reflexes, mild distal weakness. **Dx:** *Labs:* SPEP, immunofixation electrophoresis, urine studies for light chains/Bence Jones proteins, CBC, MAG ab, disialosyl-ganglioside IgM. *Imaging:* Skeletal bone survey. *Biopsy:* Bone marrow biopsy or aspirate if monoclonal spike >1.5 g/dL. Sural nerve biopsy: Nerve fiber loss, segmental demyelination, & axonal degeneration. Congo red stain for amyloid deposits. *EMG/NCS*: Demyelinating or axonal features; disproportionate prolongation of distal motor latencies in anti-MAG. *CSF:* Elevated protein in demyelinating forms or w/amyloidosis. No pleocytosis. **Rx:** Optimal Rx not established. No Rx if minor sx. If similar features to CIDP, may respond to immunomodulatory therapies. For MAG + neuropathy, consider rituximab but most pts do not respond well.

**Multiple myeloma:** Neuropathic syndromes include (1) cord & root compression from plasmacytoma or

pathologic fracture, (2) mild distal sensorimotor polyneuropathy, and (3) pure sensory neuropathy. Amyloid light chain amyloidosis may complicate neuropathy in 30%-40% cases. **Si/Sx:** Fatigue, bone pain, painful dysesthesias, smallfiber sensory sx, autonomic dysfunction, CTS. **Dx:** Labs: Serum M protein > 3 g/dL. *Skeletal survey:* Osteolytic lesions. *Bone marrow biopsy*: >10% plasma cells. *Sural nerve, rectal, or abdominal fat biopsy*: Amyloid seen in 2/3 of cases. *EMG/NCS*: Reduced sensory & motor response amplitudes. **Rx:** No improvement in neuropathy w/Rx of myeloma.

**Osteosclerotic myeloma or POEMS:** POEMS: Polyneuropathy, organomegaly, endocrinopathy, M protein, & skin changes. Motor > sensory neuropathy w/symmetric weakness & variable sensory loss. **Si/Sx:** 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:** *Labs:* IgG or IgA lambda monoclonal gammopathy, elevated serum VEGF. *EMG/NCS:* Demyelinating features & axonal loss. *CSF:* Elevated protein (>100 mg/dL). *Skeletal survey*: Sclerotic bone lesions. **Rx:** Irradiation &/or surgical excision for solitary plasmacytoma. Prednisone ± melphalan or high-dose chemo & stem cell transplant for multifocal lesions.

**Waldenström Macroglobulinemia:** Proliferation of malignant lymphocytoid cells in bone marrow, lymph nodes that secrete an IgM monoclonal spike >3 g/dL. Si/sx: Progressive fatigue, weight loss, anemia, bleeding, hyperviscosity. Typically chronic symmetric, predominantly sensory polyneuropathy, pure sensory or motor neuropathies, multiple mononeuropathies. May have associated cold agglutinin dz or



amyloidosis. **Dx:** Labs: Immunoelectrophoresis or immunofixation, anti-MAG abs in some, urine studies for evaluation of light chains/Bence Jones proteins, CBC. *Skeletal bone survey*: No lytic lesions. Bone marrow aspirate or biopsy if monoclonal spike >1.5 g/dL. *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. **Si/Sx:** Fever, malaise, weight loss, HTN. Painful sensory & motor deficits. **Dx:** *Labs:* ESR, CBC w/diff, chem7, UA, LFTs, RF, ANA, C3, C4, c-& p-ANCA, cryoglobulins, anti-Ro & La, hepatitis B, C Ag & Ab. *EMG/NCS:* Asymmetric axonal sensorimotor neuropathy. *Sural nerve biopsy*. **Rx:** High-dose prednisone 1 mg/kg/d & cyclophosphamide, methotrexate, or rituximab for induction of remission.

**Rheumatoid arthritis:** May cause compression neuropathy, distal sensory polyneuropathy, mononeuritis multiplex, or sensorimotor polyneuropathy. **Dx:** *Labs:* As above. *Sural nerve or muscle biopsy*: Necrotizing vasculitis. **Rx:** As above.

**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:* 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. Nerve biopsy: Vasculitis, perivascular inflammation in pts w/CREST. Rx: As above if vasculitic.

**Sjögren syndrome:** Sensory ganglionopathy & painful small-fiber neuropathy, transverse myelitis most common. Sensorimotor neuropathy, polyradiculoneuropathy, multiple mononeuropathies, & trigeminal sensory neuropathy seen less often. **Dx:** Clinical sicca symptoms (dry eyes, dry mouth), anti-Ro & La, Schirmer test, rose bengal testing, salivary gland biopsy. EMG/NCS: Axonal features. Sural nerve biopsy: Usually shows axonal loss; may see perivascular infiltrates or vasculitis. **Rx:** Inconsistent evidence for response to immunomodulatory therapies. Can consider trial of steroids vs. IVIg. Symptomatic rx of neuropathic pain.

**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:** Labs: Elevated serum ACE (low sensitivity). *EMG/NCS*: Axonal degeneration. *CSF*: Pleocytosis, high protein, & IgG index. *Imaging:* Chest CT (or PET if high suspicion). *Biopsy*: Lymph nodes, muscles, conjunctiva, or BAL. *Sural nerve biopsy*: May see sarcoid granulomas, evidence of angiitis. **Rx:** Corticosteroids ± other immunomodulating 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:** *Labs:* Serum $B_{12}$ <170 pg/mL; folate normal. Elevated homocysteine & methylmalonic acid. May have ab to intrinsic factor. *EMG/NCS*: Axonopathy. *Sural nerve biopsy*: Axonal degeneration. **Rx:** Cyanocobalamin 1,000 µg IM qd × 5-7 days, followed by qwk injections × 12 doses & then maintenance injections of 1,000 µg q1-3mo.

**Copper deficiency:** In setting of bariatric surgery, zinc toxicity (dietary supplementation, denture wearers), or hereditary Menkes dz. Similar to subacute combined degeneration, dysfunction of dorsal columns results 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 qd. 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% pts. 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 ganglionopathy. **Dx:** Pyridoxine levels. **Rx:** Pyridoxine 100 mg qd.

**Folate deficiency: Si/Sx:** Axonal sensory polyneuropathy w/diminished joint position, vibratory sensation, & diminished reflexes. May affect spinal cord & cause encephalopathy. **Dx:** Folic acid levels. **Rx:** Folic acid supplementation. Exclude $B_{12}$ deficiency because folate therapy w/o cobalamin may exacerbate neurological sx.

**Vitamin E deficiency:** Occurs w/chronic malabsorption. **Si/sx:** Spinocerebellar syndrome w/loss of vibratory sensation & proprioception, ataxia, areflexia, ophthalmoplegia, pigmentary retinopathy. **Dx:** Labs: Vitamin A & D levels, amylase, LFTs, blood smear to look for acanthocytes. *EMG/NCS*: Low-amplitude or absent SNAPs, *72-h fecal fat study*. **Rx:** Vitamin E supplementation.

## NEUROPATHIES ASSOCIATED WITH INFECTIOUS DISEASE

(See chapter *Neurologic Infectious Diseases*)

**Peripheral neuropathies associated with HIV: Distal symmetric polyneuropathy**: EMG/NCS: Borderline to low-amplitude sensory & motor responses. Sural nerve biopsy: Loss of myelinated & unmyelinated fibers. **Lumbosacral polyradiculoneuropathy:** (1) CMV polyradiculoneuropathy: Uncommon but devastating. Si/Sx: Rapidly progressive, flaccid paraparesis, sphincter dysfunction, perineal sensory loss, & lower limb areflexia. Dx:

*EMG/NCS*: Low-amplitude CMAPs, prolonged or absent F wave latencies, reduced or absent SNAPs. *CSF*: 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 in HIV include 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. Dx: Test for CMV & if negative, nerve biopsy to evaluate for vasculitis. **AIDP:** Presents during seroconversion & early stages of dz. Si/Sx: 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 a/w HIV. CSF: Pleocytosis. Rx: Plasmapheresis or IVIg. Cranial neuropathies: May occur early in HIV, particularly facial nerve.

**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 more common. May present as segmental recurrence or disseminated dz. **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×/day × 10 days.

**Hepatitis:** Hepatitis B: A/w GBS, mononeuritis multiplex, necrotizing vasculitis. Hepatitis C: A/w cryoglobulinemia, vasculitic neuropathy, mononeuritis multiplex.

**HTLV-1:** Typically affects spinal cord but pts may have sensorimotor polyneuropathy 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. **Si/Sx:** Classified into tuberculoid & lepromatous forms based on host 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. *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. **Dx:** *EMG/NCS*: Reduced amplitudes of CMAPs & SNAPs w/focal conduction slowing. *Skin or nerve biopsy*: Intense granulomatous inflammation in tuberculoid dz; multiple acid-fast organisms, demyelination, & nerve fiber loss in lepromatous dz. **Rx**: *Tuberculoid:* Dapsone 100 mg qd + rifampin 600 mg qd for >6 mo, followed by



dapsone monotherapy for 3-5 yr. *Lepromatous*: Dapsone 100 mg qd + rifampin 600 mg qd + clofazimine 50 mg qd for minimum of 2 yr or until skin smear neg.

**Diphtheria:** Caused by *Corynebacterium diphtheriae*. Neurological complications in 15% & pts. **Si/Sx:** 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:** *CSF*: Normal or elevated protein (>100 mg/dL). *EMG/NCS*: Segmental demyelination w/sparing of axons. **Rx:** Antitoxin w/in 48 h, respiratory support if necessary. Recovery over several wks & 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 (often CN VII), radiculoneuropathy, lymphocytic meningitis. Mo-yrs after infection, late neurological syndrome w/sensory polyradiculoneuropathy. **Dx:** *Labs:* Serum Lyme Abs (ELISA & Western blot). *CSF*: Lymphocytic pleocytosis & mildly elevated protein; Lyme PCR. *EMG/NCS:* Widespread axonal, sensory > motor involvement in polyradiculoneuropathy. **Rx:** If CSF normal, oral doxycycline or ampicillin. If CSF abnormal, ceftriaxone 2 g IV qd for 2-4 wk w/improvement over 3-6 mo.

**American trypanosomiasis (Chagas disease):** Caused by protozoan *Trypanosoma cruzi*. **Si/Sx:** Three phases: (1) Acute: Asymptomatic or general malaise, lymphadenopathy, GI sx. (2) Second phase: At 3 mo-yr. Asymptomatic & serologies for trypanosoma become +. (3) Third phase: Begins 10-20 yr after infection. GI, cardiac, & neurological sx. 10% develop predominantly sensory neuropathy. **Dx:** *Labs:* Trypanosomiasis serologies. *EMG/NCS*: Low-amplitude sensory & motor responses, reduced NCVs, distal neurogenic motor unit potential changes. **Rx:** Itraconazole & allopurinol for underlying dz; little data to support improvement in neuropathy.

# Radiculopathy and Plexopathy

Adam Chen

David Chad

## RADICULOPATHY

### CERVICAL RADICULOPATHY

**Definition:** Caused by spinal nerve root compression or irritation. Structural causes most common: Spondylosis (e.g., degenerative arthritis, osteophyte) or disc herniation. Incidence: C6, C7 > C8 >> C5 (Amato AA, Russell JA. *Neuromuscular Disorders*. McGraw Hill, 2008). Nonstructural causes less common: Infection (HSV, VZV, Lyme), immune-mediated neuropathy (focal demyelination in CIDP), neoplasia (leptomeningeal infiltration), sarcoidosis (granulomatous involvement).

**Si/sx:** Numbness & paresthesias in fingers in dermatomal distribution; lancinating or deep aching pain radiating into scapula, shoulder/arm; weakness depending on cervical roots involved. H/o trauma or exertion in only 15% (*Brain* 1994;117:325-335).

**Exam:** Weakness and/or sensory loss in upper extremities depending on affected roots (see chart below). Provocative maneuvers: Spurling (passive cervical extension w/lateral flexion toward the affected side), vertical traction (*N Engl J Med* 2005;353:392-399). Be careful in performing maneuvers if spinal instability, trauma, RA.

**Dx:** MRI C-spine. EMG/NCS: Most useful >3 wk after symptom onset, less informative in first 2-3 wk. LP: Consider when investigating nonstructural radiculopathy.

- **NCS:** Sensory responses are normal; motor responses typically normal except if severe axon loss (e.g., ulnar motor responses may be reduced in severe C8 radiculopathy). NCS useful to exclude other dx (e.g., mononeuropathy, brachial plexopathy, polyneuropathy).
- **EMG:** Day 1: Only reduced recruitment. Weeks 2-3: Fibrillation potentials & positive sharp waves. Months 3-4: Abnormal motor unit potentials (i.e., long duration, high amplitude). Test 2 muscles supplied by same root but different peripheral nerves & 1 paraspinal muscle (to confirm preganglionic site of lesion). Paraspinals may be normal due to multisegmental innervation (Preston DC, Shapiro BE. *Electromyography and Neuromuscular Disorders.* Elsevier, 2013).



**Rx:** Often self-limited if structural cause (*Brain* 1994;117:325-335). Urgent surgical evaluation if C-spine instability, progressive root deficit, myelopathy, or intractable pain (*N Engl J Med* 2005;353:392-399). Otherwise conservative Rx 3-6 wk (e.g., ice/heating pad, muscle relaxants, NSAIDs, short course [10 days] of oral steroids [*Phys Med Rehabil Clin N Am* 2011;22:127-137], gentle massage, stretching, PT). Consider cervical epidural steroid injections. If conservative Rx fails, consider surgery (pain responds well; myelopathy can be arrested; long-term benefit for radicular weakness likely but not clearly established) (*Spine* 2002;27:736-747).

### LUMBOSACRAL RADICULOPATHY

**Definition:** Caused by nerve root compression or irritation. Structural causes most common: Spondylosis (e.g., foraminal/spinal stenosis, ligamentous hypertrophy) or disc herniation. Incidence: L5, S1 > L4 > L3 (*Neurol Clin* 2007;25:387-405). Nonstructural causes less common: Diabetes (see Diabetic Amyotrophy), infection (Lyme, HSV, VZV, CMV, *Mycoplasma*), immune-mediated neuropathy (AIDP, CIDP), neoplasia (leptomeningeal infiltration), inflammatory processes (sarcoidosis, vasculitis).

**Si/sx:** Lancinating or deep aching radiating pain, often worse w/standing. Weakness, numbness in distribution of

affected root. *L3-L4*: Back pain, radiates to anterior thigh & medial calf. *L5*: Back pain, radiates to posterior thigh & lateral calf. *S1*: Buttock pain, radiates to posterior thigh/calf & heel (Preston & Shapiro 2013).

**Exam:** Weakness and/or sensory loss in lower extremities depending on affected nerves (see chart below). Rectal tone to evaluate sphincter tone if concern for cauda equina syndrome. Straight leg raise: Good sensitivity, low specificity for disc herniation (*Phys Med Rehabil Clin N Am* 2011;22:7-40).

**Dx:** MRI L-/S-spine. EMG/NCS: See Cervical Radiculopathy for findings. LP: Consider if nonstructural cause.

- **H-reflex**: Assess afferent/efferent S1 fibers (akin to ankle reflex). Abnormal in S1 radiculopathy.

**Rx:** Often self-limited (*Spine* 1983;8:131-140). Urgent surgical evaluation if rapidly progressive motor deficits, cauda equina syndrome, or intractable pain. Otherwise, conservative rx initially (e.g., ice/heating pad, NSAIDs, muscle relaxants, massage, PT, TENS). May consider epidural steroid injections. Surgery if conservative rx fails (*Phys Med Rehabil Clin N Am* 2011;22:161-177).

| Common Radiculopathies | | | | |
|---|---|---|---|---|
| **Root** | **Sensory loss** | **Weakness** | **Reflexes** | **Disc** |
| **C5** | Shoulder, lateral proximal arm | Shoulder abduction & external rotation; elbow flexion | Biceps, brachioradialis | C4-C5 |
| **C6** | First digit, lateral forearm, & arm | Shoulder abduction & external rotation; elbow flexion; forearm pronation | Biceps, brachioradialis | C5-C6 |
| **C7** | Second & third digits | Elbow extension; forearm pronation; finger, wrist flexion & extension | Triceps | C6-C7 |
| **C8** | Medial forearm & hand, fourth & fifth digits | Intrinsic hand muscles (ulnar, median); finger & wrist extension; distal phalanges extension | Finger flexor | C7-T1 |
| **L3/L4** | Knee, medial leg | Hip flexion & adduction; knee extension | Patellar | L3-L4 |
| **L5** | Lateral leg, dorsum of foot, large toe | Hip abduction; knee flexion; ankle dorsiflexion, eversion, & inversion; large toe dorsiflexion | None | L4-L5 |
| **S1** | Lateral foot, small toe, sole of foot | Hip extension; knee flexion; ankle plantar flexion; toe flexion | Achilles | L5-S1 |

# PLEXOPATHY

## BRACHIAL PLEXOPATHY

**Definition:** Injury/irritation of brachial plexus most often 2/2 shoulder trauma (e.g., stretch injury, fracture/dislocation, rarely in complex orthopedic surgical procedures [reverse shoulder arthroscopy]). Considerable number idiopathic or presumed immune mediated. May also be 2/2 radiation (often upper trunk, delayed for months-years), malignancy (often lower trunk, very painful, associated w/Horner syndrome & arm edema), infection. Rarely genetic or 2/2 thoracic outlet syndrome.

**Dx:** EMG/NCS: Reduced sensory & motor responses, active/chronic denervation in multiple myotomes, myokymia if radiation plexopathy, paraspinal muscles typically normal (Preston & Shapiro 2013). MRI C-spine & brachial plexus. Plain films if h/o trauma.

### Neuralgic amyotrophy (Parsonage-Turner syndrome)

*Si/sx*: Acute, severe shoulder/upper limb pain radiating to arm, neck, & back (often nocturnal). Weakness & prominent atrophy of shoulder girdle/scapular muscles (often as pain subsides). Often affects upper trunk. Presentation can vary greatly (e.g., diaphragm hemiparesis 2/2 isolated phrenic nerve palsy, winged scapula 2/2 long thoracic nerve palsy, isolated mononeuropathies of anterior interosseus, axillary, musculocutaneous, suprascapular, spinal accessory nerves). B/l involvement in 30% (*Nat Rev Neurol* 2011;7:315-322).

*Cause*: Majority are idiopathic. Often antecedent event (e.g., viral illness, trauma, strenuous exercise, immunization, childbirth, hospitalization). Rarely occurs in context of systemic autoimmune disorder (e.g., SLE). Familial cases described (hereditary neuralgic amyotrophy 2/2 SEPT9 mutation) (*J Med Genet* 2010;47:601-607).

*Rx*: Conservative management, PT. Consider trial of oral steroids (may ease pain in some) (*Cochrane Database Syst Rev* 2009;(3):CD006976). Natural history: Improvement in motor function in >70%; return of function may take up to 3 yr if distal (i.e., hand intrinsic muscles) involvement.

**Erb-Duchenne palsy (upper trunk plexopathy)**

*Si/sx*: Weakness, atrophy of deltoid, biceps, brachioradialis, brachialis. Arm internally rotated & adducted ("waiter's tip" position). Sensation often normal but may involve lateral surface of upper arm. Diminished biceps or brachioradialis reflexes.

*Cause*: Lesions of C5, C6 roots or upper trunk. Often 2/2 trauma separating head & shoulder, traction on shoulder, or birth injury (i.e., shoulder dystocia).

*Rx*: Conservative management, PT.



**Dejerine-Klumpke palsy (lower trunk plexopathy)**

*Si/sx*: Weakness of wrist/finger flexion & intrinsic hand muscles, claw hand. Sensation may be lost on medial forearm & ulnar aspect of hand. Ipsilateral Horner syndrome may be present.

*Cause*: Lesions of C8, T1 roots, or lower trunk. Usually 2/2 trauma (e.g., arm traction). Associated w/lung cancer (Pancoast tumor) or other mass lesions.

*Rx*: Conservative management, PT.

**Thoracic outlet syndrome**

*Si/sx*: Lower trunk or medial cord is affected. Recurrent pain, paresthesias, numbness in ulnar border of hand & medial forearm. Motor & reflex exam similar to lower plexus lesion. Vascular sx: Coldness, cyanosis, pallor of hand, supra-/infraclavicular bruit. Provoked by elevation or sustained use of arm/hand.

*Cause*: True neurogenic TOS is very rare. Compression of neurovascular bundle in space between 1st rib & clavicle by a ligamentous band in setting of cervical rib or enlarged C7 transverse process. Rarely associated w/muscle anomaly (e.g., scalene hypertrophy) (*Muscle Nerve* 2012;45:780-795).

*Rx*: Conservative management or surgery in refractory cases.

## LUMBOSACRAL PLEXOPATHY

**Definition:** 2/2 injury or irritation of lumbosacral plexus. Structural causes: Tumor infiltration, retroperitoneal hematoma (in anticoagulated pts), trauma (uncommon 2/2 deep protected location of plexus), pregnancy (rare, large fetal head in narrow pelvic brim can compress lumbosacral trunk & cause reversible foot drop). Nonstructural causes: Diabetes (most common), idiopathic (presumed immune mediated, common), radiation (often delayed months-years), malignancy (extension or meningeal spread), infection (VZV, Lyme, HSV2), inflammatory disorders (SLE, Sjögren, sarcoidosis).

**Dx:** EMG/NCS: Reduced sensory & motor responses, active & chronic denervation in multiple lumbosacral myotomes, paraspinal muscles typically normal, myokymia if radiation plexopathy (Preston & Shapiro 2013). MRI L-spine & L-/S-plexus.

### Diabetic amyotrophy (diabetic polyradiculoplexopathy)

*Si/sx*: Acute, severe hip pain followed by weakness of iliopsoas, quadriceps, thigh adductors. Proximal & distal sensory loss. Attenuated or absent patellar reflex. Typically asymmetric. Autonomic symptoms common. Coexisting polyneuropathy common.

*Cause*: Possibly immune-mediated "microvasculitis" *(Neurology* 1999;53:2113-2221). Usually in recently diagnosed or well-controlled type 2 diabetes. Associated weight loss common.



*Rx*: PT, pain control. Natural history is for improvement in motor & sensory function to occur over months-years. No randomized studies to show proven benefit from immunotherapy (*Cochrane Database Syst Rev* 2013;(12):CD009722).

### Idiopathic lumbosacral plexopathy

*Si/sx*: Similar to diabetic amyotrophy (see above). Often no coexisting polyneuropathy.

*Cause*: Possibly immune-mediated “microvasculitis.”

*Rx*: PT, pain control. Natural history is for improvement to occur over months-years. No randomized studies to show proven benefit from immunotherapy.

# Neuromuscular Junction Disorders

Alexis Lizarraga

James Berry

**Neuromuscular junction (NMJ):** Composed of presynaptic, synaptic, & postsynaptic regions. Dzs affect one of these three → failure of transmission across NMJ. Fluctuating symptoms are 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

**Epidemiology:** 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.

**Pathophysiology:** 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. Abnormalities at the level of the thymus (intrathymic autosensitization against AChR) &/or peripheral immunoregulatory system (antigenic mimicry) lead to anti-AChR ab, disaggregation of AChR (anti-MuSK/anti-LRP4 ab), & simplification of nl, highly infolded NMJ surface. This loss of functional AChRs → decrease in end-plate potential amplitudes → muscle fiber not depolarized to threshold → NM transmission failure. Muscle-specific tyrosine kinase (MuSK) mediates postsynaptic clustering of AChR, maintains presynaptic structures (*Lancet Neurol* 2009;8:475-490).

**Presentation:** *Pt history*: Variable or fatigable wkns, 20% p/w pharyngeal wkns or hoarse voice, diplopia (blurred vision in subtle cases), orthopnea 2/2 diaphragmatic wkns. *Neurologic exam*: Nl pupillary reflexes, + ptosis (usu asymmetric & fatigues w/upgaze), asymmetric ophthalmoparesis, hypercontracted frontalis to maintain eye opening, Cogan lid twitch, “myasthenic snarl,” transverse pucker. Wkns of jaw closure, bulbar muscles, palate, axial & prox limbs, neck flex > ext. Tachypnea & shallow respirations, intact sensation, variably depressed reflexes.

**Other subtypes: (1)** *Anti-MuSK*: Young F w/prominent oculobulbar, neck, shoulder, & ventilatory muscle wkns, frequent crises, & typically not assoc w/thymoma, +/- triple furrowing of tongue. **(2)** *Ocular*: Sx limited to ocular wkns for >2 yr → 90% do not generalize; electrodiagnostic challenge; mono-Rx w/AChEIs may be sufficient; immunosuppression may have a role. **(3)** *Anti-LRP4 (low-density lipoprotein receptorrelated protein):* Effects on AChR clustering & agrin-LRP4 interaction could lead to the identification of a new MG subtype. Pts appear to respond to immune suppression. Anti-agrin also under investigation (*Arch Neurology* 2012;69:445-451; *Neuromuscul Disord* 2013;23:568-570). **(4)** Double *Ab negative (AChR & MuSK)*: Classic presentation, neg ab tests.

**Ddx:** Motor neuron dz (MND), Lambert-Eaton myasthenic syndrome (LEMS), GBS, diphtheria, tick paralysis, thyroid ophthalmopathy, mitochondrial d/os, CMS, botulism, organophosphate & other toxins, inflammatory myopathy, skull-based tumors, cholinergic crisis, oculopharyngeal muscular dystrophy, AIDP.

**Dx: (1)** *Ab testing.* **(1a)** *AChR abs*: Binding Ab: Se 80%-85% in generalized MG, Se 55% in ocular MG. Blocking Ab: + in isolation in ˜1% of MG. Modulating ab: + in 3%-4%

MG in isolation, ↑ freq w/thymoma. At presentation, AChR Ab can be negative and then become detectable later in the course of dz. Ab level does not indicate severity. **(1b)** Anti-muscle-specific tyrosine kinase abs (*Anti-MuSK*): Present in 40%-50% of MG pts w/o AChR Abs. **(1c)** *Striated muscle ab*: Se 75%-95% for MG w/thymoma; often present in older MG pts w/o thymoma; utility limited by poor Sp. **(1d)** *Anti-LRP4:* 7-33% of double seronegative (MuSK/AChR) pts are +. Not yet commercially available. **(2)** *EMG/NCS*: *Repetitive nerve stimulation*: Low rates of rep stim (2-5 Hz) deplete ACh → decrement >10% (Se 30%-98% for generalized MG & 10%-40% for ocular MG). *SFEMG*: + blocking &/or increased jitter (variation in contraction time b/n muscle fibers) (Se 80%-99%) (*Muscle Nerve* 1992;15:720-724). **(3)** *Bedside evaluation.* **(3a)** *Tensilon test (edrophonium, an AChEI):* IV test dose 2 mg, if no response after 30 s, administer 2 mg at a time up to 10 mg every 10-15 s. Follow clinically observable deficit & only accept unequivocal improvement as (+). Abort if side effects. Onset 30 s, lasts 5-10 min. *Side effects*: Salivation, sweating, nausea, cramping, fasciculations, bradycardia, ↓ BP, & resp distress. AMBU bag/code cart & atropine at bedside, telemetry. *Utility*: Se ~90%. **(3b)** *Ice test*: Put ice pack on closed eye × 3 min—ptosis improves by at least 2 mm (Se 80%-97% in pts w/ptosis, use in pts w/contraindication to Tensilon test) (*Neuromuscul Disord* 2006;16:459-467; *Muscle Nerve* 2013;48:902-904).

**Additional testing:** TFTs, Chest CT, or MRI to eval thymoma.

**Prognosis:** Prognosis varies & depends on underlying dz distribution & severity. 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. 15%-40% of pts w/an isolated ocular presentation will not develop generalized MG. Of those that do, transition to generalized MG is usually within 2 yr (*Ann Neurol* 1983;14:516-519).

## TREATMENT: ACUTE EXACERBATIONS/CRISIS

**Definitions:** *Myasthenic crisis*—Acute flare of wkns generally w/respiratory failure, often requiring intubation & ICU admission or delay of extubation ≥24 h after surgery.

**Causes:** (1) Dz progression, (2) Infxn/stressor, (3) withdrawal/↓ in MG Rx, (4) contraindicated medication.

**Plasma exchange (PE):** Requires large-bore catheter & performed qod. *Potential side effects:* Line infection, cardiovascular instability, pneumothorax, electrolyte shifts, bleeding.

**IVIg:** 2 g/kg in divided doses over 2-5 days. *Potential side effects:* Aseptic meningitis, flulike symptoms (n/v, myalgias, fevers, chills), ARF, CHF exacerbation, allergic Rxn (test IgA levels prior to r/o IgA deficiency), headache common, very rare thrombotic events (MI/stroke).

**Pyridostigmine:** In intubated pts, might avoid due to increase in secretions. If not intubated, initial adult dose 15-30 mg tid-qid; gradually titrate as necessary (max 360 mg daily). Onset ~30-60 min—pts w/dysphagia can take 30 min before meal.

**Steroids:** In intubated pts, can start IV methylprednisolone together w/PE or IVIg at 500-1,000 mg/day for 5 days followed by 0.8 mg/kg IV daily until able to take PO steroids. If not intubated, initiate prednisone at a dose of 1-1.5 mg/kg/day × 2-4 wk (max 100 mg/day), then taper by 5-10 mg q2-4 wk to lowest tolerated dose. May worsen exacerbation acutely; thus, should use caution & consider hospitalization for monitoring and/or starting PE or IVIg prior to initiating steroids during an exacerbation. Onset of action ≥2 wk.

**Supportive care:** Aspiration precautions, temporary NPO or NG tube feeding, close resp monitoring w/NIF & VC, ventilatory support if necessary.

**Differential:** Cholinergic crisis (salivation, lacrimation, diarrhea, bradycardia). Rx: hold or ↓ AChE meds.

## CHRONIC TREATMENT

### Principles

Time to benefit: (1) Immediate = cholinesterase inhibitors. (2) Very rapid (days) = plasma exchange, IVIg. (3) Short term (2-6 wk) = corticosteroids. (4) Long term (2-12 mo) = mycophenolate mofetil, azathioprine, rituximab, thymectomy.

*Prior to initiation of immunosuppression*: Negative PPD, baseline CBC w/diff, CMP, HbA1c, bone density prior to prednisone.

**Nonimmune modulatory:** Pyridostigmine. Dosing adjusted PRN. Ocular symptoms: Prism glasses.



**Immune modulatory:** Steroids, steroid-sparing agents, & thymectomy (Amato AA, Russell JA. *Neuromuscular Disorders*. McGraw Hill, 2008:457-528).

- **Steroids:** Initiate at a dose of 1-1.5 mg/kg/d × 2-4 wk (max 100 mg/day). Once in remission or improvement plateaus, ↓ dose &/or administration interval (e.g., decrease by 5-10 mg q2-4 wk) to lowest tolerated. *Side effects:* Cataracts, HTN, osteoporosis, immune suppression, ↑ wt, mood d/o, psychosis, skin sensitivity to sun, glucose intolerance/DM, peptic ulcers, avascular necrosis, steroid myopathy, growth stunting in children.
- **Thymectomy:** Indicated if thymoma on CT chest (~15% cases). May be done in absence of thymoma in generalized MG, AChR ab+, & onset <50 yo (randomized controlled clinical trial ongoing [MGTX]).
- **Steroid-sparing immune therapies.**

**Steroid-Sparing Immune Therapies**

| Medication | Mechanism | Efficacy/Use | Dosing | Side Effects |
|---|---|---|---|---|
| Azathioprine (Imuran) | Purine antimetabolite; inhibits T-& B-cell proliferation | Effective in >70% Onset takes 6-12 mo. Use w/steroids or to ↓ steroid dose. | Initiate 50 mg/day PO; ↑ weekly by 50 mg/day to 2-3 mg/kg/day | Hepatotoxicity, leukopenia, pancreatitis (rare) Idiosyncratic rxn (~10%): fever, n/v, rash. Can check TPMT activity prior to initiation |
| Cyclosporine (Sandimmune, Neoral) | Calcineurin inhibitor—↓ T-cell & IL-2 production | Used if intolerant/refractory to azathioprine or prednisone | 3-4 mg/kg/day PO divided bid; max 6 mg/kg/day | Renal failure, hirsutism, tremor, gum hyperplasia, HTN |
| Cyclophosphamide (Cytoxan) | Alkylating agent | Rarely used; only for severe, refractory, | Monthly IV pulses of 500 $mg/m^2$ | Bladder ca, ↓ bone marrow, alopecia, hemorrhagic cystitis, |

| | | | | |
|---|---|---|---|---|
| | | generalized MG | | infertility, GI upset |
| Mycophenolate mofetil (CellCept) | Purine synthesis inhibitor | RCTs revealed no sig difference b/n prednisone vs. prednisone + mycophenolate | 1,000 mg PO bid | Diarrhea, peripheral edema, nausea, fever, leukopenia |
| Rituximab (Rituxan) | Chimeric monoclonal antibody against CD-20 lymphocytes | • Case reports indicate benefit in refractory AChR (+) or MuSK (+) MG.<br>• NINDS NeuroNEXT trial ongoing | Dosing not standardized: 1. 1 g IV q2wk × 2 then 1 g prn worsening sx 2. 375 mg/m2 qwk × 4-6 wk, then qwk-qmo × 2-6 mo | Infusion reactions including fever, chills, hypotension, dyspnea. PML reported in non-MG pts. |
| Tacrolimus (FK506, Prograf) | Calcineurin inhibitor | Less evidence; early reports encouraging | 3-5 mg/day | ARF, hyperglycemia, PRES, hypomagnesemia, GI upset, paresthesias |

**Medications exacerbating MG: (1)** *Absolutely contraindicated:* Penicillamine, botox telithromycin, IFN-α. **(2)** *Relatively contraindicated: Antibiotics:* fluoroquinolones (ciprofloxacin, levofloxacin, etc.), macrolides (erythromycin, azithromycin, etc.), aminoglycosides (gentamicin, tobramycin, etc.), quinine, *class IA antiarrhythmics* (procainamide, quinidine, lidocaine, etc.), iodinated contrast dye, magnesium, neuromuscular blocking agents. **(3)** *Use w/caution:* Ca channel & β-blockers, Li, statins, steroids.

## 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 >> N-type voltage-gated channel on presynaptic membrane → low Ca entry & fewer vesicles released into synapse.

**Si/sx: (1)** Fatigable wkns; fatigue >> wkns. **(2)** Proximal LE followed by UE wkns (UE wkns in 80% at some point in dz). **(3)** Muscle aching/stiffness after exercise. **(4)** Heat → ↑ wkns. **(5)** Ocular sx, dysarthria, dysphagia (less common than in MG). **(6)** Autonomic sx: Xerostomia, xerophthalmia, blurred vision, constipation, urinary hesitancy, impotence.

**Exam:** Sluggish pupillary rxn. Ptosis may improve w/upgaze. Wkns worst on initiation of movement, then potentiates, but may fatigue w/prolonged effort. DTRs: ↓ initially but ↑ following brief sustained effort.

**Dx: (1)** *Serum*: Abs for P/Q-type voltage-gated Ca channels in 85%-90%. Abs for N-type Ca channel in 74% of paraneoplastic & 40% of nonparaneoplastic pts. AChR ab in 13%. **(2)** *Electrodiagnostics*: CMAP amplitudes

diffusely reduced, decrementing CMAP w/1-5 Hz RNS, amplitude facilitation w/10 s exercise or fast rep stim. *EMG*: Low amplitude, short motor units that may increase w/sustained effort. *SFEMG*: Jitter ± blocking in all/most muscles (not patchy like MG) (*N Engl J Med* 1995;332:1467-1474).

**Rx: (1)** *Resection of tumor*: Can be curative; if no known tumor → close surveillance. **(2)** *Symptomatic Rx*: **(2a)** *AChEI* (see MG Rx for details); response variable. **(2b)** *Guanidine*: ↑s ACh released but side effects limit use—myelosuppression, renal & hepatotoxicity, GI discomfort. **(2c)** 4-DAP: Use limited by CNS toxicity → sz, confusion. **(2d)** 3,4 DAP: Not FDA approved; clinical trials ongoing (Jacobus & Catalyst Pharmaceuticals); available on compassionate use basis. **(3)** *Plasmapheresis*: ↓s sx w/transient effect peaking at 2 wk. **(4)** *IVIg*: Studied only in small studies suggesting transient effect. **(5)** *Other immune-modulating therapy* may be helpful (see MG section).

## CONGENITAL MYASTHENIC SYNDROMES

**Epidemiology:** Rare group of syndromes 2/2 genetic defects in NMJ structure & fxn. Typically in neonates-children, but can occur in adolescents/young adults. Transient neonatal myasthenia gravis is not CMS; rather, it 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 (immune therapy not indicated).

**Clinical features:** *Neonates-children*: Reduced fetal movements, hypotonia, underdeveloped muscles, arthrogryposis, 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.

**Ddx:** Infants-young adults w/MG, seroneg MG, myopathy, peripheral neuropathy, MND.

**Dx:** Ab testing always neg in CMS; next-generation (whole exome) sequencing can be used to screen for congenital myasthenic syndromes.

**Rx:** Symptomatic Rx depends on the entity (see table). Some respond to AChEIs, albuterol, ephedrine, 3,4-DAP. No role for immunotherapy; genetic counseling advisable (*Curr Opin Neurol* 2013;26:561-568).



| Syndrome | Pathophysiology | Notes |
|---|---|---|
| | **Presynaptic** | |
| **Choline acetyltransferase deficiency (ChAT def)** | Due to *CHAT* gene mutation; AR inheritance | In severe cases in infants, crises of wkns, ptosis, dysphagia, & hypoventilation. Sx lessen in teens, adults w/mild sx. FH of “sudden infant death.” Decremental response to rep stim in proximal muscles. Partial response to AChEIs |
| **Paucity of synaptic vesicles** | Unknown | Infants: hypotonia & poor feeding. Children: fatigable ptosis, limb/bulbar wkns. 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** | | |
| **End-plate acetylcholinesterase (AChE) deficiency** | ↓ AChE → ↑ ACh w/in synapse → EPP prolonged; desensitization & loss of AChR | *COLQ* mutation, encoding AChE anchoring protein. Infants-young children w/wkns, pupillary involvement, & myopathy. Decrement w/slow or fast rep stim. Afterdischarges may be seen. Lack of response to AChEIs. |
| **Postsynaptic** | | |
| **Reduced AChR expression: AChR subunit mutations** | ↓ Density & abnl distribution of AChR | Most common cause of CMS; AR inheritance. Resembles seroneg MG; ± hypotonia, arthrogryposis, feeding difficulties. CMAP decrement w/fast > slow rep stim. β-subunit mutation: common, mild form. γ-subunit mutation: Escobar syndrome. Improves w/AChEIs |
| **Rapsyn mutations** | Rapsyn deficiency → decreased AChR density & distribution | Homozygotes present as neonates; may p/w arthrogryposis, arched palate, & fixed wkns. Mild cases subclinical until late childhood. ± mild ptosis/ophthalmoparesis. Improve w/AChEIs |
| **Dok-7 "downstream kinase" mutations** | Dok-7—protein that activates MuSK; involved in AChR aggregation | Clinically identical to AChR def. Onset <age 5; ± reduced fetal mvmts, then static/slowly progressive wkns. Decrement w/slow rep stim. Response to AChEIs variable; ephedrine produces mild benefit. |
| **AChR kinetic abnormality: slow channel (SCCMS)** | Gain-of-function mutation → increased duration of channel opening. AD w/var penetrance | Fatigable & progressive wkns. Severe cases present in infancy, mild as adults. Neck & distal arm wkns predominates. Decrement w/slow rep stim. Afterdischarges may be seen. Rx: quinidine & fluoxetine; w/o Rx wkns worsens. No response to AChEIs (may worsen). |
| **Fast channel (FCCMS)** | Loss-of-function mutation decreasing time of channel opening | Presents in infancy or childhood w/ptosis, ophthalmoparesis, dysphagia, dysarthria, & exertional wkns; static/slowly progressive. Mild decrement w/slow rep stim. Rx: AChEI & 3,4-DAP to stimulate ACh release |

## TOXINS THAT CAUSE NMJ DYSFUNCTION

**Presynaptic:** Botulinum toxin, corticosteroids, Mg, aminoglycosides, calcium channel blockers, aminopyridines, hemicholinium-3; tetrodotoxin, saxitoxin, ciguatoxin, venoms (Mamba, Australian Tiger snake, Pandinus 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, wkns of extremities, SOB, xerostomia, blurred vision, constipation.

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*In infants*: Variable sx (mild to sudden death); listless, ↓ spontaneous mvmts, ↓ suck, hypotonia ("floppy baby"), ↓ DTRs. Drooling, CN wkns worrisome; ~50% → ventilation. Wks to recovery.

**Exam:** Ptosis, ↓ gag, dysphagia, dysarthria, facial diplegia, tongue wkns, ± 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, ± MUAPs 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*: ↓ 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*: Foodborne & infantile botulism (controversial). **(5)** *Wound debridement*: For wound botulism. **(6)** If abx initiated, first give antitoxin to avoid sx worsening as bacteria lyse. **(7)** Foodborne illness: identify others exposed & test food.

## TICK PARALYSIS

**Epid:** Children > adults (3:1). M > F. Peak incidence in spring & summer.

**Pathophysiology:** Varies by species; *Ixodes holocyclus* (Australia) ↓s ACh release presynaptically. Other tics cause NMJ dysfunction or acute neuropathy.

**Si/sx:** Ascending wkns over hours-days; ophthalmoplegia, facial wkns, dysarthria, dysphagia, resp failure, sensory sx (pain, numbness, paresthesias, sensory ataxia); ↓ DTRs.

**Ddx:** MG, GBS, diphtheria, botulism.

**Dx:** Serology & CSF nl. EMG/NCS: possible mild sensory neuropathy. CMAP amplitudes & motor conduction velocities mildly ↓s in paretic limbs. Pseudofacilitation on rep stim. EMG: abnl recruitment.

**Rx:** Remove tick; supportive Rx for resp wkns; prognosis favorable if pt supported.

# Myopathy

Laura Rosow

Anthony Amato

**Introduction:** Can be *inherited* or *acquired*. Inherited myopathies can present in infancy ("congenital") or well into adulthood. Acquired myopathies usually present in adulthood & may be due to systemic disease (e.g., hypothyroidism), inflammatory, toxic, or metabolic etiologies.

## Approach to myopathy

*History:* **(1)** Onset of weakness (progression over days/months/yr). **(2)** Pattern of weakness: *Proximal* (trouble going up staircase, washing hair), *distal* (frequent tripping, trouble opening jars), or other (facioscapulohumeral). **(3)** Associated si/sx (muscle pain, dysphagia, dyspnea, diplopia, myotonia/paramyotonia, atrophy or hypertrophy, scapular winging). **(4)** Toxin exposures (statin, steroids). **(5)** Signs of systemic disease (weight loss, arthralgias, rash). **(6)** Family history.

*Exam:* **(1)** General—skin changes/rash, edema, cachexia. **(2)** Pulmonary: if tachypneic, check NIF & FVC (consider intubation for NIF < 20 or FVC < 15 mL/kg). **(3)** Neuro: *Cranial nerves*—extraocular mvts, facial strength, tongue strength. *Motor*—axial vs. appendicular, proximal vs. distal weakness. Watch for "breakaway" (initial good strength w/sudden give), which may be due to pain, fatigue, ↓ effort w/o actual weakness. *Reflexes*—if increased, consider alternative/superimposed UMN etiology.

*Diagnostic testing*: Serum CK, EMG/NCS, muscle biopsy.

## MUSCULAR DYSTROPHIES

### DUCHENNE MUSCULAR DYSTROPHY (DMD)

**Genetics:** Dystrophin gene mutation, Xp21.2 (X-linked recessive). **Epid:** Incidence: 1 in 3,500 male births. Prevalence: 1 in 18,000 males. Female carriers may have mild sx because of lyonization (skewed X-inactivation).

**Si/Sx:** Usually nl at birth or mildly weak/hypotonic. Gait affected between 2 and 6 yo (wide based, waddling, toe walking, difficulty running/jumping). Then develop arm/



torso weakness. Usually wheelchair bound by 12 yo. Exam: Calf pseudohypertrophy, Gower sign when arising from floor, symmetric weakness, diminished DTRs (though ankle jerks may remain, even late in disease), Achilles/hamstring contractures, kyphoscoliosis. Cardiac muscle is involved, leading to cardiomyopathy, EKG abnormalities, sinus tachycardia. Many pts have cognitive impairment. Pts develop respiratory decline leading to death, usually in early 20 s.

**Dx:** Genetic testing. CK (50-100× nl or greater). EMG: ↑ spontaneous activity; may have myopathic changes. Muscle MRI: Fatty replacement. Muscle biopsy: Reduced/absent dystrophin on immunohistochemistry & Western blot.

**Rx:** Corticosteroids (stabilizes/improves strength & can delay wheelchair dependence), annual PFTs, regular echocardiography/EKGs, cardiology follow-up.

### BECKER MUSCULAR DYSTROPHY (BMD)

**Genetics:** Dystrophin gene mutation, Xp21.2 (X-linked recessive).

**Epid:** Incidence: 5 in 100,000 male births.

**Si/Sx:** Similar to Duchenne, but milder phenotype, presents later. Pts ambulatory past 15 yr of age, but ~50% lose ambulation by 4th decade.

**Dx:** Genetic testing. CK (20-200× nl). Muscle biopsy: Reduced/absent dystrophin on immunohistochemistry & Western blot.

**Rx:** Monitor respiratory & cardiac function.

## LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMD)

Large, clinically heterogenous group of disorders; AD or AR inheritance. AD: LGMD 1, subtypes A-H incl myotilin, lamin A/C, caveolin-3 forms. AR: LGMD 2, subtypes A-S incl calpain-3, dysferlin, sarcoglycans, telethonin, TRIM 32, fukutin-related protein (FKRP), titin forms.

**Si/Sx:** Predominantly limb-girdle weakness, though additional muscle groups are involved to varying extents.

**Dx:** Targeted genetic testing based upon inheritance pattern & clinical phenotype (e.g., presence/absence of facial weakness, scapular winging, calf atrophy, contractures, early cardiac/respiratory involvement).

## MYOTONIC DYSTROPHIES

Myotonia: Delayed relaxation of a muscle, usually worse w/cold or stress. Seen commonly in facial & hand muscles. May be elicited by percussion (e.g., thenar eminence, extensor digitorum communis) or strong contraction (e.g., grip myotonia, eyelid myotonia). Often described by pts as muscle “stiffness.”

*Dystrophia myotonica 1 (DM1):*

*Genetics:* AD, caused by unstable trinucleotide repeat on DPMK gene (19q13.2). Up to 27 repeats nl, but pts w/DM1 can have 50-4,000 repeats w/↑ repeats correlating w/worse disease severity. # of repeats often increases in successive generations, causing earlier/more severe presentation (anticipation).

*Epid:* Incidence of 13.5/100,000 live births & prevalence of 3-5/100,000.

*Si/Sx:* Can present at any age (incl severe congenital form). Pts develop distal then proximal limb weakness, neck flexor weakness, facial weakness/atrophy leading to characteristic “hatchet face” appearance, may develop bulbar weakness as well. Often have frontal balding. Clinical myotonia on exam (percussion, grip, eyelid). Multisystem involvement: Cardiac (conduction defects), GI (reduced gastrointestinal motility w/pseudoobstruction), respiratory (alveolar hypoventilation, sleep apnea), ophtho (cataracts), endocrine (testicular atrophy, insulin resistance), neurobehavioral (cognitive/mood issues).

*Dx:* Genetic testing; EMG w/electrical myotonia (“dive bomber” sound), ↑ spontaneous activity, myopathic motor unit potentials.

*Rx:* Mexiletine or phenytoin for disabling myotonia; annual EKGs; ophthalmological exams; consider sleep study to eval for sleep apnea; genetic counseling if planning to have children.

*Dystrophia myotonica 2 (DM2)*: Also known as “proximal myotonic myopathy” (PROMM), resembles DM1 (myotonia, weakness, cataracts, cardiac issues), but often presents between 20 and 60 yo.

*Genetics:* AD, caused by unstable CCTG repeat expansion on chromosome 3q21. More prevalent in northern European families.

*Si/Sx:* Slowly progressive proximal & distal weakness that may fluctuate over time. Myotonia, which often manifests as muscle stiffness/pain w/“warm-up” phenomenon (improves w/repeated contractions).

*Dx:* Genetic testing, myotonia on EMG.

### OTHER MUSCULAR DYSTROPHIES

*Facioscapulohumeral (FSH) dystrophy*: AD, sx typically manifest between 3 and 45 yr of age, though can be later. Variable penetrance, even in members of the same family. Exam: Facial weakness, scapular winging, proximal arm weakness that spares forearms ("Popeye" arms), inverted axillary folds. Weakness may be asymmetric. Dx: Genetic testing (there are two genetically distinct subtypes).

*Scapuloperoneal muscular dystrophy*: P/w foot drop (often asymmetric) followed by scapular winging w/in first 2 decades of life. Rx: Supportive—AFOs for foot drop, consider surgery to stabilize scapula.

*Emery-Dreifuss muscular dystrophy*: X-linked or AD. Pts p/w early contractures (elbows, ankles, neck) & slowly progressive weakness, as well as cardiac conduction defects. May require prophylactic pacemaker or intracardiac defibrillator. Rx: Annual EKGs, PT to reduce contractures. Dx: Genetic testing (emerin mutations are most common form of X-linked cases, while most dominant cases are caused by mutations in lamin A/C).

*Oculopharyngeal muscular dystrophy (OPMD)*: Usually AD, more commonly seen in pts of French-Canadian descent. P/w slowly progressive ptosis (often asymmetric) in 4th-6th decade, accompanied by restricted EOMs, pharyngeal weakness w/dysphagia, & proximal limb weakness. Pts may require surgery to help w/ptosis, cricopharyngeal myotomy for dysphagia. Dx: Genetic testing.

## CONGENITAL MYOPATHIES

Myopathies presenting preferentially, but not exclusively, in infancy. Often associated w/hypotonia, delayed motor milestones. Can also present in adolescence & adulthood.

### CENTRAL CORE MYOPATHY

**Genetics:** Mutation in ryanodine receptor gene (chromosome 19), AD > AR.

**Si/Sx:** Proximal & mild facial weakness beginning in infancy/early childhood, contractures, kyphoscoliosis, pes cavus, cardiac abnormalities.

**Dx:** Genetic testing; biopsy w/round areas of clearing ("cores") in type I fibers on NADH-TR staining.

**Rx:** Pts at risk for malignant hyperthermia & should avoid certain anesthetics (e.g., halothane), neuromuscular blocking agents (e.g., succinylcholine). Monitor cardiac function (EKG, TTE).

### CENTRONUCLEAR/MYOTUBULAR MYOPATHY

**Genetics:** X-linked myotubularin gene mutations account for 90% of cases, have a more severe phenotype. AD dynamin mutations are milder.

**Si/Sx:** X-linked: severe neonatal hypotonia, progressive weakness of limb girdle & neck muscles, facial weakness, dysarthria, ptosis, EOM weakness. Children w/AD mutation may be nl or mildly hypotonic at birth, have a slower progression.

**Dx:** Genetic testing; muscle biopsy w/myonuclei in the center of fibers.

**Rx:** Supportive; early initiation of tube feeding, mechanical ventilation if needed. Prognosis is often poor for X-linked mutation, w/death in infancy. Milder cases present in childhood or adulthood, progress more slowly.

### CONGENITAL FIBER-TYPE DISPROPORTION

**Genetics:** At least three different genetic defects (tropomyosin 3, α-actin, selenoprotein N).

**Si/Sx:** Static limb-girdle weakness associated w/myopathic facies, dolichocephaly, high-arched palate, occasional scoliosis. May occur in isolation or as a component of another disease (e.g., Krabbe, congenital myotonic dystrophy). Most cases static, but some have progressive weakness & respiratory insufficiency.

**Dx:** Genetic testing; muscle biopsy w/disproportionate ratio of type I to type II myofibers, type I fibers are smaller than usual & type II are nl to enlarged.

**Rx:** Supportive: PT/OT; tube feeding, mechanical ventilation if needed.

### NEMALINE MYOPATHY

**Genetics:** Five associated genes (AD & AR) w/variable penetrance, code for thin filament-associated proteins (nebulin, α-actin, troponin, α-tropomyosin, β-tropomyosin).

**Si/Sx:** Most commonly presents in infancy/early childhood w/generalized hypotonia, static/slowly progressive weakness (incl facial weakness, ptosis), dysmorphic facies.



Can also see severe infantile form (often fatal in 1st yr) or adult-onset form w/mild proximal & distal weakness, at times associated w/cardiomyopathy.

**Dx:** Muscle biopsy w/nemaline rods (best seen on trichrome stain, EM); genetic testing.

**Rx:** Supportive (PT, bracing). In severe infantile form, aggressive early rx of respiratory & feeding difficulties.

### MULTIMINICORE MYOPATHY

**Genetics:** AR: Mutations in ryanodine receptor (RYR1) & selenoprotein N genes.

**Si/Sx:** Hypotonia, proximal > distal weakness (occasionally hand muscles involved). May p/w facial weakness, ptosis, ophthalmoparesis. Skeletal abnormalities (kyphoscoliosis, club feet, high-arched palate) often present. Contractures of neck extensors/trunk cause rigidity of spine. Cardiomyopathy & respiratory weakness may develop.

**Dx:** Muscle biopsy: NADH stain w/multiple small “cores” (areas w/no oxidative enzyme activity). CK usually nl or mildly elevated.

**Rx:** Supportive; pts may need bracing or surgery for contractures; may require noninvasive ventilation. Similar to central core, pts may be at higher risk of malignant hyperthermia. Monitor cardiac function.

## METABOLIC MYOPATHIES

### DISORDERS OF CARBOHYDRATE METABOLISM (GLYCOGEN STORAGE DISEASES)

*Pompe disease*: *Genetics*: AR defect of lysosomal acid α-1,4-glucosidase. *Si/Sx:* Can present in infancy (severe) or as milder form in adults in the 3rd-4th decade w/generalized proximal > distal weakness, occasionally involving face/tongue. EKG abnormalities/cardiomyopathy can be seen. May have restrictive ventilatory insufficiency as well. *Dx*: Dried blood spot assay for α-1,4-glucosidase activity; if abnormal, further testing indicated (may include genetic testing). Muscle biopsy shows glycogen-filled vacuoles in muscle fibers. *Rx*: Enzyme replacement.

*McArdle disease*: *Genetics*: AR mutation in PYGM gene (encodes myophosphorylase). *Si/Sx:* Usually exercise intolerance (cramps, muscle pain) in children/young adults. “Second wind phenomenon” can occur after ~10 min exercise (due to mobilization of additional glucose). Up to 1/3 of pts may develop weakness & contractures over time, but many are nl between attacks. *Dx*: Elevated CK; exercise test w/appropriate rise in ammonia but not lactate. Pathology shows accumulation of glycogen, absent myophosphorylase staining. Genetic testing can confirm. *Rx*: No proven medical rx. Counsel pts to avoid intense weight lifting/aerobic exercise, tend toward mild-to-moderate aerobic conditioning.

### DISORDERS OF LIPID METABOLISM

*CPT2 deficiency*: *Genetics*: AR mutation in CPT2 gene on chromosome 1p32 → deficiency in carnitine palmitoyltransferase 2. *Si/Sx:* Rhabdomyolysis w/intense/prolonged exertion or w/prolonged fasting, infection. Usually presents in 2nd-3rd decade of life. *Dx*: Genetic testing. CK ↑ w/fasting or intense physical activity. Exercise test nl (helps distinguish from glycogen storage diseases). *Rx*: Avoid fasting or high fat meals, esp during illness.

*Lipid storage myopathies*: Include primary carnitine deficiency, multiple acyl-CoA dehydrogenase deficiency (MADD), & neutral lipid storage disease. P/w proximal or distal weakness. *Dx:* Muscle biopsy w/lipid droplets on oil red O staining. Carnitine & acylcarnitine levels can help distinguish between diagnoses (carnitine markedly ↓ in primary carnitine deficiency; acylcarnitine levels of various carbon length ↑ in MADD; both levels are nl in neutral lipid storage disease). Blood smear for Jordans bodies (lipid droplets in blood cells) in suspected neutral lipid storage disease. Genetic testing confirms dx.

# MITOCHONDRIAL MYOPATHIES

## MYOCLONIC EPILEPSY AND RAGGED RED FIBERS (MERRF)

Si/Sx: Myoclonus, generalized seizures, ataxia, dementia, sensorineural hearing loss, optic atrophy, progressive weakness (esp proximal arms & legs). May have a generalized sensorimotor polyneuropathy as well. Dx: Nl to mildly elevated CK, serum lactate. May see EEG & MRI abnormalities. NCS may show axonal neuropathy. Muscle



biopsy w/ragged red fibers & COX-negative fibers w/↑ SDH uptake. Rx: No specific rx. Use caution w/sedating/anesthetic agents, as can cause hypoventilation in pts w/mitochondrial myopathies.

## MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTIC ACIDOSIS, & STROKE-LIKE EPISODES (MELAS)

*Si/Sx*: Usually si/sx by midteens, incl muscle weakness, stroke-like episodes (headaches, n/v, focal neurological deficits, sometimes provoked by exercise, infection). Pts may have short stature, sensorineural hearing loss. *Dx*: ↑ serum/CSF lactate. Muscle biopsy w/ragged red fibers, COX-negative fibers w/↑ SDH uptake. MRI brain w/cortical atrophy & FLAIR abnormalities in cerebral cortex, basal ganglia, thalamus. Genetic testing. *Rx*: No specific rx.

## KEARNS-SAYRE SYNDROME (KSS)

*Si/Sx*: Usually onset before age 20: Triad of progressive external ophthalmoplegia, pigmentary retinopathy, cardiomyopathy. Also p/w proximal weakness, short stature, hearing loss, dementia, ataxia, hypoventilation (esp w/sedatives/anesthetic agents), endocrinopathies. *Dx*: ↑ serum lactate, pyruvate, CSF protein. Muscle biopsy w/ragged red fibers, most of which do not stain w/COX. Genetic testing. *Rx*: Creatine supplementation may be helpful. Caution w/sedation, anesthetic agents.

## PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (PEO)

*Si/Sx*: Ptosis, ophthalmoparesis w/or w/o muscle weakness. None of the other features of KSS are present (e.g., endocrinopathies, short stature, cardiomyopathy). *Dx*: May have ↑ serum lactate, pyruvate, CSF protein. Muscle biopsy identical to KSS. Genetic testing. *Rx*: Surgery can help correct ptosis. Caution w/sedation, anesthetic agents.

# INFLAMMATORY MYOPATHIES

## DERMATOMYOSITIS (DM), POLYMYOSITIS (PM), INCLUSION BODY MYOSITIS (IBM), IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)

| | DM | PM | IBM | IMNM |
|---|---|---|---|---|
| Sex | F > M | F > M | M > F | M = F |
| Age | Juvenile & adult | Adult (<50) | Elderly (>50) | Adult & elderly |
| Pattern of weakness | Proximal > distal | Proximal > distal | Proximal & distal, esp finger flexors & knee extensors | Proximal > distal |
| CK | ↑ (up to 50×) | ↑ (up to 50×) | Nl or mild ↑ (<10×) | ↑ (>10×) |
| Skin findings | Gottron papules, shawl sign, heliotrope rash, erythroderma | None | None | None |
| Biopsy | Perimysial perivascular inflammation, perifascicular atrophy | Endomysial inflammation | Endomysial inflammation, rimmed vacuoles, amyloid deposits | Necrotic muscle fibers, absent inflammatory infiltrate |
| Other manifestations | Malignancy, myocarditis, interstitial lung dz, connective tissue dz (CTD) | Malignancy, myocarditis, interstitial lung dz, CTD | Sicca, Sjögren, sarcoidosis | Malignancy, CTD, possibly triggered by statin use |
| Rx response | Good | Good | None or minimal | Good; can be difficult to treat |

From *J Neurol Neurosurg Psychiatry* 2009;80:1060-1068.



## DERMATOMYOSITIS (DM), POLYMYOSITIS (PM), IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)

**Epid:** Prevalence 1/100,000; 2 F:1 M. Peak age 40-50 yr.

**Si/Sx:** Subacute or insidious development of symmetric proximal weakness; ↑ CK; EMG w/myopathic Δs; characteristic biopsy findings.

**Associated conditions:** **(1)** Increased risk of malignancy w/in 3 yr of dx, DM > PM/IMNM; 70% are solid tumors (cervix, lung, ovaries, pancreas, bladder, stomach). **(2)** Interstitial lung disease in 10% of DM/PM (esp if antisynthetase ab+). **(3)** Myocarditis: Usually mild; check troponin I. **(4)** Other connective tissue diseases (scleroderma, SLE, RA, mixed connective tissue disease [MCTD]). **(5)** Statin use in IMNM—weakness remains & rarely may even develop after statin is dc'd.

**Ddx:** IBM (usually more insidious onset; lower CKs; characteristic biopsy findings), other acquired myopathies,

muscular dystrophy, NMJ disorder, motor neuron disease.

**Workup: (1)** Full physical exam (look for skin changes, evidence of malignancy). **(2)** Labs: CK (can be nl in long-standing disease), CBC, comprehensive metabolic panel (incl AST/ALT), ESR, CRP, ANA (80% positive), LDH, UA, anti-Ro/Sm/RNP, HIV, TSH. Myositis-specific abs (seen in 30% of pts): Antisynthetase, Jo-1, SRP, & Mi-2 abs. Anti-Jo-1 associated w/interstitial pulmonary fibrosis. Anti-HMGCR in IMNM associated w/statin use. **(3)** EMG/NCS: ↑ membrane excitability (fibrillation potentials & positive sharp waves) & myopathic motor unit potentials w/early recruitment—supportive but nondiagnostic. **(4)** Consider MRI muscle (can show edema suggestive of inflammation, fibrosis, calcification; may use MR spectroscopy to look at muscle metabolism). **(5)** Muscle biopsy (ideally open biopsy) or skin in DM if a rash is present (less invasive). **(6)** CT chest/abdomen/pelvis to look for malignancy. **(7)** Ensure cancer screening is up to date (colonoscopy, mammogram, etc.), & maintain vigilance for underlying malignancy for 3 yr after DM/PM/IMNM dx.

**Predictors of poor outcome:** Respiratory muscle weakness/interstitial lung disease; malignancy; cardiac involvement; dysphagia; delay in initiation of rx for >6 mo after sx onset; older age at onset (*Am J Med* 1993;94:379). IMNM pts are more difficult to treat.

**Rx:** Goal is to increase muscle strength. Treat w/steroid taper ± steroid-sparing agent until remission achieved, then attempt gradual taper, usually over 6-12 mo. Recurrent or resistant disease may require steroid-sparing agent.

*Steroids*: Start at high dose, then taper to lowest effective maintenance dose. Initial dose: Prednisone 0.75-1 mg/kg/day ± steroid-sparing agent. Assess strength every few wks (more reliable than CK); if improving, taper prednisone as tolerated. If no response after 6 wk, add steroid-sparing agent (see below) if not already started. If giving >30 mg prednisone for ≥3 wk, start trimethoprim-sulfamethoxazole DS (1 tab qMWF), PPI, Ca++/vit D. Consider baseline DEXA scan.

*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. (2) *Initial dose* 25 mg/day; increase over wks to 1.5-3 mg/kg/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 while adjusting dose, then every 3 mo.

*Methotrexate*: Once weekly dosing; initial dose 15 mg/wk, ↑ by 5 mg/wk as needed, up to 25 mg/wk. *Side effects:* Stomatitis, GI symptoms, leukopenia, hepatotoxicity (avoid in pts w/liver disease or those who drink alcohol heavily), pulmonary toxicity. Reduced risk of leukopenia w/folic acid 1 mg/day.

## INCLUSION BODY MYOSITIS

**Epid:** Most common myopathy over age 50 yr. Affects 5-70 people per million, M > F.

**Si/Sx:** Insidious onset of weakness, often asymmetric. Predominantly affects wrist & finger flexors & quads (look for forearm & thigh atrophy); pts may complain of difficulty using hands, getting out of chairs, going up staircases. Knee jerk may be lost due to quad atrophy. Myalgias may be present. Up to 60% w/dysphagia; may be presenting feature. Most pts have a nl life expectancy.

**DDx:** PM; muscular dystrophy w/rimmed vacuoles or hereditary inclusion body myopathy; drug-induced myopathies (e.g., colchicine); motor neuron disease.

**Dx: (1)** Labs: Nl or <10× elevated CK; cytosolic 5′-nucleotidase 1A abs. **(2)** EMG/NCS: ↑ membrane irritability & mixed large & small motor units; may be misinterpreted as neurogenic. **(3)** MRI: Can help distinguish IBM from PM. IBM involves vastus lateralis & medialis w/sparing of rectus femoris, more asymmetric than PM. **(4)** Biopsy: Endomysial inflammation; basophilic rimmed vacuoles w/in muscle fiber sarcoplasm (on frozen biopsy only);

eosinophilic inclusions; fiber size variability. Muscle fiber inclusions w/staining for p62, TDP-43, & amyloid deposits. Electron microscopy: Filamentous inclusions (difficult to find).

**Rx:** Generally poor response to rx, including steroids or other immunosuppressants. PT/OT. May need referral to ENT for cricopharyngeal myotomy if severe dysphagia.



## HIV MYOPATHY

**Si/Sx:** Resembles PM: Symmetric proximal weakness, myalgias. More often occurs in AIDS, though may occur early in HIV infection as well. No correlation w/CD4 count.

**Pathogenesis:** HIV triggers T-cell-mediated/MHC-1-restricted immune response against unknown antigens on muscle fibers.

**Dx:** CK ↑ up to 10×. EMG/NCS w/↑ membrane irritability, myopathic changes. Biopsy: Perimysial, endomysial, & sometimes perivascular inflammation. May see rimmed vacuoles.

**Rx:** High-dose steroids (prednisone 1 mg/kg/day) over 1-2 mo then taper. Monitor strength & muscle enzymes.

**Ddx:** (1) *NRTI myopathy*: Due to nucleoside reverse transcriptase inhibitors (NRTI). P/w proximal weakness, severe muscle atrophy, myalgias, CK ↑ up to 10×. Originally described w/zidovudine (causes mitochondrial dysfunction). Biopsy: Muscle fiber size variability, no inflammatory infiltrate. *Rx:* Stop drug. If no improvement in 1-2 mo, consider HIV myopathy as the cause. (2) *Toxoplasmosis myositis*: P/w diffuse muscle weakness, wasting, tenderness. CK ↑. Often associated w/CNS infection. Biopsy: Necrosis, variable inflammation, intracellular *T. gondii* cysts. *Rx:* Pyrimethamine & sulfadiazine.

## MYOPATHY ASSOCIATED WITH ENDOCRINE DISEASE

**Hypothyroid myopathy:** *Si/Sx:* Proximal weakness, myalgias, cramps, generalized fatigue. May see delayed relaxation of DTRs & *myoedema* (painless mounding of muscle tissue when firmly percussed). *Dx*: CK ↑ 10-100× nl; EMG nl or w/myopathic changes; biopsy often unnecessary but may show myopathic changes w/o inflammation. *Rx:* Thyroid hormone replacement. Weakness may persist up to 1 yr after euthyroid.

**Hyperthyroid myopathy:** *Si/Sx:* Proximal weakness & atrophy; can have esp severe shoulder girdle weakness w/scapular winging. May see dysphagia, dysphonia, respiratory distress, extraocular muscle, or distal weakness. Severity of myopathy does not correlate w/severity of thyrotoxicosis. *Dx:* CK often nl or low nl. EMG may show fasciculation potentials. Biopsy nonspecific. *Rx:* Treat underlying hyperthyroidism. Strength generally improves over months, but extraocular muscle weakness can last yrs.

**Hyperparathyroidism:** *Si/Sx:* Symmetric, proximal weakness legs > arms, neck extensor weakness (head drop), brisk reflexes (though pts may have concomitant peripheral neuropathy). *Dx:* CK usually nl. Elevated PTH. Elevated or low Ca++ & low 1,25-dihydroxy vitamin D (depending on whether primary or secondary hyperparathyroidism). Biopsy usually shows type 2-predominant atrophy. *Rx:* Myopathy usually responds well to rx of hyperparathyroidism.

**Diabetic muscle infarction:** Usually occurs in poorly controlled diabetes. *Si/Sx:* Acute pain, swelling in one thigh, less often in the calf. May palpate a tender mass. *Dx:* CK usually nl. MRI/CT shows signal abnormality in area of infarction. Biopsy should be avoided due to risk of hemorrhage into infarcted muscle. *Ddx:* Focal myositis, sarcoma (can p/w similar MRI abnormalities). *Rx:* Usually supportive (immobilization, pain control), w/resolution of pain/swelling over wks. Prednisone can be used; monitor serum glucose closely.

## MYOPATHY DUE TO ELECTROLYTE IMBALANCE

**Hypokalemia:** Most common electrolyte imbalance causing myopathy. K+ level usually needs to be less than

2.5 mEq/L for muscle breakdown & weakness to occur. *Si/Sx:* Proximal weakness, myalgias, cramps. *Dx:* CK usually elevated (can develop rhabdomyolysis). EMG may show ↑ insertional/spontaneous activity (fibrillations, positive sharp waves) & myopathic features. Biopsy after repeated episodes can show vacuoles & necrotic fibers. Check EKG & perform medical workup for causes of hypokalemia. If repeated episodes w/o clear medical cause, consider familial hypokalemic periodic paralysis. *Rx*: Replace potassium.

**Hyperkalemia:** Can p/w generalized weakness. May see evidence of muscle/nerve hyperexcitability on exam (e.g., Chvostek/Trousseau signs). Check EKG. Consider familial hyperkalemic periodic paralysis if no medical cause of hyper-K+ found.

**Hypophosphatemia:** Serum phosphate <0.4 mM/L can cause generalized weakness, rhabdomyolysis, myoglobinuria ± paresthesias. May see hyporeflexia on exam.



**Hypomagnesemia:** Severe generalized & ventilatory weakness can occur, but rapidly resolves w/correction of hypomagnesemia. May see evidence of muscle/nerve hyperexcitability on exam (e.g., Chvostek/Trousseau signs).

## CRITICAL ILLNESS MYOPATHY

Pts usually p/w flaccid quadriparesis & difficulty weaning from ventilator (often prolongs ICU stay). *Risk factors*: IV steroid use, sepsis, intubation, use of nondepolarizing neuromuscular blocking agents (e.g., vecuronium, succinylcholine).

**Dx:** CK moderately elevated in 50% of pts, but often normalizes after first few wks, even if weakness is pronounced. NCS w/low amplitude motor responses, relatively nl sensory studies (though pts may have pre-existing peripheral neuropathy); EMG w/early/nl recruitment of brief, small, motor unit potentials; may have fibrillation potentials. *Biopsy*: Myopathic changes, myosin loss on EM.

**Rx:** Supportive care. Avoid steroids, nondepolarizing neuromuscular blockers if possible. Improvement generally occurs over months.

## TOXIC (DRUG-INDUCED) MYOPATHY

**Statin myopathy:** Myalgias can occur in 2%-7% of pts on HMG-CoA reductase inhibitors, while severe myopathy is more rare (0.1% of treated pts) (*JAMA* 2004;292:2585). Exact mechanism unclear. ↑ risk w/renal insufficiency, hepatobiliary dysfunction, cotreatment w/other drugs (esp Cyp3A4 inhibitors, such as cyclosporine, gemfibrozil, macrolides). Most cases occur w/in 6 mo of starting statins, but can occur at any time during rx. In rare cases, pts can develop an immune-mediated necrotizing myopathy associated w/HMGCR abs (see inflammatory myopathy section), w/progression of weakness months after discontinuation. These pts may require aggressive rx w/immunosuppression.

*Si/Sx:* Myalgias; proximal, symmetric weakness.

*Dx*: ↑ CK (may also be seen in asymptomatic pts on statins). EMG of affected muscles may show myopathic units w/fibrillations, positive sharp waves, & myotonic discharges. Biopsy shows muscle fiber necrosis w/phagocytosis, ± lipid-filled vacuoles w/in myofibers, cytochrome oxidase-negative fibers.

*Rx*: Stop statin, encourage PO fluids. When CK nl, consider restarting a statin w/less muscle toxicity or another agent. If weakness doesn't improve or worsens after discontinuation, check for HMGCR abs, muscle biopsy, & treat w/immunosuppression if there is active necrotizing myopathy.

**Myopathy due to glucocorticoid (steroid) use:** *Risk factors*: Pts taking 30 mg/day or more of glucocorticoids, usually for wks or months; older age; cancer; inactivity. *Si/Sx:* Proximal weakness & atrophy, legs > arms.

Typically spares distal extremities, ocular/bulbar muscles, face. (Note: Same presentation can be seen in Cushing syndrome). *Dx:* CK nl; EMG usually nl, unless the weakness is pronounced. Biopsy: Nonspecific atrophy of type 2b fibers. *Rx:* ↓ steroid dose if possible, look for sx improvement in 3-4 wks. Can be confounded if steroids used for inflammatory myopathy (i.e., ↓ dose could worsen weakness).

**Alcohol myopathy:** *Acute*: Usually w/in hrs after binge, causes acute muscle pain, cramps, swelling, & weakness. CK can be markedly elevated.

*Chronic*: Gradual-onset proximal weakness, especially in lower limbs. CK usually nl. **Cocaine:** Variable presentation from asymptomatic CK rise to rhabdomyolysis. Mechanism may be due to vasoconstriction w/muscle ischemia/infarction or due to direct toxic effect.

**Colchicine:** Can cause a generalized toxic neuromyopathy (proximal myopathy + length-dependent toxic neuropathy). *Risk factors:* Age >50, chronic renal failure. Onset usually w/in 2 wks of rx. *Dx:* CK elevated up to 50×. EMG/NCS: myopathic changes & mild axonal polyneuropathy, occasional myotonic discharges. Biopsy: Vacuolar changes of lysosomal origin. *Rx*: Discontinue drug → resolution of symptoms w/in 4-6 mo.

**Penicillamine:** Occurs in up to 1% of pts 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 polymyositis). *Rx*: Stop drug; consider high-dose prednisone (40-60 mg/day).

**Other drugs that can cause myopathy:** Zidovudine (see HIV Myopathy above), vincristine, chloroquine, hydroxychloroquine, amiodarone, cyclosporine, labetalol, propofol.

# Nerve Conduction Studies and Electromyography

Sara Mayer

Erik Ensrud

## INTRODUCTION

**Purpose of electromyography (EMG)/nerve conduction studies (NCS):** Localization of disorder as (1) neuropathic, (2) myopathic, (3) neuromuscular junction, or (4) central etiology; assess disease severity; & narrow the differential diagnosis.

**Cautions w/EMG/NCS:** Use caution w/bleeding disorders/coagulopathy.

### NERVE CONDUCTION STUDIES

Electrodes on skin, stimulate nerves w/electrical impulses. NCS record large myelinated fibers. Small myelinated & unmyelinated fibers (autonomic & somatic pain nerves) not recorded by this test.

**Most common NCS:** Motor & sensory conduction studies & late responses measuring compound muscle action potentials (CMAPs), sensory nerve action potentials (SNAPs), F-waves, & H-reflexes.

**Definitions:** *Conduction velocity*: Speed of 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*: Stimulating away from the sensory receptor. *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. *Temporal dispersion:* An increase in the duration & decrease in the amplitude of the action potential due to variation in the firing times & conduction of individual nerve fibers.

**Motor NCS:** CMAP: Summated record of synchronously activated muscle action potentials.

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**Sensory NCS:** Represents sum of individual SNAPs.

- SNAPs are nl in lesions proximal to dorsal root ganglia (DRG)—i.e., radiculopathy—as DRG & peripheral axon remain intact.

**Late responses:** F-wave & H-reflex may be used to assess 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.

**H-reflex:** Pathway: Afferent sensory fiber → synapse at spinal cord → efferent α motor neuron; electrical equivalent of the ankle reflex.

**Repetitive nerve stimulation:** Nerve stimulated at different frequencies, assessing for decremental/incremental response.

## NEEDLE ELECTROMYOGRAPHY

Needle inserted into muscle & electrical activity recorded. No electrical stimulation is given. Allows evaluation of spontaneous activity & motor unit action potentials (MUAPs).

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### Components of the EMG

**Insertional activity:** Electrical activity associated w/inserting or moving the needle through muscle fibers which causes a brief depolarization.

- *Increased insertional activity*: Electrical activity lasting longer than 300 ms; may be present in both myopathic & neuropathic conditions.

**Spontaneous activity**: Nl muscle should not have spontaneous activity at rest w/the exception of noise & potentials in the muscle endplate region. Several types of abnl spontaneous activity:

- *Positive sharp waves*: Spontaneous depolarizations of muscle fiber w/initial (+) phase then long (-) phase.

Equivalent to fibrillation potentials. Occur in neuropathic & myopathic states.

- *Fibrillation potentials*: Spontaneous depolarizations of muscle fiber w/initial (+) deflection. Occur in neuropathic & myopathic states.
- *Complex repetitive discharges*: Spontaneous depolarizations of muscle fiber w/ephaptic spread to surrounding fibers. Occur in neuropathic & myopathic states, usually indicate long-standing injury (>6 mo).
- *Myotonic discharges*: Spontaneous depolarizations of muscle fiber w/characteristic waxing & waning of potentials. Occur in myotonic dystrophy, myotonia congenita, paramyotonia congenita, other myopathies, hyperkalemic periodic paralysis, chronic radiculopathies, & neuropathies.
- *Myokymic discharges*: Groups of spontaneous motor unit potentials w/a regular firing pattern & rhythm. Typically seen in radiation-induced nerve injury, but also a variety of other conditions, such as facial myokymia in MS, GBS, & pontine tumors.

**Analyzing the motor unit**: Analyze the MUAP morphology while pt contracts muscle slightly. Assess amplitude, rise time, duration, & phases. ↑ amplitude & duration can be seen in neuropathic processes, while ↓ amplitude & duration can be seen in myopathic processes. ↑ phases (polyphasia) can be seen in both myopathic & neuropathic processes.

**Recruitment**: The orderly addition of motor units as firing rate increases to ↑ the force of muscle contraction. Neuropathic pattern: ↓ recruitment of motor units w/↑ firing rate. Myopathic pattern: Early & ↑ recruitment of motor units.

## COMMON PATTERNS OF DISEASE

### Neuropathic Lesions

**Demyelinating:** 2/2 lesions affecting myelin sheath, such as compressive neuropathies, hereditary neuropathies (Charcot-Marie-Tooth disease), or inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy):

- *NCS*: Slow conduction velocity (slower than 75% lower limit of nl) & prolonged latencies (>130% upper limit of nl).
- *EMG*: Nl unless there is conduction block → decreased recruitment.
- *Prognosis:* Remyelination can occur over a short period, typically w/in wks. It is important to remember that the prognosis of a demyelinating neuropathy is dependent on the etiology.

**Axonal:** 2/2 processes affecting nerve axon, typically caused by toxic, metabolic, or genetic causes.

- *NCS*: Amplitudes ↓ after wallerian degeneration occurs (typically days to develop). Conduction velocity & distal latency relatively preserved (conduction velocities are not <75% of the lower limit of nl & distal latencies are not >130% of the upper limit of nl).
- *EMG*: ↓ recruitment of MUAPs (typically seen immediately). Abnl spontaneous activity can be seen (typically wks to develop). MUAP morphology w/↑ duration, amplitude, & number of phases (typically months to develop).
- *Prognosis:* When estimating recovery period for an axonal lesion, keep in mind that axons regrow at a rate of 1 mm/day. The prognosis is worse for an axonal lesion when compared to a demyelinating lesion secondary to the duration required for axonal regrowth.

### Motor Neuron Disease

- *NCS*: SNAPs are nl. CMAP amplitude ↓. Latency & conduction velocities are nl, except w/severe axonal loss where there is mildly ↑ latency & decreased conduction velocity.

- *EMG*: Abnl spontaneous activity: (+) sharp waves & fibrillation potentials. May see fasciculations, complex repetitive discharges. MUAPs w/↑ amplitude, duration & phases, indicating reinnervation. ↓ Recruitment.



## Diseases of the neuromuscular junction

### *Myasthenia gravis*

- *NCS*: SNAPs & CMAPs nl.
- *RNS*: W/3 Hz RNS, >10% ↓ in CMAP amplitude. Abnl in 50%-70% w/generalized myasthenia, but often nl in isolated ocular myasthenia.
- *EMG:* Typically nl, although MUAP may be unstable, short, & w/small, polyphasic MUAPs. Single-fiber EMG: jitter & blocking.

### *Lambert Eaton*

- *NCS*: SNAPs nl. CMAP amplitudes are diffusely low or borderline at rest.
- *RNS*: 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*

- *NCS*: SNAPs nl. CMAP amplitudes diffusely ↓ or absent.
- *RNS*: CMAP amplitude ↑ at 30-50 Hz RNS or after 10 s of exercise.
- *EMG:* Abnl spontaneous activity, including fibrillation potentials, (+) sharp waves. MUAPs may be unstable & short, small, & polyphasic. Nl or ↓ recruitment.

## Myopathy

- *NCS*: SNAPs are nl. CMAPs usually nl, except in cases of myopathy involving distal muscles where CMAP amplitude may be ↓.
- *EMG*: MUAPs typically ↓ amplitude & duration & ↑ phases w/early recruitment. May see ↑ spontaneous activity: (+) sharp waves, fibrillation potentials, myotonic discharges, & complex repetitive discharges.

## Radiculopathy

- *NCS*: SNAPs & CMAPs are typically nl, except CMAP may be ↓. NCS are useful in radiculopathy primarily to exclude other dx, such as peripheral neuropathy. *H-reflex*: Assesses afferent & efferent S1 fibers (similar to the ankle reflex).
- *EMG*: Acute setting: Fibrillation potentials & (+) sharp waves. Chronic setting: Abnl motor unit morphology, 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*: SNAPs & CMAPs are nl.
- EMG: MUAP morphology & recruitment are nl but there is ↓'d activation.

# Neurorheumatology

Sharmik Bhattacharyya
Tamara B. Kaplan
Nagogopal Venna

Wide spectrum of primarily autoimmune systemic d/os that can affect the CNS, PNS, & autonomic nervous systems. Expression depends on genetic & environmental factors. 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 ↑ dz activity. Sometimes neurologic si/sx = presenting manifestations of systemic rheumatologic dz.

| Clinical Sx Suggesting Systemic Rheumatologic Dz | |
|---|---|
| Constitutional | Fever, fatigue, malaise, wt loss, anorexia |
| Glandular | Dry eyes or mouth |
| Musculoskeletal | Joint pain or swelling, myalgias, prolonged morning stiffness |
| Renal | Proteinuria, urinary cellular casts |
| Vascular | Unexplained thrombosis or thromboembolism; Raynaud's, livedo reticularis |
| Cutaneous | Malar or discoid rash, photosensitivity, psoriasis, oral or genital ulcers, petechiae, subcutaneous nodules, alopecia, erythema nodosum |
| Ocular | Uveitis, scleritis, conjunctivitis |

## ORDERING RHEUMATOLOGICAL LABORATORY MARKERS

Labs alone insufficient for diagnosis & MUST be guided by clinical suspicion. Screen w/sensitive markers before ordering panels.



| Guide to Rheumatologic Dx & Tests by Syndrome | |
|---|---|
| **Syndrome** | **Brief Immunological DDx & Initial Testing** |
| Ischemic stroke (Infarct) | **DDx:** SLE, APLS, vasculitis, sarcoidosis, Behçet disease<br>**Lab:** ESR, CRP, C3/C4, ANA (further serologic testing if positive), lupus anticoagulant, anti-cardiolipin IgG/IgM, anti-β2-glycoprotein I IgG/IgM, ANCA, lumbar puncture (cell count w/diff, protein, glucose), ACE (serum & CSF) |

| | |
|---|---|
| Myelitis | **DDx:** Multiple sclerosis, NMO, SLE, Sjögren syndrome, paraneoplastic, vasculitis, sarcoidosis, Behçet disease (see other sections for infxn, neoplastic, vascular, & degenerative etiologies)<br>**Lab:** NMO-IgG, anti-Ro/La, ESR, CRP, ANA, ANCA, ACE, lumbar puncture, (cell count w/diff, protein, glucose, oligoclonal bands, ACE). Paraneoplastic panel *if* malignancy, CSF inflammatory, or initial workup negative |
| Meningitis | **DDx:** IgG4 related disease, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, SLE (rare)<br>**Lab:** IgG subsets, RF, anti-CCP, anti-Ro/La, ANA, ESR, CRP, serum & CSF ACE |
| Encephalopathy | **DDx:** SLE, Sjögren syndrome, APLS, multiple sclerosis, NMO, Hashimoto encephalopathy, vasculitis, paraneoplastic, neuronal surface antibody, sarcoidosis (large ddx guided by imaging & hx)<br>**Lab:** ESR, CRP, ANA, anti-Ro/La, lupus anticoagulant, anti-cardiolipin IgG/IgM, anti-β2-glycoprotein I IgG/IgM, ANCA, lumbar puncture (cell count w/diff, protein, glucose, oligoclonal bands), anti-TPO, anti-thyroglobulin, NMO-IgG (if suggestive imaging). If evidence of malignancy or CSF inflammatory, consider sending for paraneoplastic antibodies. If appropriate syndrome, test for neuronal cell surface antibodies (see *Neuro-Oncology chapter*). |
| Neuropathy | **DDx:** Can accompany many rheumatologic disorders & tx. SLE, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, vasculitis, scleroderma<br>**Lab:** ESR, CRP, ANA, RF, anti-CCP, anti-Ro/LA, serum ACE, ANCA, cryoglobulin, HBV sAg, HCV Ab, anti-Scl70, anti-centromere (further testing guided by EMG/NCS results) |

# DIFFUSE CONNECTIVE TISSUE DISEASES

## SYSTEMIC LUPUS ERYTHEMATOSUS

*Neurol Clin* 2002;20:151; *Continuum* 2008;14:94; *Lancet* 2007;369:587.

**Epid:** Prev ~40-50/100,000; more common: (1) F > M, (2) Asian, African, Latino ancestry, (3) young adults. **Dx of SLE** (*Arth Rheum* 1982;25:1271 & 1997;40:1725): 11 criteria of American College of Rheumatology (ACR); require ≥4. Criteria used in research; pt may have SLE w/o ≥4 criteria.

**Dz Activity:** ↑ ESR, CRP. ↓ C3, C4, CH50. ↑ anti-dsDNA titers. Other tests organ specific.

| ACR Criteria for Dx of SLE | |
|---|---|
| **System** | **Criteria** |
| Cutaneous/dermatologic | 1. Malar rash (fixed erythema over malar eminences)<br>2. Discoid rash (red raised patches w/scaling & follicular plugging)<br>3. Photosensitivity (skin rash from unusual reaction to sunlight)<br>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 thrombo-cytopenia (<100 k/mm$^3$ w/o offending drug present) |
| Immunologic/serologic | 10. ⊕ anti-dsDNA or anti-Sm or antiphospholipid ab (elevated IgG/IgM anticardiolipin, LA, IgG/IgM β2-glycoprotein I)<br>11. ⊕ ANA (in the absence of drugs a/w drug-induced lupus) |

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**Neuropsychiatric SLE (NPSLE):** NPSLE replaces terms “CNS lupus,” “neurolupus,” & “lupus cerebritis.” Can present before or after clinical dx of SLE, including quiescent periods. Nineteen proposed CNS/PNS syndromes to provide standardized nomenclature but *not specific* to SLE. Other causes need to be excluded first.

**NPSLE syndromes** (19 described; dx criteria, exclusions, associations, w/u on ACR website [http://www.rheumatology.org/publications/ar/1999/aprilappendix.asp]).

**Central Manifestations:** Acute confusional state, anxiety disorder, aseptic meningitis, cerebrovascular disease, Cognitive disorder, demyelinating syndrome, headache, mood disorder, movement disorder, myelopathy, psychosis, seizure disorder

**Peripheral Manifestations:** Autonomic neuropathy, cranial neuropathy, Guillain-Barre syndrome (AIDP), mononeuropathy, myasthenia gravis, plexopathy, polyneuropathy

| **Specific ACR Neuropsychiatric SLE Syndromes** | |
|---|---|
| **Syndrome** | **Notes** |
| Cerebrovascular Dz | Cause 20%-30% of deaths in SLE. ~65% of pts w/stroke & SLE have anti-phospholipid antibodies. Can be small vessel, large arterial territory, or venous sinus thrombosis. **Dx**: MRI, IgG/IgM anti-cardiolipin, IgG/IgM, anti-β2-glycoprotein I, lupus anticoagulant, TTE (marantic endocarditis), vessel imaging (MRA/CTA/angiogram). **Tx:** Thrombolysis (if acute), anticoagulation (INR 2-3) for APLS, efficacy of new anticoagulants unclear, aggressive risk factor control like obesity, HTN, HLD, DM (a/w steroids). |
| Seizure | Can be provoked (uremia, acute infarct) or occur in isolation. Generalized or focal. Hx of stroke & anti-phospholipid Ab risk factors. ~88% of sz are single episode. **Dx**: MRI, EEG. **Tx**: AED only if recurrent sz, MRI/EEG abnl. |

| | |
|---|---|
| Mood disorder | Depression (unclear if related to disease or reaction) |
| Psychosis | A/w SLE systemic dz activity. Steroid often contributing factor. **Tx:** Antipsychotics. Immune suppression for other SLE dz activity. |
| Cognitive disorder | Prevalent; mild to severe impairment in *majority* on testing. |
| Acute movement disorders | Hemichorea, generalized chorea w/or w/o APL & w/or without basal ganglia infarctions |
| Myelopathy | Often longitudinal (>3 vertebral segments). Can be a/w neuromyelitis optica IgG (NMO-IgG/anti-aquaporin 4 Ab) *or* seronegative aggressive necrotic myelopathy. **Dx:** LP (pleocytosis lymphocytic or neutrophilic, ↑protein, glucose can be low), MRI spine, serum NMO IgG. **Tx:** Steroid pulse, rituximab (esp if NMO IgG +), plasmapheresis, IVIg. *Arthritis Rheum* 2009;60:3378. |
| Neuropathy | Variable. Typically axonal length dependent. Usually polyneuropathy, can also be multiple mononeuropathy, cranial (esp isolated trigeminal) or small fiber neuropathy. **Dx:** EMG/NCS, **Tx:** No trials. Steroids, IVIg, plasma exchange, or rituximab all reported. |
| Headache | Common. In *isolation*, does not correlate w/dz activity or flare. **Tx:** symptomatic. *Brain* 2004;127:1200. |

## RHEUMATOID ARTHRITIS

*Neurol Clin* 2002;20:151; *Continuum* 2008;14:120.

**Epid:** Prevalence ~1/100; F > M; > w/↑ age.

**Dx of rheumatoid arthritis (RA):** Different criteria exist. Best known ("1987 ACR criteria") gives 7 criteria; need 4 criteria for dx; Se 91%-94%, Sp 89% w/≥4 criteria for established disease (*Arth Rheum* 1988;31:315). These criteria *not sensitive* for early disease; updated criteria exist for early disease (*Ann Rheum Dis* 2010;69:1580).



| 1987 ACR Criteria for Dx of RA | |
|---|---|
| **System Involved** | **Criteria** |
| Musculoskeletal | 1. Morning stiffness, ≥1 h × 6 wk<br>2. Arthritis ≥3 joints (PIP, MCP, wrist, elbow, knee, ankle, or MTP) simultaneously × 6 wk; observed by physician<br>3. Arthritis ≥1 hand joint (PIP, MCP, or wrist) × 6 wk<br>4. Symmetric joint arthritis × 6 wk |
| Cutaneous/derm | 5. Rheumatoid (SQ) nodules observed by physician |

| | |
|---|---|
| Immunologic/serologic | 6. ⊕ RF (Se 67%, Sp 79%). [anti-citrullinated peptide antibody has Se 67% & Sp 96%; part of newer criteria] |
| 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/advanced RA.

**Atlantoaxial subluxation:** Dislocation of atlas horizontally from the axis. **Sx:** asymptomatic → pain in neck & occiput → cord compression & myelopathy (often mild spastic quadriparesis, atrophy/sensory loss in hands/upper cervical dermatomes).

**Cranial settling:** Vertical upward migration of dens into foramen magnum. **Sx:** Dysfxn of pons/medulla w/drop attacks, sudden death; lower cranial neuropathies including trigeminal neuropathy & myelopathy.

**Subaxial subluxation:** Involvement of facets below C1/C2; radiographic "staircase 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:** Cervical spine dz present in ~70% of MRI but sx less frequent; unclear how to treat radiographic dz; cervical spine decompression in symptomatic dz.

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 wkns. Multiple causes: disuse, steroids, vasculitic; ~5% polymyositis or dermatomyositis.

4. **CNS dz:** Meningitis [rare; (*Neurology* 2007;68:1079)]; Likely direct inflammation of CNS, usually in long-standing RF⊕ dz. Rare pachymeningitis **W/u:** LP (r/o infxn, DDx inflam CSF), MRI, consider meningeal bx. **Rx:** No RCT or consensus on optimal Rx, ? immunomodulation.

## SJÖGREN SYNDROME

*Semin Neurol* 2014;34:425; *Continuum* 2008;14:120.

**Epid:** Prev: ~0.6%. F:M - 10:1, average age at dx: 55 Can be 1° or 2° (w/other autoimmune dz; most common RA). 2/2 lymphocytic infiltration of salivary/lacrimal glands (large ddx).

**Dx of Sjögren syndrome (SS):** six criteria (Am. Europ. Consensus Group (AECG); *Ann Rheum Dis* 2002;61:554).

**1°:** 4/6 criteria (must incl. # 4 or 6) OR 3/4 objective crit. (#'s 3-6); Se 96%, Sp 94%.

**2°:** Presence of autoimmune dz + crit: # 1 or 2 & any 2 of #s. 3-5; **Exclusions:** H/o head/neck XRT, hep C, AIDS, lymphoma, sarcoidosis, GVHD, anticholinergic use (w/in $t_{1/2}$ × 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.<br>2. Daily dry mouth × 3 mo, recurrent/persistent salivary gland swelling, or frequent liquids to aid swallowing dry food.<br>3. ⊕Schirmer test or Rose Bengal score.<br>4. Minor salivary gland focal lymphocytic sialoadenitis on histopath (focus score ≥1).<br>5. ↓ whole salivary flow, diffuse sialectasias on parotid sialography, or abnormal salivary scintigraphy. |
| Serologic | 6. ⊕ anti-Ro (SSA) or La (SSB) |

**Neurologic manifestations of SS**

1. **PNS:** Most common findings: symmetric sensorimotor polyneuropathy & cranial neuropathy. No definite findings to distinguish from neuropathies of other causes.

**Rx:** No

RCT or consensus on optimal Rx for pts w/neuropathy & SS; IVIg often used for painful neuropathy while corticosteroids used for multiple mononeuropathies.



Other immune modulating agents like rituximab, infliximab, or plasmapheresis also used.

2. **CNS:** Longitudinal TM often w/⊕ NMO-IgG; **W/u, Rx:** same as for NMO (see Chapter 18). Also a/w recurrent meningoencephalitis (*Neurology* 1983;33:593).

| Peripheral Neuropathies Described in SS | | |
|---|---|---|
| **Suspected pathology** | **Type/Sx** | **Also consider** |
| Dorsal sensory root ganglionitis (lymphocytic infiltration) | Sensory ataxia: distal paresthesias → severe joint position/vibration loss | Paraneoplastic (SCLC, anti-Hu) |
| | Trigeminal sensory: CN V 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 | Lyme, hepatitis, TB, HIV, sarcoid, GCA, carcinomatous, mass |

| | | |
|---|---|---|
| | nerves | lesion |
| | Multiple cranial neuropathies | |
| Small-fiber | Sensory w/o ataxia: painful distal dysesthesias & pain/temp loss | |
| Demyelinating | Sensorimotor polyneuropathy. Dist > proximal | AIDP, myelopathy |

(Adapted from *Continuum* 2008;14:124; Orig. data: *Brain* 2005;128:2518.)

## 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. ↑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 Scleroderma | |
|---|---|
| **System** | **Criteria** |
| Dermatologic | Major: Thickening/tightening/induration of skin on fingers extending prox. to MCP/MTPs |
| | Minor:<br>**1.** Sclerodactyly—as above, but limited to fingers<br>**2**. Digit pitting/loss of finger pad (2/2 ischemia/prolonged Raynaud's)<br>**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 Scleroderma

1. **Neuropathy:** Cranial (most common), peripheral and/or autonomic.

**Pathophysiology:** Vasculopathy, compression, or antibody-related.

**Trigeminal:** Most common of cranial neuropathies, although any may be affected. Involves sensory > motor, often b/l, & a/w painful dysesthesias. 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:** ↓ GI motility & impotence.

***Neuropathy w/u*:** No sp. 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 if prox wkns. Typical pattern: nonprogressive, mild CK ↑, EMG: polyphasic motor units w/nl ampl. & duration w/o e/o ↑ insertional activity or denervation, muscle bx w/fibrosis w/o inflam. Must distinguish from inflam myositis. **W/u:** see *Myopathy* chapter. **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 +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), & high titer **anti-U1RNP**. More common: F>M, 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 # 4 or 5 (*J Rheum* 1989;16:328). **(2)** Se 62%, Sp 86% (*J Rheum* 1996;23:2055). Dx can take yrs 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.

## IgG4 RELATED DISEASE

Immunoglobulin G4-related disease (IgG4-RD) can affect many organs & characterized pathologically by tumefactive lesions with storiform fibrosis, obliterative phlebitis, & lymphoplasmacytic infiltrate rich in IgG4 plasma cells. Named b/c IgG4 elevated in serum in 60%-70%. Epi unclear. Can cause autoimmune pancreatitis, biliary inflammation, lung nodules, tubulointerstitial nephritis, salivary gland inflammation, thyroiditis, retroperitoneal fibrosis, etc.

**Neurological Involvement:** *Not known* to cause brain/spinal cord parenchymal dz.

1. **Pituitary**: Sx from ant./post. Hypopituit. Imaging: pit. mass/thick stalk. Most described cases w/concurrent IgG4-RD elsewhere & ↑serum IgG4 (*Endocr J* 2009;56:1033). Tx w/steroids.

2. **Hypertrophic pachymeningitis**: Sx from compression of neurovascular structures from meningeal

hypertrophy—headache (67%), CN palsy (33%), vision disturbance (21%), wkns (15%), numbness (12%), & others. 30% w/isolated meningitis & no systemic involvement (*JAMA Neurol* 2014;71:785). MRI w/localized or multifocal pachymeningeal thickening to mass lesions. CSF from nl to mildly ↑protein, ↑lymphs. Serum IgG4 elevated in 70%-90% (*JAMA Neurol* 2014;71:785). Meningeal biopsy gold standard dx. Tx with steroids plus steroid sparing agents (such as rituximab, methotrexate, azathioprine, & others).

## VASCULITIS

**Definition**: Inflammation, necrosis 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, can rupture, (b) stenosis & occlusion → ischemia/infarct. Localized (one organ) or systemic; affects vessels of different calibers. **Sx (variable):** Fever, rash, fatigue, wkns, pain, wt loss **Si:** Oral/genital ulcers, hemoptysis, HTN, hematuria, petechiae (small vessel vasculitis), palpable purpura (medium vessel).

**Neurologic manifestation:** HA, seizures, infarction, encephalopathy, psychosis, hemorrhage, peripheral neuropathies.



**Diagnostic modalities:**

- **Biopsy** involved sites (*gold standard*).
- **Angiography** (look for sequential stenosis & dilatation, i.e., beading, aneurysms); Nonspecific: Atherosclerosis, fibromuscular dysplasia (FMD), post-XRT can appear similar.
- **EMG/NCS** for infarction of peripheral nerves**.**
- **Laboratory features:** Hypoalbuminemia; anemia, ↑ plt, polys, eos; ESR > 100 mm/h, CRP > 10 mg/dL → r/o vasculitis if no infxn/CA; RF, ANA ⊖ in 1° vasculitis. **Other diagnostic testing**: BCx, hepatitis serologies, HIV, CMV, Utox, TTE, antiphospholipid Ab, SPEP; CSF VZV, HSV, syphilis.

**DDx:** endocarditis, hepatitis, drug abuse, malignancy, other infxn.

### COLLAGEN VASCULAR DISEASES ACCORDING TO VESSEL TYPE/SIZE

| | Veins | Ven-ules | Capillaries | Arterioles | Small art. | Large art. |
|---|---|---|---|---|---|---|
| CRYOGLOBULINEMIA | | | | | | |
| PAN | | | | | | |
| CHURG-STRAUS | | | | | | |
| WEGENER'S | | | | | | |
| SS | | | | | | |
| RA | | | | | | |
| SLE | | | | | | |

MAP

PAN, polyarteritis nodosa; SS, Sjögren syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus;

MPA, microscopic polyangiitis.

## LARGE-SIZED VESSEL VASCULITIDES

PACNS, Takayasu, GCA. Involve 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. Presentation**:

- **Systemic findings:** Unequal pulses/BP, absent radial pulse, bruits, HTN, pulm HTN, MI, heart failure, aortic regurgitation, CVAs.
- **Sx:** constitutional sx, HA, angina, vertigo; triphasic pattern (vague sx ~ "viral prodrome" → vessel pain (e.g., carotidynia) & tenderness).
- **Neurologic features:** Retinopathy, carotidynia, carotid stenosis → bruits, 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 [blood vessels grow into cornea] + vestibulo-auditory sx).

**Dx**:

- **Serology:** ↑ ESR, CRP, platelets; anemia.
- **Imaging:** Gold standard = angiography, ⊕long segmental stenosis, occlusions, aneurysms. MRA + gado → wall thickening, stenosis, thrombus. PET⊕ in inflamed vessel wall.
- **Bx:** cellular infiltrate like in 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: 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.

***Presentation (JAMA* 2002;287:92)**:

- **Sx:** New HA, TA/scalp tenderness (Se 52%), blindness, jaw claudication, facial pain, arthralgias, ↓wt, depression, fatigue, malaise. **Si:** Raynaud's, anemia, symmetric shoulder/hip pain & stiffness worse in a.m. (40% p/w PMR), FUO (1/3 GCA presentations), rigors, sweats.

- **Neuro si:** (?painless) sudden onset blindness (usually due to posterior ciliary artery necrosis) w/o ocular pain but w/temporal headache, 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.

***Dx***

- **Lab:** ESR > 50 mm/h (Se 83%); (wnl if on prednisone); 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 ⊖.
- **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***: Prednisone 40-60 mg 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 ischemic optic neuropathy(ti) (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:** thromboembolism, vasculopathy (such as Ehlers-Danlos, FMD, segmental mediolytic arteriopathy).

**1. Polyarteritis nodosa (PAN): Pathology:** Focal segmental necrotizing inflammation of medium/small arteries > arterioles, venules; fibrinoid necrosis, w/disruption of elastic laminae; ⊕ polys, lymphs, eos. **Etiology:** Idiopathic. **Epid:** M > F (2:1), 40-60 yo; ~7% prevalence in Hep B a/w PAN. **Sx:** arthralgias, myalgias, rash, abd pain, angina, testicular pain.

***Presentation***:

- **Si:** HTN, testicular tenderness, palpable purpura, livedo reticularis, acral necrosis, renal dysfn.
- **Neuro si**: Very high prevalence of neuropathy; presenting features of dz (30%) painful mononeuritis multiplex (50%-70%), wkns, paresthesias, sz, stroke, blindness.
- **Associated conditions:** Hep B, CMV, HTLV-1, parvo B19, EBV, Hep C, SLE, RA, DM, Cogan synd (interstitial keratitis + vestibulo-auditory sx), allopurinol, sulfa, hairy cell leukemia.
- **Exam:** Wkns, sensory deficits, retinal hemorrhages.

***Dx***

- **Serology:** ↓C3/C4 in active dz; ⊕ Hep B sAg (10%-50%), HBeAg, HBV DNA; ± ⊕ Hep C, ↑ ESR, CRP, Plt; anemia, ↓ albumin; ANCA ⊖.
- **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 not specific for PAN.

***Rx*: If ⊖ HepB** → High dose steroids, if severe, IV pulse dose methylprednisolone 1 g/day × 3 day, then prednisone 1-2 mg/kg/d 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 ⊕ INFα2b or lamivudine; **Rx success** = HBeAg ⊕ → ⊖

## 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** (or granulomatosis w/polyangiitis): 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.

***Presentation*: 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, subglottic stenosis, stridor, respiratory distress. **Neuro si:** Ocular findings (50%); PNS (10%-25%) > CNS (8%) involvement; mononeuritis multiplex, retro-orbital pseudotumor (in 15%) → scleritis, episcleritis, uveitis, optic neuritis, conjunctivitis, retinal artery thrombosis, sz, CVA. Hypertrophic pachymeningitis causes compressive cranial nerve palsies, radiculo-myelopathies **Exam:** Periph neuropathy, proptosis, ↓ visual acuity, disconjugate gaze, CN palsies.

***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. **CSF:** Lymphocytic pleocytosis, ↑ protein, ↑ IgG. **Serology:** c-ANCA ⊕ (anti proteinase 3); Se 90% (in limited dz 40%), Sp 98%; ↑ 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/adjacent muscle bx → vasculitis + noncaseating granulomas of small arteries, focal demyelination. Blood vessels abundant in muscle, sparse in nerves

***Rx*:** Cyclophosphamide 2 mg/kg/d + prednisone 1 mg/kg/d; gradual steroid taper if responsive; maintenance of remission w/MTX or azathioprine; other acute Rx: Rituximab + steroids instead of cyclophosphamide (*NEJM* 2010;363:3); w/o Rx → <1 yr 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.

***Presentation*: Sx:** New onset/newly progressing asthma (>95%), allergic rhinitis (70%), nasal polyps. **Si:** Triphasic evolution: **(1)** Prodrome → allergic rhinitis, asthma, polyposis. **(2)** Eosinophilia → like 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:** PNS (65%) mononeuritis multiplex (~75%), muscle vasculitis, panuveitis, keratitis, CVA vasculitis, optic neuritis, cranial neuritis. **Exam:** Paresthesias, wkns, atrophy, asymmetric sensorimotor polyneuropathy (legs > arms), AMS, cognitive changes, sz, SAH, intraparenchymal hemorrhage, psychosis.

***Dx*: ACR criteria** (need 4/6): **(1)** asthma, **(2)** eosinophilia >10%, **(3)** neuropathy (mono or poly), **(4)** transient pulmonary infiltrates on CXR, **(5)** paranasal sinus abnormalities, **(6)** ⊕ extravascular eosinophils. **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); ↓/⊖ 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, gradual taper over mo; IV methylprednisolone for severe/refractory dz if immunosuppressants, (e.g., azathioprine, MTX, mycophenolate mofetil, 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).

***Presentation*: Sx:** Constitutional sx, rash, hemoptysis, abdominal pain, bleeding, arthralgias. **Si:** Pulmonary capillaritis ± rapidly progressing necrotizing glomerulonephritis, HTN, hemorrhage, palpable purpura. **Neuro si:** PNS (40%-50%), mononeuritis multiplex (~60%), sz (~10%), meningeal vasculitis (~10%), ocular manifestations. **Exam:** Paresthesias, wkns, atrophy, wrist/foot drop, retinal hemorrhage, scleritis, uveitis, conjunctivitis, episcleritis.

***Dx*: 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*:** Prednisone 1 mg/kg/d + cyclophosphamide 1.5-2 mg/kg/d; other acute Rx: Rituximab + steroids instead of cyclophosphamide (*NEJM* 2010;363:3); MTX or azathioprine for maintenance IVIg, plasma exchange in pulmonary/renal failure. ***Complications*:** Severe pulmonary hemorrhage.

4. **Henoch-Schonlein purpura (HSP): Path:** IgA1 deposition, complement activation via alternate pathway → vasculitis of small vessels, usu postcapillary; also release of cytokines, inflammatory mediators. **Etiology:** Unk.; 2/3 w/antecedent URI 1-3 wk; usu, self limited, resolves over wks-mos. **Epid:** M:F 2:1; Mean age 5 yo; in adults & females can be severe, ↑ renal dz.

***Presentation*: 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 Δs, wkns, paresthesias (rare PNS involvement).

***Dx*: Imaging:** Cortical, WM stroke from vasculitis. **Serology:** ↑ IgA1 (in 50%), ↑ IgA1 circulating immune complexes, ↓ factor XIII (correlates w/dz activity), ↑ WBC, ↑ eos, ↑ plt, ↑ d-dimer, ↑ ASO titer (30%), ↓ CH50, ± ↓ C3, C4. **Bx:** IgA1 deposits on direct IF, leukocytoclastic/necrotizing vasculitis; ⊖ IgA1 → r/o Wegener's.

***Rx*:** Supportive (avoid NSAIDs if GI/renal involvement), 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 temp. 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's, coccidioidomycosis, toxoplasmosis, malaria, schistosomiasis; autoimmune dz, lymphoma, CLL. **Epid:** ⊕ drug use, ⊕ Hep C; F:M = 3:1; mean age 40-50 yo.

***Presentation*: Sx:** Rash, ulcers, arthralgias, wkns (Meltzer triad in 25%-30% Types II, III), fever, abd pain, SOB, cough. **Si:** Recurrent lower ext. palpable purpura (Type II, III > Type I); ulcers (Type I), Raynaud's, nephritic/nephrotic synd. (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, wkns, foot or wrist drop, numbness, papilledema, ↓cognition, AMS, TIA/CVAs, impaired vision.

***Dx*: Serology:** collect at 37°C to avoid false neg; ⊕ Hep C 70%-100%; âœ" 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, Vogt-Koyanagi-Harada syndrome, Sjögren, MS, CA, (carcinomatous meningitis, lymphoma, glioblastoma cerebri).



***Presentation*: Sx:** Oral ulcers, arthralgias, visual Δs, rash. **Si:** Aphthous ulcers, genital lesions, recurrent eye inflammation, erythema nodosum, folliculitis, skin ulcers, pulm hemorrhage 2/2 to aneurysm rupture, painful scrotal/vulvar ulcers, GI ulcers ˜ IBD, migratory asymmetric arthritis, thrombophlebitis, ⊕ factor V Leiden 33%, arterial/venous thromboses, myo/pericarditis. (*Lancet* 2009;8:192.)

**Neuro features:** Occur in ˜9%. M:F 3:1; mean age 20-40 yo. *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 (most frequent brainstem/diencephalon) vs. nonparenchymal (Middle East/France >> elsewhere); 40% mortality rate w/CNS dz. **Exam:** ⊕ cells on slit lamp;

retinal vasculitis; CN palsies, confusion, personality changes, ataxia, papilledema, wkns, pseudobulbar palsy, extrapyramidal signs.

Recurrent meningitis, rare, may be neutrophilic w/low glucose.

***Dx***: ≥3 oral ulceration in 1 y & ≥ 2 of: **(1)** Recurrent genital ulcerations, **(2)** eye lesions, **(3)** skin lesions, **(4)** ⊕pathergy test (sterile pustule at venipuncture site; common in Turkish, Japanese pts). **CSF:** ↑ protein, leukocytosis (early PMN & late lymphs). **Serology:** ↑ serum IgG, IgA, IgM, CRP, ESR, α2-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/d prednisone or IV 1 g/day methylprednisolone (solumedrol) × 3d; chlorambucil 0.1-0.2 mg/kg/d; AZT/cyclosporine(CsA)/cyclophosphamide/chlorambucil if life-threatening, severe ocular/CNS dz.

| **Key Features of Neuro-Behçet Dz (NBD)** | | |
|---|---|---|
| | **Parenchymal NBD** | **Nonparenchymal NBD** |
| **Neuro findings** | CN palsy, hemiparesis, sensory loss, sz, cognitive dysfxn, psychosis, encephalopathy, dementia, ataxia, sphincter dysfxn; pyramidal, brain stem dysfxn, spinal cord signs (rare; poor prognosis); diffuse meningoencephalitis (75%) | Stroke (2/2 to vascular dz)<br>↑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<br>Acute → ± contrast enhancement | Cerebral VST ± venous infarcts; aneurysms, extracranial dissection<br>MRS → ↑ lactate, ↓ NAA peak |
| **CSF** | pleocytosis (early PMN & late lymph) ± 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, meningoencephalitis; demyelination; gliosis, axonal injury in chronic lesions, atrophy (brainstem >> cortical = chronic NBD) | Venous infarcts (WM ± GW jxn, w/hemorrhage); SSS thrombosis (b/l cerebral convexity WM); deep cerebral vein thrombosis (BG, thalami) |
| **Rx** | Methylprednisolone, immunosuppressive agents; TNF-inhibitors, rituximab | VST → anticoagulation |
| **Prognosis** | Acute lesions ± reversible w/steroids | Better if treated early |

## SERONEGATIVE SPONDYLOARTHROPATHY/ANKYLOSING SPONDYLITIS (AS)

**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). **Note:** Called "seronegative" because RF⊖.

***Presentation***: **Sx:** Back pain, morning & nocturnal stiffness >1 h; 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%), resolves over months, commonly recurs; 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 transection, cauda equina syndrome [⊕ h/o longstanding AS; vertebral fx → nerve injury). **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.

***Dx Criteria*** (New York): LBP ⊕ inflammation > 3 mo, L-spine ↓ motion in sagittal, frontal planes, ↓ chest expansion; b/l sacroiliitis ≥ grade 2, unilateral sacroiliitis ≥ grade 3. **Serology:** ↑ ESR, ↑ CRP ∝ dz activity 75%; normocytic anemia; ↑ alk. phos., ± ↑ CK, ↑ serum IgA level; *HLA B27* status; ANA, RF ⊖;âœ" VDRL, ACE, RPR, PPD. **Imaging:** *Fluorescein angiography* → retinal vasculitis; *X-ray spine*→ bamboo spine; **symmetric sacroiliitis**, 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.

# IDIOPATHIC INFLAMMATORY MYOPATHIES

Includes dermatomyositis, polymyositis, inclusion body myositis. Can be 1° or 2°. See *Myopathy* Chapter 24).

# 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-inflamm. (inhibit PLA2, COX-1, COX-2); *SEs*: myopathy, psychosis, euphoria, depression, cataracts, weight gain, GI conditions, HPA axis suppression, fractures

**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*: cerebral demyelination (TNF), sz/drowsiness (inflix), drowsiness/dizziness paresthesias/neuralgia (adalimumab).

**Dapsone:** *MOA*: folate synth inhibitor, immunosupp.; *SEs*: HA, psychosis, periph 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, paresthesia, neuropathy.

**Mycophenolate mofetil (cellcept):** *MOA*: purine synth inhibitor; *SEs*: insomnia, HA, tremor.

**NSAIDs:** *MOA*: nonselective COX inhibitor; *SEs*: HA, dizziness, tinnitus, aseptic meningitis.

**Penicillamine:** *MOA*: ↓T-cell, macrophage inhibition, ↓RF, ↓IL-1; *SEs*: RA or SLE-like synd, PM/DM, myasthenia gravis.

**Sulfasalazine:** *MOA*: ↓ inflammatory mediator synthesis; *SEs*: ataxia, aseptic meningitis, vertigo, tinnitus, insomnia, depression, hallucinations.

**Tacrolimus:** *MOA*: FKBP12 inhibitor, calcineurin inhibitor; *SEs*: HA, insomnia, paresthesias, tremors, PRES.



## 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 holding agents in surgery, severe infxn. Review **pregnancy** plans/birth control w/reproductive age women.

### Immunosuppressants & cancer risk

- Cyclophosphamide—life-long ↑ cancer risk, particularly bladder cancer- UA q3-6 mo.
- TNFα inhibitors—melanoma (?solid cancer, lymphoma).
- AZA—?lymphoma.
- MMF—?skin cancer.

**Monitoring of Specific Immunotherapy**

| Drug | SE | Monitoring/Care |
|---|---|---|
| NSAIDs | GI bleed; ↑ CV risk | GI ppx |
| Corticosteroids | HTN, hyperglycemia, | Routine BP, glucose; weight-bearing exercises, Vit D3 800-2,000 IU qd + Ca 1,200-1,500 mg qd, |

| | | |
|---|---|---|
| | osteopenia, ↑WBC | DEXA in pts >40, bisphosphonates<br>PPI—if on steroids + NSAIDs, prednisone >1,000 mg, >30 day, elderly, hx of ulcers<br>TMP-SMX PCP prophylaxis if needing >20 mg/day, > 1 mo, esp receiving another immunosuppressive |
| Azathioprine, chlorambucil, cyclophosphamide, gold penicillamine, sulfasalazine | Myelosuppression | Periodic CBC, urine protein for gold/penicillamine[a]; urine cytology for cyclo-phosphamide[b]; TPMT genotype for azathioprine; 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 |
| Methotrexate | LFT Δ, myelosuppression | CBC w/diff, LFT q2-3mo |
| TNF-α inhibitors | Infxn, demyelinating dz | CBC w/diff, LFT q6mo; close clinical monitoring |
| [a]May cause proteinuria.<br><br>[b]May cause hemorrhagic cystitis. | | |

**PML Risk;** Reactivation of JCV risk: natalizumab > RTX > CYC, MMF, AZA, MTX, TNF-α inhibitors, glucocorticosteroids.

- Risk stratification in pts on natalizumab based on anti-JCV serology, duration of treatment, & previous chemotherapy.

# Neuro-Oncology

Nancy Wang

Mikael L. Rinne

**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; primary > met. Presenting si/sx in: 50% of melanoma mets, oligodendrogliomas, hemorrhagic tumors. More sz complications 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 distinguish 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.

**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's; 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 if BBB breakdown, often reflects malig. *Exceptions*: Some benign tumors enhance vividly, some malig don't (~40% nonenhancing gliomas are high-grade). **MRS** may help distinguish tumor [↓ *NAA* (neuron terminals); ↑ *choline* (cell membrane); ↑ *lactate* (necrosis/anaerobic metab)] from another process (tumor/stroke/infxn). **FDG-PET** may distinguish highvs. 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 ↓ 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). Steroids ↓ 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; BID dosing for outpatients.*

**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 ppx for >6 wk steroids: TMP-SMX SS PO qd or DS qMWF. Consider if on dose equivalent of ≥20 mg prednisone for >4 wks. GI ppx for perioperative/high dose steroids: PPI daily. Stress dose steroids occ required. Calcium + vitamin D may prevent osteoporosis.

**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: may 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 chemosensitive (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 XRT (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 (SRS): 1-5 fractions of high intensity radiation. Head fixation crit for accuracy—some systems req rigid head frame placed by neurosurg, others frameless. Photon-& proton-based approaches biologically equal affect on tumors. 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 Rxfor: 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 (TMZ) | Glioma | Nausea, HA, fatigue, myelosuppression, hepatotox, constipation |
| Carmustine (BCNU) | Polymer wafer implant for glioma | Nausea, myelosuppression, pulm fibrosis, leukemia |
| PCV (procarbazine, CCNU, vincristine) | Low-grade glioma | Myelosuppression |
| Cisplatin, vincristine, & cyclophosphamide or CCNU | Medulloblastoma | Nausea, nephrotox, peripheral neurop, myelosuppression, hemorrhagic cystits |
| Methotrexate | Lymphoma | Nausea, fatigue, renal insufficiency, stomatitis, hepatotox, pneumonitis, myelosuppression |

## PRIMARY CNS TUMORS

**Epid:** 1° brain tumors = 2% of cancers = ~21/100,000 person-yrs; ↑ing. M > F for malignant tumors, opposite for nonmalignant. Non-Hispanic > Hispanic (excl pituitary), Whites > Blacks (excl mening, pituitary, craniopharyngioma) > 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 (see Genetic Synd below), prior XRT ↑ meningiomas, astrocytomas, sarcomas.

**Classification:** WHO system (named for cell of origin). Gliomas most common (glial cells). Gliomas not easily biopsied named for location (brainstem glioma, optic glioma, 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 (GBM) & anaplastic astrocytoma:** (*NEJM* 2008;359:492; *JAMA* 2013;310:1842) Diffusely infiltrating, arise from glial cells, typically in white matter.

**Epid**: Most common brain tumors (80% of malig tumors, 5/100,000 people). Most common in 6-8th decade, ↑ing, unclear why (? improved imaging). Ionizing radiation is only known 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 ± TMZ* (*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/m2, after RT = 150-200 mg/m2 × 5 d, q28d × 6-12 cycles. Prolongs survival: 15 mo vs. 12 mo for surg + XRT alone, 2-yr survival 25% vs. 10%, respectively. *MGMT* (DNA methylation repair enzyme) silencing increases sensitivity to TMZ. Monitor liver function, blood counts, PCP/PJP prophylaxis while on TMZ + XRT. **NovoTTF-110A:** a portable, battery-operated device for chronic administration of alternating electric fields to region of tumor via surface electrodes. Shown to have comparable outcomes to standard therapy in recurrent GBM with fewer side effects, phase III trial w NovoTTF + TMZ shows improved PFS (7.1 vs. 4 mo), OS (19.6 vs. 16.6 mo), and 2-yr survival (43% vs. 29%) vs. TMZ alone (NCT00916409). **Recurrence:** Almost



all recur (median = 7-10 mo after XRT + TMZ). 1 mo MRI ↑enhance in 40% = half "pseudoprogression" (vascular permeability from XRT).

**Rx after recurrence**: Repeat surgery in some cases for cytoreduction, mass effect, histo/molecular update. Anti-angiogenic therapy increasingly important (decreases vessel permeability, MRI enhancement): bevacizumab approved for progression following standard therapy. Also, consider TMZ rechallenge, other cytotoxic chemotherapy.

**Prognosis**: Age, grade, resection, performance status, IDH mutation, & MGMT status influence survival. Long-standing sxs, no AMS, small size may be a/w longer survival. 90% recur at original site.

**Recursive Partitioning Analysis Stages for Survival w/GBM Treated w/XRT + TMZ**

| Stage | Characteristics | Median OS | 2-yr OS |
|---|---|---|---|
| III | Age <50, PS 0 | 17 mo | 32% |
| IV | Age <50, PS 1-2<br>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 (2/3)*, thickening of corpus callosum, loss of gray-white differentiation.

**Rx**: No standard Rx. Not amenable to surgery because of extent of spread. WBXRThigh rate of stabilization,

impact on survival unclear. Up front chemo benefits some pts, may be preferred: Rxw/TMZ/PCV (procarbazine, CCNU, vincristine).

**Prognosis**: Median survival = 14.5-18.5 mo (11 mo w/no tx). *Better prognosis*: Young, high performance status, lower grade, male, oligodendroglial type, 1p/19q codeletion, MGMT methylation. *Poor prognosis:* ↑gray matter involvement (*Neurology* 2009;73:445; JNO 2013;112:267).

**Low-grade gliomas:** (*Oncologist* 2006;11:681, Oncologist 2014:14:403) 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 giant-cell astrocytoma (SEGA); WHO II: diffuse astrocytoma, PXA (pleomorphic xanthoastrocytoma). New enhancement or↑ MR perfusion may reflect transformation to high grade.

**Rx**: Optimal Rx unclear. **Surgery:** Increase data for early resection vs. obs & delay intervention. Surgery for large, symptomatic tumors; Max safe resection appears to improve survival. **XRT:** Given at dx; ↑ time to progress & ↓ szs but no survival benefit. Typical dose = 45-54 Gy. Obs if small, min. sxs. Chemo options following XRT include TMZ and PCV; PCV shown to improve PFS and OS in LGG when given after XRT (13.3 yrs vs. 7.8 yrs). TMZ often used for better side effect profile. *Szs*: Mgt difficult, may require surgery.

**Prognosis**: 1p/19q deletion a/w superior survival, enhanced sensitivity to Rx in low-grade oligodendrogliomas. IDH1/2 mutations a/w prolonged surgical, enhanced sens to treatment (esp TMZ). *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 distinguish 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 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). Often present in first 2 decades of life with sz, signs of ↑ICP. Near foramen of Monro (classic)/on ependymal surface of lateral ventricles. MRI: T1 iso, T2 hyper, common enhancement, often calcified. Asymptomatic tumors do not require Rx. Surgical excision for symptomatic tumors, everolimus (mTOR inhibitor) associated with ↓ size, sz freq.

**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 (2/3 <18 yo), <1% of all astrocytic tumors, WHO Grade II. BRAF V600 mutation in ~60%. Uncommon, usu supratentorial, typically adherent to meninges, may be cystic with mural nodule. Often present w/sz. 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*. Often present w/hydrocephalus, signs of ↑ICP, cranial nerve abnormalities.

**Dx/imaging**: *MRI* prefer'd for dx & f/u. Often can't bx if intrinsic to brainstem; dx on MRI alone. *Ddx*: Consider NF1 (only risk factor). Mimics: Brainstem encephalitis (viral/autoimmune), brainstem encephalop (mitochondrial), vasc malformations, MS, hamartomas.

**Oligodendroglioma & mixed gliomas:** (*JCO* 2006;24,1246; Oncologist 2009;14:155). 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 Δ, 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. *Chemosensitive* (due at least in part to 1p19q): chemo occasionally given up front to delay XRT. *PCV or TMZ* effective, response up to 100% in 1p19q compared w/23%-31% in non-1p19q. PCV improves both PFS and OS when combined w/XRT compared to XRT alone (RTOG 9802). Can initially give one PCV or TMZ, then the 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; *Curr Neurol Neurosci Rep* 2010;10:240) 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, subependymoma (WHO Grade I). Ependymoma (WHO Grade II). Anaplastic ependymoma (WHO Grade III).

**Rx/prognosis**: *Surgery:* Gross total resect improves survival, but often complicated. Potentially curative for WHO Grade I tumors. Higher grade, incomplete resection younger age, male, intracranial tumor location, associated with worse clinical outcome.

*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, consider platinum-based regimen.

Even w/surgery & radiation, *prognosis poor* w/~50% local recurrence.

## MENINGEAL TUMORS

**Meningioma**: (*Neurosurgery* 2005;57:1088; *Curr Neurol Neurosci Rep* 2013;13:337): Most common benign BT (54%). 36% of all 1° brain tumors. 7.33/100,000 person-yrs; 98% intracranial. F > M (intracranial 2:1; spinal 9:1). Originate in arachnoidal cells. Most *slow growing & benign* (78%) = WHO Grade I. *Atypical* (20%-38%, WHO II), *malig* (1%-3% WHO III; more aggressive; more common in men). Usu single, but can be mult (*familial synd/NF2*). *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, population incidence (~1%) ↑'s w/age. Location: any meningeal tissue, esp dural reflections (60% parasagittal, convexity, tuberculum sella, and sphenoid ridge).

**Dx**: Diagnosed by imaging. Biopsy not always required for Rx (XRT 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 (meningothelial/fibrous/transitional/psammomatous/angiomatous/microcystic/secretory/lymphoplasmacyte-rich/metaplastic). *WHO II* = atypical (choroid/clear cell. ↑'d mitotic activity ≥4 mitoses/10 hpf & ≥3 of: ↑ nuc: cyt ratio/prominent nucleoli/sheet-like growth/foci of necrosis, or brain invasion). *WHO III* = anaplastic AKA malig (papillary, rhabdoid. ↑ degree of abnormality, larger areas of necrosis, ↑ mitotic activity ≥20 mitoses/10 hpf). Secretory meningiomas a/w ↑ edema.

**Ddx**: Lymphoma, dural mets, CNS sarcoid, extramedullary hematopoiesis, 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 <3 cm lesions. Definitive XRT similar outcome to surgery. Postop XRT of SimpsonIV/high grade ↓'s recurrence 2-4×. **(4)** *Systemic therapy*: Investigational: anti-angiogenic drugs, somatostatin analogs, hormonal receptor antagonists, hydroxyurrea, TMZ.

**Prognosis**: **(1)** *Degree of resection:* OS at 10 yr w/Simpson I-III resection 80%. With Simpson IV risk of death

increases by RR 4.2×. **(2)** *Tumor grade*: relapse rate for WHO grade I/II/III 7%/40%/80%, median survival >10/11.5/2.7 yrs. **(3)** *Hormone receptor status*: 5% median recurrence rate if PR+, 30% if ER+ or PR/ER-.

**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:** (*Am J Clin Oncol* 2014;Epub ahead of print) Rare aggressive mesenchymal tumors arising from pericytes surrounding endothelial lining of capillaries and venules. 2.5% of mening tumors, <1% intracranial tumors; avg age 44 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, often challenging 2/2 high vascularity; subtotal resection ↓ OS (111 mo vs. 158 mo). Local recurrence, distant mets common, often late. XRT ↑ local control & OS (123 mo XRT vs. 93 mo).

**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, early age at dx). ~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; *Nat Rev Neurol* 2013;9:317) Rare tumor affecting *brain, spinal cord & eyes*. Intermediatehigh-grade non-Hodgkin lymphoma (most B cell).

Responds to steroids, chemo, XRT, but relapse common. 2%-8% have systemic lymphoma (CXR, CT abd/pelvis). Immunocompromise is main risk factor.

**Epid**: Incidence 0.47/100,000 person-yrs; 2% of intracranial tumors. Any age; most commonly 50-60 s; M > F (slightly).

**P/w**: Perivent WM, subcort/cortical, leptomeninges/CSF (40%), vitreous (20%). 30%-40% mult. Sxs vary w/location; Typical: focal defs, cognitive dysfunction. Others: HA, sz, personality Δs, lethargy, amnesia, 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:** Brain MRI: Iso/↑ T1, ↑ T2, homog enhance, diffusion restriction. HIV-related: MRI mult ring-enhancing ↑ T2. Image spine if clinical suspicion of cord involvement **(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. Check CSF EBV if immunocompromised. **(4) Ophtho** Exam w/slit lamp exam for vitreous involvement. **(5)** Body imaging (CT chest/abdomen/pelvis or PET/CT) to r/o systemic dz. Consider testicular U/S. **(6) Bone marrow biopsy. (7) Laboratory Eval:** CBC, CMP, HIV, LDH.

**Ddx:** glioma, met, sarcoid, vasculitis, MS, CLIPPERS, Langerhans cell histiocytosis; immunocompromised: TB, toxo

**Rx**: **(1)** Dramatic *temporary* response to corticosteroids. **(2)** No resection—does not improve prognosis, may worsen deficits **(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. Investigational use of stem cell transplant.

**Prognosis**: Performance status, age are prognostic. 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 compression or invasion → 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.

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**Craniopharyngioma:** (*J Neurooncol* 2009;92:283; *Horm Res* 2008;69:193; *Handb Clin Neurol* 2014;124:235-253) In children/adol (30%-50%) 0.11/100,000 person-yrs; 0.8% of BTs (1%-4% in children). In adults, peak 50-70 yo. Benign epithelial *sellar* tumor; often extends into surrounding structures.

**P/w**: Sxs from compress of optic chiasm, pituitary & 3rd vent. Headache, visual field defects, hormone aberrations (80%-90%), 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:** Adamantinomatous more common in children, lobulated cystic mass w/areas of palisading columnar epithelial cells, keratinization/calcification common. Papillary more common in adults, solid tumor, sheets of squamous epithelial cells. >90% papillary subtype have BRAF V600 mutation.
- **Neuro-ophtho eval:** Funduscopy, 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. Also ↑ cardiovascular, cerebrovascular, respiratory mortality. Subtotal resection + XRT = 80%-95% success.

**Pituitary adenoma:** (*NEJM* 2006;355:2558; *Curr Opin Neurol* 2012;25:751) 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 antpituitary 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 (dopamine agonists, cabergoline > bromocriptine); somatostatin analogs for GH-screting adenomas. *Surgical*—transsphenoidal resection; esp if visual field def. Gross total resect usu not possible. *XRT*—after subtotal resect. TMZ can be used for pituitary carcinomas. *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, lightnear 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) vs. 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. Adjuvant XRT to subtotal resection does not increase survival.

**Pineoblastomas: Def:** Primitive neuroectodermal tumor (PNET). Most aggressive pineal tumor. **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. Median survival 20 mo.

**Intracranial germ cell tumors:** (*Oncologist* 2008;13:690; *J Neurooncol* 2010;96:143; *Med Oncol* 2013;30:496) Germ cell tumors from multipotent embryonal cells. Identical to extracranial GCTs: testicular seminomas & ovarian dysgerminomas. 90% < 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** (18%; mature & immature); often considered separate category.

**Epid**: 12-40 yr; 0.10/100,000 person-yrs; 0.5% of intracranial tumors. 50% pineal region tumors are germ cell tumors. Pineal GCTs: M > F (15:1); 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 distinguish* germinomas & NGGCTs. MRI of spine for staging (10%-15% have leptomeningeal spread, esp NGGCT).

- **LP:** CSF & serum pre-op *or* 10-14 days post-op (cytology & markers). Check CSF for *cytology* to diagnose leptomeningeal mets. CSF more sensitive than serum for tumor markers.
- **CSF & serum:** *AFP*—↑ in yolk sac tumors/immature teratoma; *B-HCG*—↑ in choriocarcinoma/immature teratoma/rarely germinoma; *hpALP*—↑ in germinoma; *CEA*—↑ increased in malignant teratoma.
- **Biopsy:** ↑ AFP or marked (>200 IU) ↑ CSF B-HCG sufficient to dx NGGCT; no bx needed. ↑ β-HCG → bx to distinguish 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. Immature teratoma can treat with additional chemo + XRT.

## EMBRYONAL CARCINOMAS

**PNETs:** Highly *aggressive*, spread via CSF (send CSF cytology). Tumors of childhood & young adulthood, 80% diagnosed < 10 yo. **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 but recurrence common.

**Medulloblastoma:** (*Nat Rev Clin Oncol* 2014;11:714; *Clin Onc* 2013;25:36) Most common PNET, generally post fossa. 50%-60% in 1st decade, peak in 20s. 20% of brain tumors in children (*most common pedi CNS tumor*), 0.4%-1% adults.



**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 wk postop. *Risk stratification*: **(1)** Avg risk (66%) (>3 yo, <1.5 cm2 resid dz after resect, M0 by craniospinal MRI & CSF). **(2)** High risk (34%) [<3 yo, subtotal resect, >1.5 cm2 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.

**Path:** Histological classification: classic (80%), demosplastic nodular (15%), medulloblastoma with extensive nodularity, and anaplastic large cell. 4 recently described clinical/molecular subtypes: Wnt, sonic hedgehog, group 3, and group 4.

**Rx**: **Surgery:** Posterior fossa craniotomy, total resection is goal. CSF diversion only after surgery; 30%-50% require VP shunt. Surgery alone almost all recur. **Chemo + XRT:** Standard of care in all risk groups. In young children, often avoid XRT 2/2 neurocog effects. 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, TMZ, bevacizumab. Trials on auto stem cell transplant.

**Prognosis**: Relates to dz extent, subtype. 5-yr OS with standard therapy of resection, XRT, adjuvant chemo: >90% for Wnt, 40%-60% for group 3, 75% for group 4, sonic hedgehog. Large cell anaplastic has poor prognosis. *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%, develops typically within 24-48 hrs of surgery, can take months to resolve), blindness, ototoxicity, endocrine, cognitive defs, second malignancy.

**AT/RT (atypical teratoid/rhabdoid tumor):** (*J Neuro-oncol* 2005;75:309) *Highly malig* embryonal tumors. Rare (<2%) 1° CNS pediatric tumor; majority in pts < 3 yr. Often p/w ↑ ICP/hydro: HA, n/v, lethargy; may also have ataxia, motor regression, CN palsies. CNS variant of primary malig rhabdoid tumor can manifest in other sites.

**Dx**: **Imaging:** Bulky, solid, & cystic w/hemorrhage. 2/3 cerebellar, 25% supratentorial, 8% multifocal. *MRI*: iso/↓T1; iso/↑ T2 (heterog), heterog enhance. 30% leptomeningeal spread: Image entire neuraxis, send **CSF cytology**. Difficult to distinguish 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 gangliocytoma 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). A/w BRAF V600E mutation.

**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.

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**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/high MIB-1 index/atypical histologic features. 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 distinguish 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, usually 3rd-5th decade of life. 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. Mostly sporadic, although ~1/3 may be associated with inherited syndrome (e.g., MEN2, NF1, VHL).

**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, hyperdense, intense enhancement. Generally not biopsied for dx because of vascularity/characteristic imaging.

**Rx**: **Surgery** first line, >90% long-term control rate; risk of CN palsies, CSF leak. **XRT:** Inoperable/large can Rxw/fractionated XRT (~54 Gy) w/>90% control rate; small inoperable tumors treated w/SRS w/similar results (>90%); Rx goal = to stop progression, not shrink (though ~40% shrink).

## CHOROID PLEXUS TUMORS

(*Neuro Oncol* 2013;15:255) **Def/Epid**: Ventricular tumors from CSF-producing CP. 0.5% of intracranial tumors (~15% if <1 yo), mean age at dx 3.5 yrs. Vent distribution proportional to choroid: 50% lateral, 40% 4th, 5% 3rd, 5% multifocal. More commonly lateral vent (L>R) in children, 4th in adults. WHO grades I-III: papilloma, atypical papilloma, and carcinoma depending on mitotic activity, histologic appearance. **CP Papilloma (CPP)** (80%) benign, resemble choroid, hamartomatous (WHO I). **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:* well-circumscribed, cauliflower appearance. *CT* enhancing, 25% calcified (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, MIB > 5%, 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. Chemo: Reports of chemo (vincristine, etoposide, carboplatin/cyclophos) in pediatric population, for recurrent/metastatic CPPs. 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. Commonly posterior fossa. Similar in behavior, development, histology & imaging. Slow sx onset (~2 yr). Sx relating to



location/mass effect, frequently involve CNs, ICA, causing HA, visual sxs, cranial neurop, sz. Rare cyst rupture: asymptomatic or → chemical meningitis (can be fatal).

**Rx**: Obs if asymptomatic. Surgery if symptomatic.

**Prognosis**: Benign; rarely transform into squamous cell carcinoma. 20-yr survival >90%.

## 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 (20-50 s), 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 prostate,

breast, lung); often extend vertebral bodies, invade/compress. Occ 1° tumors: Sarcoma, chondrosarcoma, chordoma, Ewing's, plasmacytoma, multiple myeloma, 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 occur 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 high-grade or incompletely resected low-grade astrocytomas, 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, may have cystic spaces, often rim of T2 hyperintensity (corresponds to arachnoidal gliomatosis). NF1: more tortuous, kinked. non-NF1: fusiform. Unlike meningioma, cannot distinguish nerve from tumor. **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, usually 5th decade of life.

**Sxs:** classically painless progressive vision loss, although may have pain w/eye movement, orbital HA.

**Dx:** *CT*: Tubular involvement of optic nerve sheath (enhancement around nonenhanced nerve, “tram-track” sign). Bone remodeling/calcification in 20%-50%. *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). Incidence 1/100,000/yr, F

> M (2:1), avg age at dx 50 yo, >90% U/L. 1% population, <1% symptomatic. *Risk factors*: Acoustic trauma, parathyroid adenomas, NF-2, head/neck radiation. 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 (17%). Facial: Paresis, taste disturbance (6%). Posterior fossa: Ataxia (rare).

**W/u**: Confirm sensorineural hearing loss (Rinne & Webber, audiometry); assess other CN. Dx based on imaging; bx often not nec. *MRI*: iso-T1, well-circumscribed, ↑T2, 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 <3 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, a type of sarcoma).

**W/u**: MRI w/& w/o contrast: T1 heterog, ↑T2. Dx often only established w/excision.

**Rx**: *Observation Versus. CO2 laser:* For asymptomatic/minor dermal lesions. *Surgery*: Consider for plexiform given malig potential. *XRT:* For inoperable/malig cases.

## GENETIC SYNDROMES

*(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):** (*Lancet Neurol* 2014;13:834) Aka *von Recklinghausen* dz or peripheral neurofibromatosis. A/w neurofibromas & gliomas. *Most common* neurogenetic disorder; incidence ~1/3,000, 10× more common than NF2. *Aut dom*, complete penetrance but w/variable phenotype. Mutation in NF1 gene on *chromosome 17*q11.2 (neurofibromin: silences p21-ras). 50% sporadic, 90% diagnosed by age 7.

***Dx criteria:*** NIH diagnostic criteria = ≥ 2 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%-20%, ~4% by 3 yo; Pilocytic astrocytomas of optic nerve, chiasm, tract, hypothalamus; 4% symptomatic (proptosis/visual loss/precocious puberty); Nonoptic gliomas: 100× 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 sphenoid wing/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* (8%-13%), vasculopathy/cardiovascular abnormality (e.g., pulmonary

stenosis). *Rare*: Pheochromocytoma (0.1%-5.7%), leukemia, high-grade astrocytoma, breast cancer, GI stromal tumor (4%-25%), rhabdomyosarcoma (1.4%-6%), duodenal carcinoid tumor (1%).



| Genetic Synds A/w Nervous System Tumors | | | | |
|---|---|---|---|---|
| **Synd** | **Inheritance** | **Mutation** | **Nervous System Tumor** | **Other Common Features** |
| NF 1 | Dominant 50% sporadic 1/3,000 | 17q11.2 Neurofibromin | Neurofibromas Gliomas (optic, brainstem, hemispheres) | Café au lait macules Skin fold freckling Lisch nodules MPNST |
| NF 2 | Dominant 50% sporadic 1/25-40,000 | 22q12.2 Merlin | Schwannomas (CN VII) Meningioma Spinal ependymoma Spinal astrocytoma | Juvenile cataracts Café au lait macules |
| Tuberous sclerosis | Dominant 2/3 sporadic ~1/6,000 | 9q34 Hamartin 16p13.3 tuberin | Cortical tubers Subependymal nodules SEGA Glioma | Facial angiofibromas Shagreen patch, ash leaf Ungual fibromas Lymphangiomyomatosis Renal angiomyolipoma Cardiac rhabdomyoma Retina nodular hamartomas |
| Von Hippel-Lindau | Dominant 20% sporadic 1/36,000 | 3p25 pVHL | Hemangioblastoma | Retinal angiomas Renal cell carcinoma Pheochromocytoma Endolymphatic sac tumor |
| Cowden synd | Dominant 1/200,000 | 10q22 PTEN | Lhermitte-Duclos' Dz | Trichilemmomas Breast, Endometrial & Thyroid cancer |
| Li-Fraumeni, synd | Dominant Very rare | 17p13.1 P53 | Astrocytoma Medulloblastoma PNET Neuroblastoma | Breast cancer Sarcoma Leukemia Adrenocortical carcinoma |
| Turcot synd | Variable Dominant/recessive | Several Astrocytoma | Medulloblastoma Ependymoma | Colorectal polyposis (FAP/HNPCC) |

| | | | | |
|---|---|---|---|---|
| Gorlin synd | Dominant 50% sporadic 1/57-164,000 | 9q22.1-3 Patched-1 | Medulloblastoma Meningioma | Basal Cell Carcinoma Jaw cysts, rib abnlity Dural calcification |

**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):** (*Handb Clin Neurol* 2013;115:957) Aka "central" neurofibromatosis. A/w multiple tumors: Meningiomas, spinal gliomas & schwannomas. Incidence 1/25,000-50,000. Aut dom, full penetrance, uniform in families. ~50% w/new mutations in NF2 gene, chromosome22 ("merlin": links cytoskeletal proteins). Inactivated NF2 gene in most sporadic schwannomas, 50%-60% of sporadic meningiomas, 30% mosaicism.

**Dx criteria**: ≥1 of**: (1)** B/l Vestibular schwannomas, **(2)** NF2 FHx + (a) u/l Schwannoma or (b) ≥2 meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, or juvenile cortical cataract.

**P/w**: Sxs 17-21 yo (usu 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 (>90%), hallmark of NF2 = prog hearing loss → complete deafness by adulthood. Freq other CN (24%-51%) & spinal nerves. **(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. Other: neuropathy, cataracts,

**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*. Auditory brainstem/Cochlear implant can improve hearing loss. **Surg:** Consider early for: rapid growth, prog sxs (risk iatrogenic deafness). Minority of spinal tumors require surgery. **XRT:** for nonoperative vestibular Schwannomas (?risk transformation/second malign). **Biologic Rx:** Bevacizumab ↓ tumor volume & improved hearing for nonoperative/XRT pts (*NEJM* 2009;361:358).

**Prognosis**: Median survival 15 yr from dx.



**Tuberous sclerosis complex (TSC):** (*Handb Clin Neurol* 2013;111:323) 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 (more commonly TSC2 mutation); 1/3 cases familial, 2/3 sporadic.

**P/w**: Variable; epilepsy & cogn disability common, related to tuber number. 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* (subependymal giant cell astrocytoma): Benign slow growing periventricular glial tumor (predilection for foramen of Monro, 6%-9% symptomatic, can cause obstructive hydro, 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<br>Shagreen patch (connective tissue nevus)<br>Ash leaf spots (≥3)<br>Nontraumatic ungual or periungual fibromas<br>Lymphangioleiomyomatosis (aka lymphangiomyomatosis)<br>Renal angiomyolipoma<br>Cardiac rhabdomyoma<br>Mult retinal nodular hamartomas<br>Cortical tuber<br>Subependymal nodules<br>Subependymal giant cell astrocytoma |
| **Minor** clinical features | Confetti skin lesions (mult 1—2 mm hypopigment macules)<br>Gingival fibromas<br>Mult randomly distributed pits in dental enamel Hamartomatous rectal polyps<br>Mult renal cysts<br>Nonrenal hamartomas<br>Bone cysts<br>Retinal achromic patch<br>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. Consider CT chest for LAM in women. **(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: consider mTOR inhibitors (everolimus) in patients w SEGAs who are poor surgical candidates. Topical sirolimus used for angiofibromas, oral being studied for other indications.

**Prognosis**: 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 in >90%, tumor suppressor gene on Chrom 3p25. New mutations ~20%. *Type I:* deletion/nonsense mutation, no pheochromocytoma. *Type II:* missense mutation, high rate pheo (Type II A—low risk of RCC; Type II B—high risk of RCC; Type II C—pheo only, no RCC/hemangioblastoma).

**P/w**: Sxs childhood-early adulthood (avg 26 yo), avg age at diagnosis = 31 yrs. Post fossa: Ataxia/dysmetria/hydro.

**Dx criteria**: ≥2 hemangioblastomas OR 1 hemangioblastoma + visceral lesion (pheo, pancreatic/renal cyst, RCC) OR 1 retinal/CNS hemangioblastoma or visceral lesion + FHx of CNS or visceral manifestations

**Tumors**: **(1) Hemangioblastoma** (25% VHL (often mult), 75% sporadic): Benign vascular neoplasm w/unpredictable growth. *Most common* VHL tumor (60%-84%,



avg 29 yo), cerebellum/BS/cord. MRI: Cystic w/enhance mural nodule. **(2) Retinal angiomas:** Retina/ON hemangioblastoma; up to 70%, often bilat. Risk: Hemorrhage & vision loss. **(3) Renal cell carcinoma** in 2/3 pts, ↑ w/age, 85% recurrence by 10 yrs. **(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: (a) Starting at 1 yo: annual eval for neuro sx, vision/hearing disturbance, BP monitoring, ophtho eval. (b) Starting at 5 yo: annual blood or urinary fractionated metanephrines, audiology every 2-3 yrs, thin-slice MRI w/gad of IAC if repeated ear infections. (c) Starting at 16 yo: annual abd U/S, MRI abd every other yr, MRI brain/total spine every 2 yrs.

**Rx**: **(1) Hemangioblastoma:** *Surveillance* for asymptomatic lesions. *Surgery* if sxs; ~17% recur. XRT 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: pazopanib (NCT01436227, phase II), sunitinib (*Ann Oncol* 2011;22(12):2661). Agents approved for RCC in general but not specifically VHL: bevacizumab, sunitinib, srafenib, axitinib, pazopanib, everolimus, temsirolimus.

## RARE GENETIC NEURO-ONCOLOGY SYNDROMES

**Cowden synd:** Aut dom, 1/200,000. PTEN (chrom10) Mutation. Hamartomas in mult organs; cutaneous hallmark=trichilemmomas; often macrocephaly. Predisposition to breast (up to 67%), thyroid (35%), endometrial cancer (28%); also increased risk of RCC, GI cancer. Pathognomonic CNS feature in adults: *Lhermitte-Duclos dz* = cerebellar dysplastic gangliocytoma, *P/w:* HA/n/v/ataxia/obstr hydro. *MRI:* Wellcircumscribed nonenhancing ↑ T2 enlarged folia ("tiger striped"). Surgery if prog growth; may recur, XRT ineffective; promising initial results from phase II trial of sirolimus (NCT00971789).

**Li-Fraumeni synd:** Mutations in the *TP53* gene in 70%, higher penetrance in F than M. Early-onset tumors: breast, sarcoma, leukemia, adrenocortical carcinoma, & brain. Brain tumors (10%-15%), 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%); also pineoblastomas, gangliogliomas. Mutation in APC gene. *HNPCC (Lynch synd)*: *gliomas*, also may have café au lait spots. ↑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 chrom9q31. Basal cell carcinomas, jaw cysts, dural calcifications, rib abnlities & brain tumors including: *medulloblastoma* (3%-5%), meningiomas (5%). Also associated w/eye disorders (colobomas, cataracts, glaucoma), melanoma, lymphoma, leukemia, lung/breast cancer, rhabdomyomas. Predisposed to second malignancy after XRT.

# NEUROLOGIC COMPLICATIONS OF SYSTEMIC CANCER

**Brain mets:** *Neurologic sx* = initial manifestation in 10% of systemic cancers. Distributed proportional to blood flow: 90% cerebrum; 10% posterior fossa, tend to involve gray/white jxn or in ACA-MCA-PCA border zones; multiple in 50%; pituitary mets often from breast, melanoma, germ cell. 75% brain mets in adults = lung (~50%, esp SCLC), breast (15%, higher for ER/Her2-neu pos), melanoma (5%-10%). 10%-30% of cancer pts have brain mets at autopsy. *Single met* = one met in brain (regardless of extracranial dz) *"Solitary" met* = only met in body.

**P/w:** HA (presenting sx in 50%), sz (first manifestation in 20%, usually focal), focal signs, cognitive/behavioral changes, gait disorder.

**W/u**: Brain imaging (MR favored over CT): usually round, well-circumscribed, solid lesion often surrounded by vasogenic edema, may have central necrosis, usually at gray-white junction. Often ring-enhancing. Search for primary. **(1)** Exam (incl skin, breast, testicular). **(2)** Consider serum tumor markers (AFP, beta-HCG, CA 19.9, CA 125, CA 15.3). **(3)** CXR, Pan-CT/PET.



**Rx**: Balance need for palliative or definitive cranial Rx. Primary can change Rx & dx approach. Tissue dx almost always required for XRT therapy. **Surgery:** For single dominant/symptomatic lesion. Solitary brain met: best results = resection followed by whole brain XRT (WBRT) (*"Patchell Trial" N Engl J Med* 1990;322(8):494; *Curr Oncol* 2007;14:131): Median survival/local control/retained Karnofsky Performance Score (KPS) > 70: (1) Biopsy + WBRT = 3.4 mo/48%/8 wk. (2) Resection + WBRT =9.2 mo/80%/38 wk. **WBRT:** ↓ risk of: neurologic death, additional mets, recurrence. Lung, breast, germ cell tumors more radiation sensitive. Some studies show modest survival benefit for prophylactic WBRT in SCLC. 30 Gy/10 fractions std regimen, 35 Gy/14 fx common. >3 Gy/fraction has more severe neurocognitive effects if pt lives >6 mo. **SRS**: boost ↑ local control in pts w/≤4 lesions, but no improved survival. Best if size < 3 cm diameter. Local tumor control 70%-90% at 1yr, better if combined with WBRT. For 2-4 mets <2.5 cm each, median survival 11 mo WBRT + SRS vs. 7.5 mo WBRT alone. Similar benefit for single met. SRS alone: no diff in OS, improved neurocog outcomes but worse local control, PFS compared to WBRT + SRS. **Chemo:** For responsive tumors (e.g., lapatinib + capecitabine for HER2-pos breast cancer, EGFR inhibitors for NSCLC w EGFR mutation, ipilimumab for melanoma). **Symptomatic Rx** w/steroids, AEDs if h/o sz.

**Prognosis**: Aggressive Rx for *solitary* met occas yields long-term survivors. Primary goal often to stabilize neuro deficits and quality of life.

**RPA Stages for Brain Mets (RTOG Trials 79-16, 89-05)**

| Stage | Characteristics | Median Survival |
|---|---|---|
| 1. | KPS ≥ 70, age < 65, 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 →XRT preferred to XRT alone, may help preserve ambulation (*Lancet* 2005;366:643).

**Leptomeningeal mets (carcinomatous meningitis):** Leptomeninges infiltrated by cancer cells. ~5% of cancer pts, incr as pts survive longer. Primary dz dependent: *Common* (in order): Breast, lung, melanoma, GI, heme malignancies (non-Hodgkin lymphoma). Brain primaries: malig astrocytomas, oligodendrogliomas, medulloblastoma, pineoblastoma, germinoma, primary CNS lymphoma. Increased risk after resection of cerebellar mets.

**P/w**: Common s/sx: HA, AMS, n/v, ataxia. *Multilevel nervous system dysfxn that is prog, unremitting: Brain*: Personality changes, cognitive impairment, labile affect, ↓ alertness, szs, HA, hydrocephalus/↑ICP. *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). *NI MRI does NOT exclude*. **LP:** CSF cytology; *normal LP does NOT exclude*, Se of 3 LPs up to 98%.

**Ddx**: Mult mets, infxn, ↓ ICP (post-LP), postcraniotomy, recent head trauma.

**Rx**: Aim to palliate & extend survival; not curative. 50%-90% ↓ pain, improved defs. Advanced dz/unresp 1°: No benefit from Rxof LM. **Chemo:** Intrathecal chemo in some, Ommaya reservoir preferred. *Methotrexate* 12 mg 3×/wk or 10 mg 2x/wk for leukemias, lymphomas, solid tumors. *Cytarabine* 40-50 mg 2-3×/wk for leukemia & lymphoma; liposomal for solid. *Thiotepa*: 10 mg 2-3×/wk. Systemic chemo alternatives include high-dose methotrexate w/leucovorin (3-8 g/m$^2$), high-dose cytarabine (3 g/m$^2$, use limited by significant toxicity). **XRT:** Helps focal defs, *Focal XRT* or *WBRT* (including short course: 4 Gy × 5). Supportive: Steroids may improve HA/radicular pain/decrease ICP, AEDs for sz, palliative VPS.

**Prognosis**: *Mean survival 2-3 mo*, 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 SYNDROMES

(*Lancet Neurol* 2008;7:327; *Lancet Neurol* 2011;10:759; *Neurooncol* 2014;16:771)

**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. Commonly younger, more treatment-responsive (see section on Autoimmune encephalitis).

**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).

**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 myasthenic synd (LEMS), Dermatomyositis. **Abs:** In *CSF & serum* (can check either, NMDA typically w CSF>serum titers). May occur w/o synd or cancer; sig unclear. Common cell surface abs: AMPA, GABA, mGluR5, mGluR1, NMDA, Gly, LGI1, CASPR2. Other abs directed against intracell ags, rarely pathogenic. **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, often monophasic and limited response to treatment. 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 Rx(usu have neuronal loss).



| Classic Paraneoplastic Neurologic Syndromes | | |
|---|---|---|
| **Paraneoplastic Synd** | **Antibodies** | **Associated Cancer(s)** |
| Limbic encephalitis | Anti-AMPA | Thymoma, lung, breast, none |
| | Anti-amphyphysin | SCLC |
| | Anti-CRMP5/CV2 | SCLC, thymoma |
| | Anti-$GABA_B$ | Thymoma, lung, ~50% none |
| | Anti-GAD | Typically none |
| | Anti-Hu (ANNA-1) | SCLC |
| | Anti-Ma/Ta | Testicular, NSCLC, breast |
| | Anti-NMDA | Ovarian teratoma (≤50%), lung, pancreatic, Hodgkin's |
| | Anti-VGKC (LGI1>CASPR2) | SCLC, thymoma (NONE in 80%) |
| Cerebellar degeneration | Anti-GAD | No Cancer |

| | | |
|---|---|---|
| | Anti-Tr | Hodgkin dz |
| | Anti-VGCC, anti-Hu | SCLC |
| | Anti-Yo | Breast, GYN |
| | Any/No ab | |
| Opsoclonusmyoclonus-ataxia | Any ab | SCLC, breast, ovarian, neuroblastoma (peds) |
| | Anti-Ri (ANNA-2) | Breast |
| Encephalomyelitis | Anti-CV2/CRMP5 | SCLC, thymoma |
| | Anti-Hu | SCLC (75%) |
| Sensory neuronopathy | Anti-Hu | SCLC |
| LEMS | Anti-VGCC | SCLC |
| Dermatomyositis | Mult ANA, anti-tRNA | Breast, lung, ovary, stomach, lymphoma |
| Stiff Person synd | Anti-amphiphysin | Breast, SCLC |

**Limbic encephalitis** (*also see section on Rapidly Progressive Dementias*): Limbic system (hippocampi, amygdala, frontobasal region, insula). Subacute onset (days-mos): “quietly confused”: Mood disturbance: depression/irritability, hallucinations, sleep disturbance, short-term memory loss, szs, dysautonomia.

**Dx**: **Imaging** *MRI:* T2/*FLAIR hyperintensity medial temporal lobes* (50%-80%); *PET:* hypermetabolism (>80%); **EEG** temporal slowing/epileptiform discharges (50%-90%). **LP:** CSF w/↑ lymphs (40-90%).

**Cancer**: *SCLC, testicular, thymoma, Hodgkin's, teratoma* most common.

**Antibodies** *determine synd subtypes (also see table under Rapidly Progressive Dementias)*:

**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, nearly all paraneoplastic.

**Anti-GABABR:** often early/prominent sz, improve with immunotherapy, mainly assoc w/SCLC/thymoma. MRI often w/multifocal, extensive FLAIR/T2 abnormalities. Good response to treatment.

**Anti-GAD:** Also assoc w/stiff-person synd, cerebellar ataxia, epilepsy. Often young women who present w/temporal lobe epilepsy. Typically chronic course that stabilizes.

**Anti-Hu:** Extensive/multifocal encephalomyelitis. Often also w/s/sx of cerebellar ataxia, sensory neuropathy. EPC (tongue/limbs). A/w SCLC, others, nearly all paraneoplastic.

**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; >90% paraneoplastic. Responds to Rx: orchiectomy & immunotx (steroids/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) in age > 18 yo, rarely paraneoplastic in children. 80% F. Often moderate lymphocytic pleocytosis, OCBs, mildly ↑ on CSF (80%-90%), Ab may be present in CSF but absent in serum, 35%-50% w/MRI changes, EEG may show characteristic "delta brush" pattern. Rx: Tumor removal, immunotherapy (early steroids, IVIG and/or plasma exchange, with ritux and cyclophosphamide if needed); 65% w/near-full but slow recovery if paraneoplastic. Often chronic/relapsing if non-paraneoplastic.

**Anti-VGKC** (voltage-gated potassium channel, LGI1>CASPR2): Sleep disturbance, hypoNa (60%), hypothermia, hypersalivation, pain, hyperkinetic movement disorder. Often older, avg 2 yo, M>F. CSF often normal. <10% w/tumors (usually thymoma). Most w/o tumor. 80% respond to corticosteroids, pheresis, IVIg; often monophasic.

**Paraneoplastic cerebellar degeneration:** Most common paraneoplastic synd. 50% of pts w/late onset cerebellar degeneration have tumor. >50% with tumor have cerebellar si/sx before tumor dx. Avg age 63 yo.

**P/w**: *Rapid prog pancerebellar synd* (<12 wk): Viral-like prodrome: dizzy/N/V; symmetric: gait then limbs; severe ataxia (symmetric), dysarthria, vertigo, nystagmus, dysphag, diplopia. *Noncerebellar sxs*: Hearing loss, ΔMS, tremor, blurry vision, oscillopsia, transient opsoclonus.

**Dx**: *MRI*: NI 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. CSF usually w pleocytosis, ↑protein, ↑IgG, OCBs.

**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), over 80% precede cancer dx. **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*. No ab in up to 50%.

**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. Assoc w/neuroblastoma in children (50% of children have neuroblastoma; 2%-5% of children w/neuroblastoma have Opsoconus-myoclonus-ataxia), in adults 60% paraneoplastic (SCLC, breast, ovarian).

**Imaging**: fMRI: inhibited deep cerebellar nuclei (disinhibited fastigial ocular motor region).

**Cancer**: Most common SCLC, breast, ovary. 50% children have neuroblastoma.

**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.

**Paraneoplastic Encephalomyelitis:** Dysfxn at *>1 level of CNS,* depend on structures involved. Sx from single

level predominate. Mean age 63, M > F. *Myelitis*: Wkns & posterior column dysfxn, UMN & LMN signs. *Limbic encephalitis* (9%): Confusion, anxiety, depression, amnesia, szs, hallucinations. *Cerebellar degeneration* (10%): Dysarthria, vertigo, ataxia, nausea, tremor, nystagmus. *Sensory neuronopathy* (54%, 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 ↓ (vibratory first). Marked *asym at onset* → b/l, spreads to *all limbs* (incl. arms, trunk), *Proximal involvement* (face, scalp) suggests paraneoplastic ganglionopathy from T cell mediated attack on cell bodies in DRG. 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 distinguish from chemo-induced sensory neurop (Platinum & vincristine). CSF ↑protein, OCBs (if paraneoplastic).

**Cancer/antibody**: *80% a/w SCLC, anti-Hu ab*. Rarely CV2/CRMP5, Yo, Ma2.

**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 (unlike Myasthenia Gravis). 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, though strength may ↑ *w/effort/exercise*.

**Dx**: *EMG* w/rep stim. *CK* nl 80% of pts. **Cancer:** *50%-80% paraneoplastic*; almost all *SCLC*.

**Antibodies**: *Anti-VGCC* (presyn P/Q-type; ↓ 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; ↑ AP duration), pyridostigmine, guanidine. Good response to IVIG, immunosuppression (prednisone, azathioprine, mycophenolate, or cyclosporine) & 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 involvement (↑ 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**: up to 30% (↑ w/age); most common: *Breast, lung, ovary, stomach, & non-Hodgkin.*

**Antibodies**: Mult in ~30%: *ANA* (anti-Ro,-La,-Sm, RNP), *Anti-tRNA* (anti-Jo,-SRP,-Mi-2).

**Rx**: Treat w/steroids & immunotherapy (azathioprine or methotrexate).

**Stiff Person synd:** Axial muscle rigidity & spasms. Assoc with other autoimmune d/o, esp Type I DM. (1) Anti-GAD abs present in ~60%, < 5% paraneoplastic: thymoma. (2) Anti-amphiphysin; cancer more common—breast, SCLC. EMG w/continuous motor unit activity decreased by benzos/anesthetics. Rx w/benzos, baclofen, steroids, IVIG, plasma exchange, azathioprine.

**Neuromyotonia (Isaac synd):** Myokymia, cramps, delayed relaxation, wkns. Stiffness 2/2 continuous muscle activity. Often a/w anti-VGKC (CASPR2). Sx can → *Morvan 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 COMPLICATIONS OF CHEMOTHERAPY

DeAngelis LM, Posner JB, *Neurologic Complications of Cancer; 2nd Ed., 2009*. Hard to distinguish from complications of tumor, c/b drug interactions, radiation; dx of excl. *Peripheral neurop most common*: platinums, taxanes, proteasome inhib; often dose-limiting. 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%), infreq szs.

| **Neurologic Complications of Chemotherapy** | | | |
|---|---|---|---|
| **Symptom** | **Associated Chemotherapy/Biologic Agents** | | |
| Neuropathy<br>• Diffuse variants: (1) motor > sensory demyelinating resembling GBS (2) sensorimotor (3) pure sensory may reverse<br>• Focal uncommon | 5-Azacytidine Aromatase inhib. 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 Purine analogs Sorafenib Sunitinib malate Suramin (1) Teniposide Thalidomide TNF-α Vinca alkaloids (2) Zarnestra |
| Acute encephalopathy<br>• Identical to metabolic causes<br>• Most insomnia<br>• ± Myoclonus<br>• Occasional szs<br>• Risk for PRES (marked with*) | Asparaginase 5-Azacytidine BCNU Bevacizumab* Chlorambucil Cisplatin* Corticosteroids* Cyclophos.* Cyclosporine* | Fludarabine 5-FU Gemcitabine* HMM Hydroxyurea Ibritumomab Ifosfamide* Imatinib Interferons* Interleukins Mechloramine | Misonidazole Mitomycin C Nelarabine Paclitaxel Pentostatin Procarbazine Tamoxifen Thalidomide Thiotepa TNF-alpha Vinca alkaloids* Zarnestra |

| | | | |
|---|---|---|---|
| | Cytarabine* Dacarbazine Doxorubicin Etoposide* | Methotrexate | |
| **HA** | Asparaginase Capecitabine Cetuximab Cisplatin Corticosteroids Cytarabine Danazol Estramustine Etoposide Fludarabine Gefitinib | HMM Interferons Interleukins Ibritumomab Levamisole Mechlorethamine Methotrexate (IT) Nelarabine Octreotide Oprelvekin | Plicamycin Rituximab Retinoic acid SU5416 Tamoxifen Temozolomide Thiotepa (IT) Topotecan Tositumomab Trastuzumab ZD 1839 |
| **Subcortical dementia** | BCNU Carmustine Corticosteroids | Cytarabine Dacarbazine 5-FU + levamisole | Fludarabine Interferon-α Methotrexate |
| **Cranial neurop** | BCNU (ototoxic) Cisplatin (ototoxic) Cytarabine | Ifosfamide Methotrexate | Nelarabine Vincristine (ocular) |
| **Vision loss** | Bevacizumab BCNU (IA) Cisplatin | Etanercept Fludarabine | Methotrexate Tamoxifen |
| **Acute cerebellar synd** | Cyclosporine Cytarabine 5-FU HMM | Ifosfamide Interlukin-2 Procarbazine Tamoxifen | Thalidomide Vinca alkaloids Zarnestra |
| **Leukoencephalopathy** | Capecitabine Cisplatin Cytarabine (IT) | 5-FU + levamisole Cyclosporin-A Methotrexate (IT) | Nelarabine Sunitinib malate |
| **Aseptic meningitis** | Cytarabine (IT) Levamisole | Methotrexate (IT) | Thiotepa (IT) |
| **Myelop** | Cisplatin Cladribine Corticosteroids Cytarabine | Doxorubicin Fludarabine Interferon alpha Methotrexate (IT) | Mitoxantrone (IT) Docetaxel Thiotepa (IT) Vincristine (IT) |
| **Vasculopathy/stroke** | Asparaginase Bevacizumab BCNU (IA) Bleomycin Carboplatin (IA) Cisplatin (IA) | Cyclosporine Doxorubicin Erlotinib Estramustine 5-FU | Imatinib mesylate Methotrexate Nelarabine Tamoxifen |
| **Szs** | Amifostine Asparaginase | Etanercept | Methotrexate |

| | | | |
|---|---|---|---|
| | BCNU Busulphan Chlorambucil Cisplatin Corticosteroids Cyclosporine Cytarabine Dacarbazine | Etoposide 5-FU Ifosfamide Interferon Inteleukin-2 Letrozole Levamisole Mechloramine | Misonidazole Octreotide Paclitaxel Pentostatin Suramin Teniposide Thalidomide Vinca alkyloids |
| **Syncope** | Bevacizumab | Erlotinib | Nelarabine |

HMM, hexamethylmelamine; 5-FU, 5-fluorouracil; cyclophos, cyclophosphamide; IA, Intra-arterial; IT, Intrathecal. From Newton HB, Jolesz FA. *Handbook of Neuro-Oncology Neuroimaging*, 2008; DeAngelis LM, Posner JB. *Neurologic Complications of Cancer*, 2009; Schiff D, Wen PY. *Cancer Neurology in Clinical Practice*, 2003; Soffietti R, Trevisan E, Ruda R. *Handb Clin Neurol*, 2014.



## NEUROLOGIC COMPLICATIONS OF RADIATION THERAPY

**Overview:** Side effects depend on structures radiated, dose, & fraction schedule. Often difficult to distinguish 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 | variable | 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 |
| Vasculopathy | Unclear | Variable | Rare |

**Rx:** Dexamethasone for XRT-related edema varies w/doses & sched, depending on severity. Bevacizumab used off label for intractable radiation necrosis. Consider methylphenidate, modafinil for fatigue; donepezil, memantine can be tried for cognition. Memantine during WBRT may delay time to cognitive decline (*Neuro Oncol* 2013;15(10):1429). Select patients may benefit from shunting for clinical syndrome of NPH. Anticoagulation has been tried for radiation necrosis/myelopathy.

**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.

## Special cases

1. **Somnolence synd:** Early-delayed encephalopathy in children; can range from drowsiness to lethargy, 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 often with 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 higher risk.

5. **Pseudoprogression:** temporary increase in vasogenic edema seen w/in 6mo of XRT. Up to 1/3 of GBMs treated with TMX+XRT, has been associated with improved treatment outcome. Up to 50% in lesions treated with SRS. Improved w/steroids if symptomatic. Careful monitoring to distinguish from true tumor progression.
6. **SMART syndrome:** stroke-like migraine attacks after radiation therapy. From delayed vascular toxicity, clinical features include headache, focal neuro deficits, seizure. MRI with gyral thickening/enhancement, typically resolves.

**Spinal cord, root, & nerve 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. Often Brown-Séquard pattern. Can be very challenging to distinguish 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 can show 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.

**Cranial Nerves:** painless, progressive vision loss or constriction of visual field from injury to optic nerve/chiasm. Sensorineural hearing loss/hypoglossal and lower cranial nerves may be injured from RT for head and neck cancers; hypoglossal neuropathy can cause ipsilateral tongue weakness/atrophy. Thought to be mediated by demyelination. MRI may show nerve enhancement.

# Sleep Medicine

Matt T. Bianchi

Karim Awad

## SLEEP PHYSIOLOGY

| Stages of Sleep | |
|---|---|
| Awake | Low voltage w/fast frequency; α activity (8-12 Hz), prominent in parietooccipital areas, ↓ by eye opening & mental effort; muscle tone present |
| Stage N1 | θ activity (3-7 Hz) |
| Stage N2 | Sleep spindle (12-14 Hz) lasts for ≤2 s; K complex (sharp negative wave w/slow positive wave, ≥0.5 s); slow eye movement; muscle tone present |
| Stage N3 | δ activity (≤2 Hz) for >20% of a 30 s epoch |
| REM | Low voltage, fast frequency, chin EMG atonia, rapid eye movements |

## SLEEP-RELATED BREATHING DISORDERS

### QUANTIFYING RESPIRATORY EVENTS

*Physiological monitoring (in-lab polysomnography or at-home w/limited channels)*

*Apnea* → cessation of nasal/oral airflow for ≥ 10 s. *Obstructive apnea* → respiratory effort persists during apnea. *Central apnea* → no respiratory effort. *Hypopnea* → ↓ airflow by ≥30% w/desat of ≥4% for ≥10 s (some Defs use 3%). *Apnea-hypopnea index* (*AHI*) → number of apnea/hypopnea per hour of sleep.

*Severity:* determined by AHI (0-5 normal, 5-15 mild, 15-30 moderate, >30 severe), medical risk is proportional if untreated. Oxygen desaturation nadir can also be considered. Upper airway resistance syndrome is a mild form w/AHI<5 but occurrence of respiratory arousals (requires esophageal manometry).

### OBSTRUCTIVE SLEEP APNEA [OSA]

**Intro:** 2/2 upper airway obstruction (usu. retropalatal & retrolingual). 10%-20% adult prevalence (defined by AHI>5). *Risk factors*: Male, ↑age/BMI, smoking, EtOH, airway anatomy, FH, comorbidities (DM, HTN, CAD, stroke). *Consequences*: ↑mortality, HTN (*BMJ* 2000;320:479), CAD, CHF, Stroke, GERD, insulin resistance. *Anatomic factors*: Neck circumference > 17(men) >16 (women); retrognathia; deviated septum, small oropharynx size, macroglossia; large uvula, low-lying soft palate, large tonsils/adenoids.

**Clinical features/dx:** Daytime sleepiness not always present, even in severe cases; snoring, witnessed apneas & awakenings w/gasping/choking also variable. *Lab PSG*: Gold standard for dx; home test kits w/limited respiration channels are growing alternative, but not for routine screening. Apneas & hypopneas often more

prominent in REM & while supine. EEG arousals often follow each apnea/hypopnea. Adjunctive evaluation if surgery considered (nasopharynx endoscopy, face/neck imaging).

**Rx:** *General measures*: wt loss (if 20-50 lb lost, repeat PSG), positional therapy (e.g.: if OSA worse in supine, reduce supine position → anti-snore shirt, elevated head/trunk to 30 degrees), quit smoking, ↓ EtOH. *CPAP*: For symptomatic pts w/AHI ≥ 5/h, & any w/AHI>15. Improves sxs & nulls consequences of OSA. Only 50%-60% pts adhere long-term. Insurance requires at least 4 hrs/night on >70% of nights. *Oral devices*: Pushes mandible & tongue forward. Requires dental specialist to fit. Best for mild-mod OSA, especially for those who don't tolerate CPAP. Provent valves are adhesive patches on each nare, provide equivalent of low-pressure CPAP w/o a machine by redirecting nasal expiration back to posterior pharynx. *Upper airway surgery*: Palate reduction surgery has mixed results. Maxillo-mandibular advancement better results



but more risk. Recent FDA approval of hypoglossal nerve stimulator. Septoplasty is not a Rx for OSA, but can improve CPAP compliance.

*Positive airway pressure (PAP) machines & monitoring*: CPAP (continuous pressure), BiPAP (2-level), auto-PAP (machine adjusts w/in pre-set range according to detected apneas/hypopneas), backup rate (used w/BiPAP for select pts w/central apnea or neuromuscular weakness), adaptive servoventilation (ASV; for complex apnea). All machines collect usage data (compliance), as well as mask leak & respiratory event rates while on the mask (i.e., efficacy). Effectiveness may be less than efficacy, if PAP use is less than 100% of total sleep time (as is commonly the case).

*Types of polysomnography (PSG):* diagnostic vs. split night (if meets OSA severity criteria in first half of night → start CPAP). If first night is diagnostic only, can return for second night of CPAP titration, or try auto-PAP at home (if more than mild OSA found). One night may not reflect variability of home sleep; try to mimic home, i.e., no abrupt discontinuation of meds. *Multiple sleep latency test (MSLT):* Following overnight PSG (to r/o OSA & PLMS), pt has 5 nap opportunities q2h the following day; instructed to try to sleep; measure latency & whether REM occurs. If looking for REM (i.e., narcolepsy), must be off SSRI/TCA, which suppress REM (false negative), & stimulants for 2-4 wks (to avoid rebound sleepiness false positives). *Maintenance of wakefulness test (MWT)*: Different from MSLT b/c instructed to stay awake; less commonly used; uncertain validity for assessing work safety such as drowsy driving risk.

## CENTRAL SLEEP APNEA [CSA]

**Introduction:** Apneic episodes w/o vent. effort. Accounts for 15% of sleep-related breathing d/o. More in middle-aged men. *Features*: Like OSA. Can be idiopathic/primary or secondary (e.g., CHF: 50% have CSA; chronic opiate use). *Pathophys*: Respiratory drive → metabolic & voluntary systems. In NREM, only metabolic (hypercapneic ventilatory drive) system working. In CSA, $CO_2$ ventilatory drive↓, i.e., more CO2 must accumulate before ventilation stimulated. *PSG*: CSA usu. during sleep onset & NREM stage 1/2. Awake $PaCO_2$: nl.

**Rx:** Treat underlying cause of CSA. CPAP may worsen central apnea. If CPAP not effective, adaptive servoventilation (ASV). *Adjunctive therapy*: Supplemental $O_2$ for select pts. *Acetazolamide*: Causes metabolic acidosis thus ↑respiratory drive. *Theophylline/medroxyprogesterone*: Stimulates ventilation. *Hypnotics*: reduce transitional instability via arousals.

## COMPLEX APNEA

**Introduction:** Some pts w/OSA have paradoxical response to PAP: emergence of central apnea. Risk factors include opiates, CHF, CNS dz. *Pathophys*: Chemoreceptor sensitivity, such that PAP drives CO2 below apnea threshold (greater risk w/higher pressures, or w/BIPAP). *PSG*: obstructive pattern before PAP applied, then mixed/central events on PAP.

**Rx:** In half of pts showing this pattern, it resolves spontaneously on standard PAP; other half it persists, & thus need ASV or adjunctive therapy (see section on central apnea).

| Other Secondary CSA | | |
|---|---|---|
| Cheyne-Stokes respiration | Periodic breathing w/↑/↓ RR, separated by apneas/hypopneas.<br>Due to long circulation time, ↓ PaCO2 and ↑ hypercapneic respiratory drive. Secondary to CHF, neuro (stroke, tumor) elevation to high altitude, renal failure. | *PSG*: Usually occurs in NREM. *Tx*: Improve CHF, supplemental $O_2$, CPAP, ASV. |

| Sleep-related Hypoventilation Syndrome | | |
|---|---|---|
| Obesity hypoventilation syndrome | BMI ≥ 40 kg/$m^2$ & hypercapnia (PaCO2 > 45 mm Hg).<br>Hypoventilation not due to other dx (e.g., lung disease). May have OSA as well. Sis/sxs: sleepiness, insomnia, awakenings.<br>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 d/o. 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; interferes w/daily activity. 5% of general population. Most common causes: OSA, insufficient sleep. Treated like narcolepsy (naps, stimulants) after ensuring adequate sleep duration & quality, & ruling out 1°/treatable causes.

## NARCOLEPSY

**Introduction:** 0.05% of population, onset usu. teens/early adult. *Excessive sleepiness* w/REM intrusions into wakefulness (cataplexy, sleep paralysis, hypnagogic hallucinations). Only ~15% have all four symptoms. 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 50% of pts (usu appears ~1 yr after sleepiness). Abrupt, transient loss of postural tone. Precipitated by intense emotion (laughter > anger). Usually <2 min, gradually improves, severity varies (from mild to severe weakness). Can be asymmetric & partial (limb, head). No changes in mental status (i.e., not on the DDx of transient LOC, e.g., seizure/syncope). Respiratory & oculomotor muscles spared. Thought to be intrusion of REM atonia into wakefulness. |
| Sleep paralysis | Inability to move at onset of sleep or awakening (despite being awake). Can be present in nl people. Again spares oculomotor & respiratory muscles & no change in mentation. |
| Sleep hallucinations | 30% of pts. Occur at sleep onset or awakening. Usually fearful. |
| Sleep disturbances | 80% have repeated awakenings & poor sleep quality. |
| Other features | Automatic behavior: inapprop. behavior (i.e., say something out of context) w/o memory of event; REM behavior d/o common. |

**Pathophysiology:** a/w HLA, DR2, & DQ1. Narcolepsy can be 2/2 medical dz (brainstem or hypothalamic lesion, encephalitis, head trauma, PD). *Hypocretin deficiency*: Secreted by lateral hypothalamus, wake promoting. ↓ levels of CSF hypocretin & (postmortem) ↓hypocretin neurons → cause of narcolepsy w/cataplexy (but not w/o cataplexy). CSF hypocretin ≤ 110 pg/mL: highly specific (~99%) & sensitive (~90%) for narcolepsy w/cataplexy (*JNNP* 2003;74:1667); not sensitive for pts w/atypical, mild, or w/o cataplexy.

| Diagnosis | |
|---|---|
| PSG | Sleep fragmentation, frequent awakenings. Short sleep latency (i.e., falls asleep in <10 min). |
| MSLT | Occurs after PSG & consists of 5 naps. Mean sleep latency ≤8 min. At least 2 REM periods (can be present in nl pts, sleep deprivation, other sleep d/os). False negative in up to 30%. |

| Treatment | |
|---|---|
| Sleepiness | Modafinil, dextroamphetamine, methylphenidate; naps. If continued sx despite meds, |

| | |
|---|---|
| | look for other sleep d/o. |
| Sleep disturbances | Sodium oxybate (γ-hydroxybutyrate): First line, ↓ awakenings; helps all REM-related sxs.<br>Other hypnotic agents can be helpful (BZD, zolpidem). |
| Cataplexy, sleep paralysis, hallucinations | Sodium oxybate.<br>Meds that suppress REM sleep: SSRIs & SNRIs, (given during daytime since may have stimulant effect). TCAs (given at night, due to sedation side effect, except protryptiline, which is a stimulant). |



| Medications | |
|---|---|
| Modafinil | First line: Considered safer than amphetamines (*Neurology* 2000;54:1166). Start at 100-200 mg am, add 100-200 mg at lunch PRN. Side effects: Nausea, nervousness, cardiac; rarely SJS. Up-regulates cytochrome P450 → ↑ OCP metabolism. Note: r-modafinil is another option, longer half-life than modafinil. |
| Methylphenidate | Dopamine reuptake blocker. Dose range 10-100 mg, tolerance can occur. Side effects similar to amphetamines. |
| Amphetamines | Promote NE & dopamine release. Frequent side effects: Insomnia, nervousness, arrhythmias, HTN, headache, & mood change. |
| Sodium oxybate | Helpful for core sxs: Insomnia, cataplexy, daytime sleepiness, hallucinations (*Sleep* 2002;25:42). Start 4.5 g: Divided into 2.25 g at bedtime, then 3-4 hrs later (usu by alarm). Max dose 9 g (total). |

| Other Causes of Excessive Sleepiness | |
|---|---|
| Idiopathic hypersomnia | Severe, chronic, excessive sleepiness w/o a known cause. Up to 10% of pts referred to sleep clinic. Begins insidiously in teens/early adulthood, may be preceded by viral illness but no strong evidence of this. Pathophys unknown: ? CNS failure to inhibit NREM sleep. Other causes must be excluded. PSG to r/o other dz. *MSLT*: Fast sleep latency but no sleep-onset REM (compared to narcolepsy). *Tx*: Stimulants, 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 | Hypersomnia (excessive sleep), binge eating, & hypersexuality. Occurs in adolescent |

| | |
|---|---|
| syndrome | men, remits by adulthood. Sleeping for >16 hr for days-weeks, recurring at least 2× a yr (associated w/binge eating, hypersexuality, disinhibited behavior). *Pathophys*: Unknown. Course is self-limited. *Tx*: Not been useful, dz self-limiting. *Recurrent hypersomnia*: Hypersomnia w/o other symptoms (i.e., binge eating). |
| Post-traumatic Hypersomnia | Occurs after head trauma (especially to hypothalamus, brainstem). Gradual improvement over weeks-months. No Tx needed. |
| Other causes | *Idiopathic recurrent stupor*: Rare, w/o underlying cause, stupor last up to days, *Tx*: unknown. Flumazenil (BZD receptor antagonist) use in the past felt to be linked to BZD ingestion as cause.<br>*Subwakefulness syndrome*: Rare, only ˜50 reported cases, chronic, pt c/o sleepiness, but studies nl.<br>*Menstrual-related hypersomnia*: Sleepiness during premenstrual period, nl at other times, if disabling use OCP to stop ovulation.<br>*Medications*: anticonvulsants, SSRIs, sedatives. |
| Secondary excessive sleepiness | *Sleep d/o*: Sleep apnea, restless leg, circadian rhythm d/o<br>*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) w/progressive sleepiness → coma/death (from encephalitis) if untreated.<br>*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.<br>*Psych d/o* |

# PARASOMNIAS

**Introduction:** *Parasomnias*: Undesirable behaviors or physical acts during sleep. *Classification*: Disorder of arousal; associated w/REM or NREM sleep.

## DISORDER OF AROUSAL (SEE BOX BELOW)

Occur out of NREM (usually *Stage* N3), which is enriched in the first third of night. Mostly in children, ↓ w/age, <5% 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, panic attacks, RBD.



| 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 sexual behavior → masturbation, sex. | *PSG*: ± alpha rhythm, microsleeps, NREM sleep Stage 1 (during episode). *Tx*: TCA, BZD, scheduled awakenings (wake up 15 |

| | | |
|---|---|---|
| | | min before nl time, then let child fall back asleep). |
| Sleep terrors | Sudden awakening from NREM w/fear (w/confusion, crying). | *PSG*: Usually not needed. *Tx*: Safe sleep environment, if child gets injured → TCA, BZD, SSRIs. |
| Sleepwalking | Rare in adults (unless had it as child). Arousal from NREM, leading from simple to complex motor behaviors (driving a car). Eyes usually open, pt not interactive w/environment, incompletely awake. HLA DQB1*05 implicated. SPECT during episode → activation of thalamocingulate pathway, w/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 normal 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 (many report injury to themselves or partners). Pts often recall dreams, occur in latter half of night, when REM is more frequent. Associated with neuro dz (PD, MS, dementia, brain tumor, stroke). Strong association w/Lewy body disease. 38% of pts developed Parkinson disease by 3 yr & >80% at long-term follow-up. RBD + PD → more frequent cognitive impairment or hallucination. MSA: 90% have RBD, & in about half RBD preceded. *Pathophys*: REM sleep atonia due pedunculopontine nucleus (PPN) + other brainstem structures; In PD, PPN affected, leading to RBD.

**Dx**: Video PSG (± EMG on UE): REM sleep w/motor activation. In PD pts, movement during REM not bradykinetic, slow, but ballistic (movement bypasses BG).

**Rx**: *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. *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 w/PD*): Little evidence for its use. Treat OSA if present, especially if using BZD that can worsen breathing.



| Other Parasomnias | |
|---|---|
| Enuresis | Involuntary bedwetting in kids > 5 yo, more common in boys. *Primary* if always had bedwetting (more common), *secondary* if no bedwetting 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 w/stress/fatigue. Improves w/time. *Tx*: Clomipramine. |
| Nocturnal eating (drinking) syndrome | Repeated arousal from sleep w/involuntary eating/drinking (daytime: nl eating behavior). Pt completely or partly unaware. Associated w/RLS. More common in women. *Risk factors*: stress, mood d/o, EtOH withdrawal, & smoking. *Tx*: SSRI, BZD, topiramate, & 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 sleep-related sinus arrest | Rare, asystole can last ~9 secs. Usually in healthy young adults w/nl CV. Possibly due to autonomic dysfxn. *Tx*: usually not indicated, but pacemaker may be needed. |

## INSOMNIA

**Introduction:** Most common sleep disorder, 1/3 of adults w/occasional insomnia, 10% w/chronic or severe insomnia, F > M; Pts c/o fatigue, difficulty w/cognition, slow mentation. Often objective tests nl (e.g., PSG, MSLT), but pts w/altered perception concerning their sleep (i.e., under-estimate sleep duration vs. objective measures). Many different factors precipitate & perpetuate insomnia: stress, work, poor sleep hygiene, mood d/os, pain, etc.

| 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, & functional consequence of insomnia to gauge risks of insomnia vs. risks of medical therapies. Meds associated w/insomnia: steroids, SSRI, stimulants, nicotine, & beta-blockers. Habits: caffeine intake, lights out, naps, schedule irregularity, or other modifiable factors. Sleep log for 1-2 wk helpful. PSG: Generally not performed, but for chronic/refractor cases may be informative (treatable contributors to insomnia include OSA, PLMS). Although many pts have worse sleep in lab than at home → “first night” effect, some w/insomnia sleep better in the lab, i.e., reverse first night effect, due to psychophysiologic insomnia (negative associations of home are absent in lab).

## Acute/transient insomnia

| Etiology of Transient Insomnia | |
|---|---|
| Adjustment sleep d/o | 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 d/o | Due to shift work outside normal times (e.g., night shift). Sleep affected & misaligned from environmental/social cues. |

**Chronic insomnia:** Many different etiologies: Medical to neurologic, & primary insomnia (not caused by other sleep or medical d/o).

| 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 w/sleep. Often have conditioned arousal → can sleep better in other places than their own bed. *Dx*: By Hx, PSG generally not helpful, except when dx co-morbid sleep d/o. |
| Paradoxical insomnia (sleep state misperception) | Pt c/o extreme sleep loss, but daily fxn of pt & PSG nl, i.e., misperception of sleep as awake. Women, early to midlife. Insomnia can persist for years. |
| Idiopathic insomnia | Long-standing, starts in childhood, no underlying etiology. Insidious onset, chronic course, often refractory to Tx. |



| Other Causes of Chronic Insomnia | |
|---|---|
| Parasomnias | RBD; sleep eating. |
| Circadian-rhythm d/o | Biological & environmental clock not in sync (see below). |
| Medical | *Pulmonary*: OSA. *Cardiovascular*: CHF, CAD. *GI*: GERD, peptic ulcer, sleep-related |

| | |
|---|---|
| causes | abnl swallowing syndrome (pt w/difficulty swallowing saliva during sleep). *Pain*. *Pregnancy*: Menstrual-associated sleep d/o (insomnia during premenstrual period, cause unknown), pregnancy-associated insomnia (improves after delivery). |
| Neurologic | Dementia, Parkinson's, Huntington's, seizures, & sleep-related HAs. |
| Psychiatric | Strong correlation w/insomnia. Mood d/os, personality d/os, 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 d/o*: Usually child, refusing to fall asleep w/o 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 w/other sxs of allergies (e.g., rash, GI upset). Toxininduced → different toxins can produce insomnia. Altitude insomnia → insomnia for ascent, due to periodic breathing w/central apnea from hypoxia/resp alkalosis. |

**Rx:** Prompt Tx of acute insomnia before it develops into chronic due to learned behavior.

| **Nonpharm Tx** | |
|---|---|
| Sleep hygiene/habits | Awake at same time; get into bed when tired. No daytime naps, No EtOH or smoking near bed time. No strenuous exertion late in evening. Exercise beneficial (but not 3-5 hr w/in bedtime). For occasional insomnia, if can't sleep in 30 min, leave bed & do quiet relaxing activity (reading), but misperception & clock-watching are confounds here. Clocks: if causes anxiety, turn off. Rooms should be dark/quiet, cool temperature. Bed use only for sexual activity & sleeping. |
| Light therapy | Tx for circadian rhythm d/o, must be timed correctly. |
| Behavioral techniques | Most insomniacs benefit, but may take wks. *Cognitive behavioral therapy* for insomnia (*CBT-I*): multifactorial approach, address unrealistic beliefs w/sleep. *Relaxation*: Progressive relaxation, visualized pleasant environment. *Sleep restriction*: Limit time in bed to actual total sleep time, may cause some sleep deprivation which then improves sleep efficiency via homeostatic response, e.g., spends 9 hr in bed, but sleeps 6 hr → should only spend 6 hr in bed, then adjust time in bed according to sleep efficiency (total sleep time/time in bed If efficiency < 80%, ↓ time in bed by 15 min, if > 90% ↑ time in bed by 15 min. *Paradoxical intention*: guide pt to avoid “trying” to fall asleep (allow quiet wake to give way passively to sleep onset). |

## MEDICATIONS FOR INSOMNIA

Should only be used for short term (or very select pts w/chronic insomnia). Hypnotics → subjective improvement exceeds objective increase in sleep; daytime performance may not improve—& may get worse due to residual effects. FDA warnings regarding zolpidem, eszopiclone, in this regard (especially extended release & in women). Taper BZD slowly (consider adding *CBT-I* w/taper).

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| Medications | |
|---|---|
| Non-BZD receptor agonist | Zolpidem, Eszopiclone, Zaleplon. Unlike BZD, no anxiety or anti-Sz effect, ↓ risk of tolerance & rebound insomnia. Side effects: parasomnia, hangover, morning driving risk. |
| BZD | Mostly 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. Can make RLS, PLMS, worse. |
| Other meds | Ramelteon: Melatonin receptor agonist. Antihistamines (diphenhydramine): Few studies proving effectiveness for insomnia. Melatonin: Helpful for circadian rhythm disturbances (jet lag, shift work). Herbal supplements: valerian, chamomile, but little evidence. |

## CIRCADIAN RHYTHM D/O

(*J Clin Sleep Med* 2015;11(10):1199-1236.)

**Shift work d/o:** *Def*: Misalignment of circadian rhythms & sleep time caused by shift work. *Workup*: Sleep-wake diary, actigraphy (monitors rest/activity pattern), PSG to rule out other sleep d/os. *Rx*: Countermeasures for sleepiness include napping before or during shift, light exposure during night shift, & light restriction in morning. 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.

**Advance sleep phase d/o:** *Def:* Sleep schedule several hours earlier than conventional or desired time. *Workup*: Sleep-wake diaries. *Rx*: Evening light therapy, avoid morning light.

**Delayed sleep phase d/o:** *Def*: Sleep schedule substantially later than conventional or desired time; may present as insomnia. *W/u:* Sleep-wake diaries. *Rx*: Morning light exposure, avoid evening light. Progressively earlier bedtime until desired sleep schedule reached (chronotherapy). Timed melatonin admin 2-3 hr prior to intended sleep onset.

**Free-running circadian rhythm sleep d/o:** *Def*: Failure of entrainment w/periods of light & dark, common in the blind pts when they lose their sight, can occur in sighted individuals. *Workup*: Sleep-wake diaries, actigraphy; timing of melatonin secretion, & core body temp, are mainly research tools. *Rx*: Prescribed sleep/wake

schedules. Timed light exposure in sighted pts. Melatonin a couple of hours before bedtime.

**Irregular sleep-wake rhythm d/o:** *Def*: Relative absence of a circadian pattern to the sleep-wake cycle. *Workup*: Sleep-wake diaries, actigraphy. *Rx*: Combination of bright light exposure + physical activity. Structured schedule of activity & light exposure may help elderly/nursing home residents w/dementia. Melatonin may be helpful for children.

# RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS OF SLEEP

## Introduction/symptoms

*RLS Criteria for dx*: Urge to move legs ± associated w/unpleasant sensation, worse at night or during periods of immobility, relieved by movement. *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 w/low ferritin (often no anemia is detected). *Renal failure, rheumatoid arthritis, fibromyalgia, pregnancy*.

*Periodic limb movement of sleep (PLMS)*: sleep-related movements (ankle flexion, can also involve knee), common in RLS but most w/PLMS do not have RLS. Pt often unaware of movements. Treat if associated w/insomnia or daytime sleepiness. Unlike RLS (a clinical dx), PLMS requires PSG. Rx is same as for RLS.

**Dx:** *EMG/NCS* if associated neuropathy/radiculopathy; *Ferritin* (most sensitive test for iron deficient anemia) all pts; *Ddx*: Neuropathy/radiculopathy (no urge to move & not usually worse at night), neuroleptic-induced akathisia (i.e., motor restlessness, from antipsychotics that block dopamine receptors).

**Rx:** *Sleep hygiene*, *iron supplement* (on empty stomach, w/vit C), & underlying cause for pts w/low ferritin (<50 is cutoff, i.e., higher than anemia cutoff). *Dopaminergic drugs*



are 1st line, then consider anticonvulsants (gabapentin), & BZD (clonazepam because long acting). Opiates are last resort. Dose timing close to onset of Sxs. Start at lowest dose, titrate slowly.

*Tx complications*: **(1)** *Augmentation*: Sxs earlier, more severe, involves other body parts, due to dopaminergic meds, most commonly w/levodopa; 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

Jennifer A. Kim

Tamara B. Kaplan

Thabele M. Leslie-Mazwi

## IMAGING IN PREGNANCY

Balance risks/benefits to mother/fetus. CT & MRI entail potential risk to fetus.

**When scanning the mother during pregnancy:** Involve pt & family, obstetrician, & radiologist in discussion, & document this. Modify MRI & CT exams under direction of radiology to be as informative as possible w/as little exposure as possible (e.g., minimize sequences, contrast exposure, etc.). Avoid all imaging in the first trimester if possible, & 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, & 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. 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 & limited data, do not use unless benefit outweighs risk.

## THE NEUROLOGY OF PRE-ECLAMPSIA/ECLAMPSIA

**Epidemiology:** Preeclampsia/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:** *HTN in pregnancy* → BP ≥ 140/90 after 20 wk gestation. *Proteinuria in pregnancy* → 1+ protein reading on a random urine test dipstick. *Preeclampsia* → ↑ BP & proteinuria after the 20th wk of pregnancy. *Severe preeclampsia* → considered to be present w/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 + Preeclampsia (exclude other causes of Sz → venous sinus thrombosis, stroke, & ruptured aneurysms). Relation to delivery: >70% occur prior to delivery, 25% before labor, 50% during labor, & 25% after delivery. Eclampsia before 20 wk rare, & suspicion should be high for molar pregnancy, multiple pregnancy, or noneclamptic neurologic disease. *HELLP syndrome* → Hemolysis, elevated liver enzymes, & low platelet counts (below 100,000 to 150,000/$mm^3$).

**Cerebral pathology:** Mechanism of preeclampsia/eclampsia: unclear. Cerebral pathology due to vascular injury from ↑ BP & predisposition to coagulopathies. Entire neuroaxis subject to potential ischemia, edema, or hemorrhage.

**Imaging:** MRI preferable, w/similar findings to PRES.

**Management:** Therapeutic goals: Protecting the fetus (w/delivery if possible). Controlling HTN to w/in the normal range for the individual pt. Suppressing szs. *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 w/eclampsia often adequately controlled by stopping sz. 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 sx (e.g., pulmonary edema), because these pts often intravascularly depleted.

**Neurologic prognosis:** ~10% of pts have repeated szs w/o treatment. Up to 56% of pts w/eclampsia may have transient deficits, including cortical blindness. ICH usually associated w/BP > 170/120 mm Hg, & responsible for up to 20% of eclamptic deaths. Ischemic stroke accounts for 5% of pregnancy-related maternal deaths in the United States. Range of increased perinatal mortality is 5% (for history of preeclampsia) to 45% (for abruptio placentae). Sz duration has not been associated w/increased perinatal mortality.

## CEREBROVASCULAR DISEASE IN PREGNANCY

**Ischemic stroke:** Stroke in young pts due to: heart disease, substance abuse, coagulopathies, arterial dissection, early atherosclerosis. Pregnancy & the postpartum period ↑ relative stroke rate, w/up to 35% of strokes between ages 15 and 45 being related to pregnancy. Overall risk of stroke in pregnancy is generally low and largely the result of background risk factors. The postpartum period: greatest risk. The major specific risk factors are preeclampsia/eclampsia & 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 & 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 w/in 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 & MRI preferred over ionized radiation (see above).

## CEREBRAL VENOUS THROMBOSIS

**Introduction:** Young to middle aged pts (~75% women), ~80% of pts w/good outcome. Poor pts w/age >37 yo, male, coma, altered mental status, GCS <9, ICH on admission, DVT, CNS infection, & 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; szs 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, & CN III, IV, V palsies.

**Diagnosis:** Consider dx in younger pts w/no risk factors w/stroke sxs, unusual HA, ICH, intracranial HTN. 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 w/o risk factors.

**Treatment:** *Anticoagulation*: Heparin (even if ICH present) goal PTT 2-2.5× baseline, bridge to warfarin for 6 mo or longer w/INR goal 2-3. Two main trials: First trial: 20 pts, long treatment delay, avg. 4 wk, stopped early due to significant benefit w/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 w/LMWH, possible imbalance at baseline favoring placebo group (*Stroke* 1999;30:484). Meta-analysis of both trials: nonsignificant trend toward fewer death & dependency, anticoagulation safe w/no new ICH occurring in either trial (*Cochrane* 2004;(4):CD002005).

*Endovascular*: Reserved for pts w/poor prognosis & worsening pts despite heparin, limited evidence. Administration of urokinase or rt-PA or mechanical disruption.



*Seizures*: AED in pts w/both szs & 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 w/worsening vision & intracranial HTN, 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 w/prior cerebral venous thrombosis (CVT). Anticoagulate during pregnancy w/h/o CVT only if prothrombotic condition or other thromboembolic event (PE, DVT), dose-adjusted heparin or LMWH (w/factor Xa monitoring) in third trimester up to 8 wks postpartum.

## HEMORRHAGIC STROKE

In pregnancy, hemorrhage is usually associated w/preeclampsia/eclampsia & AVMs.

## HEADACHE IN PREGNANCY

| Primary Headache Disorders |
| --- |
| Migraine |
| Tension |
| Cluster |
| Hemicrania continua |
| Primary thunderclap headache |

| Secondary Headache Disorders |
| --- |

| Blood | CSF |
| --- | --- |
| Intracerebral hemorrhage | Idiopathic intracranial HTN |
| Ischemic stroke | Hydrocephalus |
| Vascular malformation | Spontaneous intracranial hypotension |
| Subarachnoid hemorrhage | **Parenchyma** |
| Subdural hematoma | Primary neoplasm |
| Cervical artery dissection | Secondary neoplasm |
| Pituitary apoplexy | Brain abscess |
| CVT | Encephalitis |
| Retroclival hematoma | Meningitis |
| Pre-eclampsia | |
| Vasculitic syndromes | |
| Reversible cerebral vasoconstriction syndromes | |

| Referred Head Pain |
| --- |
| Otitis media |
| Sinusitis |
| Temporomandibular joint syndrome |
| Trigeminal neuralgia |
| Acute angle-closure glaucoma |
| Cervicogenic headache |

## MIGRAINES

Migraine prevalence is higher during the reproductive years & shows a variable pattern during pregnancy. As a rule of thumb, 1/3 of pts improve, 1/3 worsen, & 1/3 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 & so should be avoided in any pt w/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 & 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 & can be used in the first trimester at a dose of 200-600 mg PO q6h



(avoid aspirin, indomethacin, & other potent prostaglandin synthesis inhibitors because of the risk of constriction or closure of the fetal ductus arteriosus). *Acetaminophen*—FDA pregnancy category B & an excellent choice.

*Narcotics*—Combinations w/acetaminophen can be safely used. *Magnesium sulfate*—The preferred treatment when it is difficult to distinguish between pre-eclampsia & migraine or when the two overlap.

**Acute treatment for associated sx (e.g., N/V):** Phosphorylated carbohydrate solution 15-30 mg PO q15min (for mild cases). Metoclopramide (Pregnancy Class B); Chlorpromazine (C); Promethazine (C); Prochlorperazine (C); Prednisone (C).

**Prophylactic therapy:** Justified if frequency & severity of migraines are disabling. Begin w/nonpharmacologic therapy such as biofeedback & 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 & pregnancy include: triptans; acetaminophen; caffeine; opioids; propanolol; metoclopramide is highly concentrated in breast milk & should be used w/caution postpartum.

# MULTIPLE SCLEROSIS IN PREGNANCY

Currently, there are no evidence-based practice guidelines on clinical decision making & therapeutic choices for women w/MS who choose to become pregnant or experience an unplanned pregnancy.

**Contraception for Female Patients with MS:**

- Pts w/decreased mobility may have an increased risk of DVT a/w HRT & OCP use.
- Alternative methods (e.g., diaphragms & sponges) may be difficult to use if pt has symptoms of paresthesia or spasticity.
- IUDs & condoms can be a safe/effective w/similar failure rate if used correctly.
- MS diagnosis is not a unique consideration is starting OCP.
- No formal drug-drug intxn studies b/n OCPs & MS DMTs, but no concerns reported.

**Fertility in MS:**

No evidence that MS impairs fertility. Factors to consider:

- Possibly, > prevalence of endometriosis, which is associated w/↓ fertility.
- Altered reproductive decision making related to chronic illness.
- Sexual dysfunction, including ↓ arousal, libido, may possibly delay conception.
- Higher prevalence of thyroid autoimmunity.
- Tx-related temporary amenorrhea or premature ovarian failure.

## Effects of Pregnancy on the Course of MS

*Data per PRIMS study (Brain 2004):*

- Pregnancy ↓ number of exacerbations, especially in second & third trimesters.
- Relapse rate may ↑ above prepregnancy rate in first 3 months postpartum.
- ARR 21 month postpartum period not significantly different from prepregnancy rate.
- Breastfeeding—not predictive of a relapse or disability progression.

Most studies failed to demonstrate neg effects of pregnancy on long-term MS outcomes, including disability progression. PRIMS, pregnancy in multiple sclerosis; ARR, annualized relapse rate.

### MS & Pregnancy Outcomes

Pregnancy, labor, delivery, & incidence of fetal complications elevated in MS.

- No difference in Apgar scores in babies of MS mothers.
- May be a slightly ↑ rate of operative deliveries in MS pts.
- No ↑ in birth defects, perinatal mortality, or other adverse fetal outcomes.

### Treatment of Relapses in Pregnancy

Prednisone, prednisolone, & methylprednisolone—levels of fetal exposure.

Betamethasone, dexamethasone—cross the placenta— may ↑ risk of cleft palate if used in first trimester or may cause ↓birth weight, & possibly delay healing for the mother after birth.

### MS Disease Modifying Therapy in Pregnancy

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| Generic (Brand) | FDA Pregnancy Category | Lactation Category |
|---|---|---|
| GA (Copaxone) | B | L3 |
| IM IFNβ-1a (Avonex) | C | L3 |
| SC IFNβ-1a (Rebif) | C | L3 |
| IFNβ-1b (Betaseron) | C | L3 |
| Fingolimod (Gilenya) | C | L4 |
| Natalizumab (Tysabri) | C | L3 |
| Dimethyl fumarate (Tecfidera) | C | ? |
| Teriflunomide (Aubagio) | X | ? |
| Mitoxantrone (Novantrone) | D | L5 |

**IFN β** (Cat. C) >1,000 pregnancies tracked—no ↑ risk of miscarriage, no ↑risk of malformations, ↓ mean birth weight/mean birth length, ↑ risk of preterm birth.

**Natalizumab** (Cat. C) Not teratogenic in animal studies ↑ risk for miscarriage in one of several animal studies. Preliminary data show no ↑ risk in humans (birth weight, malformation, abortion). During the 2nd quarter, transplacental transport of Abs observed Caveat: if given during the last quarter of pregnancy, hematological screening of the newborn is necessary (10/13 exposed NB). Crosses into human milk.

**Fingolimod** (Cat. C) Teratogenic in animal studies, Fertility is not reduced.

**Dimethyl fumarate** (DMF) (Cat. C) Animal studies showed no evidence of impaired fertility or teratogenicity. No clinical evidence of increased risk of fetal abnormalities or adverse pregnancy outcomes associated w/gestational exposure to BG-12 during 1st trimester, but data are limited. Crosses into human milk. Must decide to stop breastfeeding or stop DMF.

***Resuming MS medications after delivery & lactation***: Probably safe to breastfeed on IFN β & glatiramer acetate, natalizumab & other non-depleting mABs but not on small molecules (DMF, fingolimod).

## EPILEPSY IN PREGNANCY

**Epidemiology:** Epilepsy most common neurologic disorder in pregnant women, affecting 3-5 births per 1,000 in the US.

**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 pts taking AEDs that are associated w/enzyme induction.

| Precautions with Hormonal Contraception | Safe with Hormonal Contraception |
|---|---|
| Phenytoin | Ethosuximide |
| Carbamazepine | Valproate |
| Oxcarbazepine | Gabapentin |
| Phenobarbital | Lamotrigine |
| Primidone topiramate | Levetiracetam |

*Risk of epilepsy in offspring*: Overall risk of children developing epilepsy is higher if the mother has epilepsy (8%) compared to the father (2%), probably due to genetic contributions. *Sz profile in pregnancy*: pts should be warned that breakthrough szs are more likely due to altered bioavailability in the face of physiologic changes in gut motility, hepatic clearance, expanding plasma volume, & altered protein binding. Optimize AED therapy before pregnancy. Good sz control prior to pregnancy predicts control during pregnancy. *Szs & the fetus*: an individual sz carries risk to the fetus due to placental hypoperfusion & potential trauma. Ictally, fetal effects could include: spontaneous abortion; fetal bradycardia; fetal hypoxia w/resultant acidosis; fetal intracranial hemorrhage; intrauterine death. Repeated szs (five or more) have been a/w lower verbal IQ in child.

**Antiepileptic medications:** Individualize choice of AED. Most AEDs are rated by FDA as category C (valproate, carbamazepine, & 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 pt to maintain sz freedom.

| Drug | Free Level | Total Level |
|---|---|---|
| Valproate | Little change | Decreases markedly |
| Phenobarbital | 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 |



Prepregnancy sz-free drug level should be used as target during pregnancy. For women w/well-controlled szs, check AED levels before conception, & at 1 mo intervals w/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 pts w/epilepsy will have tonic-clonic sz during labor, & another 1%-2% will experience one during the 24-h after delivery. Most will have normal vaginal deliveries. Serial szs during labor may be managed w/lorazepam. Elective cesarean section is appropriate if frequent szs occur in the last weeks of pregnancy or if any concern for eclampsia exists. Serum AED concentration monitoring continued after delivery, w/a return to prepregnancy states, typically noted w/in 2 mo.

**Teratogenesis:** Increased risk of major congenital malformations due to intrauterine AED exposure. Major congenital malformations are defined as structural abnormalities w/medical, surgical, or cosmetic importance. Valproate → increases risk by 3-4× compared to other AEDs. Carbamazepine & phenytoin: lower major congenital malformation rates than valproate & phenobarbital. Lamotrigine: has the most data & appears safe in pregnancy.

**Dosing & breastfeeding:** AED levels transfer into breast milk at variable concentrations depending on agent. Benefits of breastfeeding far outweigh these risks, & pts should be strongly encouraged to breastfeed their infants. Monitor infant for excessive sleepiness & subsequent poor feeding. Phenytoin, valproate, & carbamazepine are so protein-bound that they are not present at high concentrations in breast milk. Lamotrigine, topiramate, & levetiracetam have low protein binding, permitting breast milk transfer.

**Supplementation & prevention:** *Vitamin K*: AEDs that induce the hepatic cytochrome P450 (CYP) enzymes can induce vitamin K metabolism & reduce the effectiveness of vitamin K-dependent clotting factors. *Folate*: AED (phenytoin, carbamazepine, & barbiturates) use may reduce folate levels → neural tube defects; Tx: Folate supplementation.

# NEUROMUSCULAR DISEASES IN PREGNANCY

## FOCAL NEUROPATHIES

**Bell palsy:** As w/nonpregnant pts, usually due to a viral infection. Treatment is generally supportive w/use of prednisone for severe cases.

**Carpal tunnel syndrome:** Most common mononeuropathy during pregnancy, likely due to ↑ fluid retention. Tx is

typically conservative (splints, PT, salt restriction), particularly when sx start during third trimester. Sx typically less severe than nonpregnancy-related CTS.

**Neuralgic amyotrophy** (also known as Parsonage-Turner syndrome or brachial neuritis)—idiopathic & autosomal dominant forms. May occur postpartum. Inherited variety can recur w/subsequent pregnancies. No known method exists to prevent attacks.

**Femoral, Obturator Neuropathy:** During delivery, the femoral nerve may be compressed at the inguinal ligament or stretched through hip abduction & external rotation. Attention to positioning in labor helps prevent lower extremity mononeuropathies.

**Fibular (Peroneal) Neuropathy**: Mechanical injury, neuroma, fat, or cysts can compress the common fibular nerve at the fibular head. Cysts may enlarge during pregnancy. Exam: weakness of ankle dorsiflexion, eversion, & toe extension. Produces a postpartum foot drop. Sensory loss—lateral aspect of the leg & dorsal foot. Tx is supportive (consider ankle foot orthotics). Full recovery in 3-6 mo. More severe injury → axonal damage → slow/incomplete recovery.

**Myalgia paresthetica:** In 80% condition unilateral. Predisposed by: ↑ abdominal girth from gravid uterus; lumbar lordosis; thigh flexion during delivery; direct injury, e.g., from retractor during C-section. Expectant tx is usually all that is required. For severe pain: local treatment: lidocaine patch, local anesthetic.

**Low Back Pain & Lumbosacral Radiculopathy:** Back pain is a common symptom during pregnancy, affecting > 50% of all women. Contributing factors: ligamentous laxity, exaggerated lumbar lordosis, postural stress, direct pressure from growing uterus. *Conservative Tx*: analgesics, PT, modification of activity

Pregnancy does not increase the risk of disc herniation. MRI needed if changes in sensation, strength, or reflexes. Do not need contrast for most common causes of radiculopathy (Gadolinium is FDA category C). Epidural anesthesia very uncommonly results in neurologic complications, including radiculitis, arachnoiditis, or epidural hematoma.



## INHERITED POLYNEUROPATHIES

**Charcot-Marie-Tooth:** 50% risk of exacerbation during pregnancy, presumably from perineurial edema & pressure from the gravid uterus; 65% of pts will not recover to prepregnancy 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, & prematurity. Not uncommon for women to be first diagnosed peripartum. In symptomatic pts → all stages of labor may be affected (needing assisted delivery & increasing risk of postpartum hemorrhage). Tocolytics may worsen myotonia & induce rhabdomyolysis & should be avoided, as should neuromuscular blocking agents. Condition autosomal dominant → suspect fetus to be affected when reduced fetal movement, polyhydramnios, & preterm labor.

**Myotonic dystrophy Type II:** Different than Type I in that no congenital form exist, & does not appear to cause polyhydramnios; risk of preterm labor; pts may develop sxs in pregnancy.

## MUSCULAR DYSTROPHY & CONGENITAL MYOPATHIES

Usually no ↑ incidence of pregnancy or labor difficulties but beware of ↑ respiratory complications if

kyphoscolosis contributes to restrictive lung disease in the mother.

## AMYOTROPHIC LATERAL SCLEROSIS

Delivery can proceed per the preferences of the obstetrician & 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 (& therefore fetal) infections. Termination of pregnancy has no effect on duration of illness in the mother, & 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 & can both be used in pregnancy w/the usual precautions & 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, & plasmapheresis (can all be used). Generally, steroid-sparing therapies contraindicated, but consider azathioprine. Like GBS, the neonate appears unaffected by the disease.

## MYASTHENIA GRAVIS (MG)

### Diagnosis during Pregnancy

- MG is unmasked or worsened in ~1/3 of pt during pregnancy.
- Thymoma is uncommon in this age group, particularly if AChR-antibody is neg. May postpone chest CT until postpartum.

### Changes in MG during Pregnancy

- Disease course during pregnancy variable, but long-term outcome remains unchanged.
- Disease exacerbations, myasthenic crisis, & even disease remission may each occur during pregnancy.
- Close monitoring for respiratory difficulties is important.
- Pts can develop hypoventilation secondary to respiratory muscle weakness. Fetus may also restrict diaphragm & worsen respiratory function.
- ↑ abdominal pressure & diaphragm elevation reduce lung capacity.
- At some point during pregnancy, ~20% of pts develop respiratory crisis requiring mechanical ventilation.

**Labor:** Uterine smooth muscle unaffected by the disease, but skeletal muscle use in labor may fatigue in stage II, necessitating assistive delivery.

**Fetal & Neonatal Complications:**

- Fetal complications include neonatal myasthenia & arthrogryposis congenita.
- Neonatal myasthenia affects up to 20% of infants born from myasthenic mothers (usually w/in the first 24 h after delivery). Tx is supportive, & anticholinesterase medications may help w/feeding to improve suck.

**Maternal Treatment**

- Thymectomy should be preformed electively before a planned pregnancy, & preferably early in the period after disease diagnosis.
- Anticholinesterase medications (category C) should be continued.
- Corticosteroids, plasma exchange, & IVIg have been used safely during pregnancy & are agents often chosen for tx of exacerbation of weakness.
- Initiation of immunosuppressive agents other than prednisone before or during pregnancy should be avoided.
- The American Academy of Pediatrics considers pyridostigmine, prednisone, & prednisolone compatible w/lactation.

| Myasthenia Gravis Treatments & Associated Risk in Pregnancy | | |
|---|---|---|
| **Drug** | **FDA Category** | **Teratogenicity** |
| Pyridostigmine | C | No clear data. |
| Prednisone | C | Animal studies have yielded an ↑incidence of cleft palate in the offspring. |
| Plasma exchange | n/a | No known data. Plasma exchange has been used successfully during human pregnancy |
| Immunoglobulins | C | Animal studies have not been reported. IVIg has been used successfully during human pregnancy. |
| Mycophenolate mofetil | D | Pregnancy loss in 1st trimester & congenital malformations in the face & distal limbs, heart, esophagus, & kidney have been reported. |
| Azathioprine | D | Sporadic congenital defects: cerebral palsy, cardiovascular defects, hypospadias, cerebral hemorrhage, polydactyly, hypothyroidism. Reported chromosomal aberrations in utero. |
| Rituximab | C | B-cell lymphocytopenia generally lasting < than 6 months can occur in infants exposed to rituximab in utero |

## DERMATOMYOSITIS & POLYMYOSITIS

For pts in remission, risk during pregnancy is less w/typically good outcomes. W/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 & respiratory functions should be followed; serum CK → an unreliable marker of disease activity. Delivery by cesarean section desirable in pts w/active disease. Neither polymyositis nor dermatomyositis transmitted to the fetus. Treat active disease

w/corticosteroids: prednisone up to 2 mg/kg/d. In steroid resistant cases, use IVIg.

## MOVEMENT DISORDERS IN PREGNANCY

**Restless Leg Syndrome (RLS):** Most common movement disorder in pregnancy. *Presentation*: Pt reports discomfort, creepy crawling sensations, or actual restlessness occurring in the legs, w/an irresistible urge to move legs. Once up & walking, feelings are relieved. RLS can occur for the first time during pregnancy, typically in second & third trimesters—usually resolves after delivery.

*Epidemiology*: Prevalence in pregnancy 10% to 26% (2.5% to 15% in general population). The ↑ prevalence of RLS in pregnancy may be linked to iron or folate deficiency, known risk factors for RLS. Majority of women w/preexisting RLS experience worsening during pregnancy, 12% experience improvement. (*Neurology* 2004;63:1065).

*Treatment*: Ropinirole have been associated w/intrauterine growth retardation, digit malformation, & fetal deaths in animals. Levodopa is thought to be safe in pregnancy & may be used as first-line therapy**.**

**Chorea gravidarum:** Ddx: Autoimmune Disorders (SLE, APLS), vascular disease (AVM, Stroke, CNS vasculitis), rheumatic fever, Wilson disease, thyrotoxicosis, drug-induced. Rx: only needed for severe chorea (marked by features such as hyperthermia, rhabdomyolysis, myoglobinuria) →Haloperidol & chlorpromazine—shown to be helpful in the second & third trimesters, appear to be safe in low doses (haloperidol 0.5-2 mg, BID or TID).

**Ataxia**: Once structural causes are eliminated, the most common cause of ataxia arising during pregnancy is Wernicke encephalopathy (WE) secondary to hyperemesis gravidarum causing vitamin B1 deficiency. 90% of WE occurs in setting of poor nutrition/



alcoholism, but can occur in any setting of compromised nutritional status. Classic triad: confusion, ataxia, & ophthalmoparesis occurs < 10% of the time. Tx: IV thiamine 200 mg TID until sx resolve.

**Essential tremor:** Prepregnancy, warn families that inheritance is autosomal dominant in half of affected pts. The majority of cases during pregnancy do not require treatment as this condition is not dangerous & medication exposure may have deleterious effects on the fetus. If necessary, tx should be initiated w/propranolol & fetal growth should be monitored.

| **Treatment of Essential Tremor** | |
|---|---|
| **Drug** | **Teratogenicity** |
| Propanolol | Category C |
| Primidone | Category D |
| Alprazolam | Category D |
| Atenolol | Category D |
| Gabapentin | Category C |

| | |
|---|---|
| Sotalol | Category B |
| Topiramate | Category D |

**Focal dystonias:** Treatment commonly involves local botulinum toxin injection. Type A & B are category C drugs but type B has been more convincingly shown to be safe\ & should be used preferentially for muscle injection if a choice is available. Drug-induced dystonia may occur when neuroleptic agents are used for tx of hyperemesis gravidarum.

**Parkinson disease (PD):** PD extremely rare in pregnancy.

| Treatment of Parkinson Disease | | |
|---|---|---|
| **Drug** | **FDA Pregnancy Category** | **Breast Feeding** |
| Levodopa-carbidopa | C | Do not use |
| Rotigotine | C | No human data |
| Amantadine | C | Do not use |
| Trihexyphenidyl | C | No data |
| Bromocriptine | B | Do not use |
| Cabergoline | B | Do not use |
| Pramipexole | C | Do not use |
| Ropinirole | C | Do not use |

**Wilson disease:** tx w/chelating agents (-penicillamine, zinc, trientine, tetrathiomolybdate) is recommended throughout pregnancy. If no tx, pregnant pts can potentially develop fatal liver disease or hemolytic anemia & fetus may develop liver damage & copper accumulation.

**Huntington disease (HD):** All pts w/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 & 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 pts (present up to 6 mo postpartum) due to changes in intra-abdominal pressure. Depending on the cause of the pt's hydrocephalus, consider amniocentesis to diagnose neural tube defects between 13-& 24-wk gestation.

**Brain tumors:** In pregnancy, hormonal changes may cause enlargement of pituitary adenomas & 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

Olga R. Rosenvald Szenberg

Joshua P. Klein

Adam B. Cohen

HISTORY: Are the visual symptoms (1) monocular or binocular; (2) transient or permanent?; (3) What was the pattern of onset and were there (4) fluctuations or (5) associated symptoms (pain, diplopia, oscillopsia)?

## AFFERENT EXAMINATION

**(1) Acuity**: Check each eye separately w/correction (>40 yo require near correction). Pinhole occlude (or paper w/pinhole) to exclude refractive error. **(2) Color vision** (color plates, red desaturation). **(3) Pupillary response to light & near**; compare size (differences in dark or light environment), symmetry, shape & look for APD (most detectable w/dim stimulus). **(4) Visual fields**, as w/other exam elements, each eye tested separately. **(5) Funduscopy**: Use dilating drops; if not possible, try small light at dimmest setting to ↓ glare; examine right eye (OD) w/your right eye & left eye (OS) w/your left eye; must be close to patient: 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), peripapillary changes (hemorrhage, swelling, infiltrates), & macula.

## EFFERENT EXAMINATION

Evaluate (1) **ductions** (eye mvmts of each eye independently) & (2) **versions** (eyes moving together), saccades (fast mvmt toward a target—are they full?; hypo or hypermetric?) & pursuits (following an object—was there any breakdown?), adventitious eye mvmts in primary & eccentric gaze, such as nystagmus, square wave jerks, nystagmoid movements, or opsoclonus. If strabismus (ocular misalignment) not apparent w/duction or version testing, do (3) **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). Observe is there is any (4) asymmetry with eyelids and orbits: ptosis, lid retraction, proptosis, tenderness on palpation, orbital bruit.

## ANATOMY OF THE AFFERENT VISUAL PATHWAY

**Retina:** Photoreceptors (outer) → retinal ganglion cells (inner) → unmyelinated NFL (innermost retina); NFL axons travel to (and 'form') 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 population 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*: vascular dzs of temporal retinal NFL & optic disc & retinal arterial supply may produce field defects that *respect horiz. meridian*; primary retinal dzs do not. (prechiasmal dzs respect vertical meridian).

**Optic nerve (ON):** Site where retinal NFL axons converge. Axons become myelinated post. to lamina cribrosa (w/in anterior ON). 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 preserved in ON. 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 and disturbs adjacent photoreceptors.

**Optic chiasm (OC):** Contains crossed fibers from nasal-& uncrossed fibers from temporal-retina. Located above pituitary/sella. *Blood supply*: Hypophyseal artery branches inferiorly (via ICA) & ACA branches superiorly. Fairly infarct resistant. *Field defects*: Categorized by affected area of OC: (1) central (crossing fibers)—inf, sup, or full bitemporal hemianopia (field defect begins near vertical midline, not peripherally); (2) anterior chiasm—junctional scotomas: ON-type defect (e.g., central scotomas) in one eye & chiasm-type defect (e.g., superotemporal defect) in the other.

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**Optic tract:** Fibers 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 (entire LGN), sectoranopia (lateral choroidal, PCA branch), reverse sectoranopia (anterior choroidal, ICA branch).

**Optic radiations:** Post-LGN tracts divided superiorly (occipitoparietal) & inferiorly (occipitotemporal; Meyer loop). *Blood supply*: Anterior radiations via ant. choroidal & MCA; superior radiations via superior MCA; inf & postradiations via MCA & PCA. *Field defects*: c/l congruent homonymous hemianopias; 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; site of synapses from LGN. *Blood supply*: mainly PCA, but occipital pole also PCA contributions. Lesions → c/l congruent homon. hemianopia; ant. mesial OL lesion can produce 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 → visuospatial deficits (e.g., Balint syndrome, visual attention, spatial organization). *"What" visual stream* is inferior (OL/TL). Lesions → semantic deficits (e.g., prosopagnosia, object recognition, color). *Blood supply*: OL/PL regions via superior MCA branches; OL/TL regions via PCA & inferior MCA branches.

**Left.** Afferent visual pathway (R sided visual structures) A: inner retina & retina nerve fiber layer; B: outer retina & photoreceptor layer; C: vitreous; D: fovea (in central macula); E: optic disc; F: optic nerve; G: optic chiasm; H: optic tract; I: dorsal midbrain (including tectum); J: lateral geniculate nucleus of thalamus; L: parietal optic radiations; M: occipital lobe. **Right.** Visual field defects. F: optic nerve –right monocular global field defect (other types also occur, e.g., central or centrocecal scotoma, arcuate defect); G: optic chiasm—bitemporal hemianopia; H: optic tract—left incongruous homonymous hemianopia; J: lateral geniculate nucleus of thalamus (J1: lateral choroidal occlusion, PCA branch; J2: anterior choroidal occlusion, ICA branch); K: temporal optic radiations; L: parietal optic radiations—left homonymous hemianopia with upper quadrant sparing; M: occipital lobe—left homonymous hemianopia with central sparing.

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**Left.** Afferent visual pathway (R sided visual structures) A: inner retina & retina nerve fiber layer; B: outer retina & photoreceptor layer; C: vitreous; D: fovea (in central macula); E: optic disc; F: optic nerve; G: optic chiasm; H: optic tract; I: dorsal midbrain (including tectum); J: lateral geniculate nucleus of thalamus; L: parietal optic radiations; M: occipital lobe. **Right.** Visual field defects. F: optic nerve - right monocular global field defect (other types also occur, e.g., central or centrocecal scotoma, arcuate defect); G: optic chiasm—bitemporal hemianopia; H: optic tract—left incongruous homonymous hemianopia; J: lateral geniculate nucleus of thalamus (J1: lateral choroidal occlusion, PCA branch; J2: anterior choroidal occlusion, ICA branch); K: temporal optic radiations; L: parietal optic radiations—left homonymous hemianopia with upper quadrant sparing; M: occipital lobe—left homonymous hemianopia with central sparing.

## TRANSIENT MONOCULAR VISUAL LOSS

**Def:** Can be ischemic (amaurosis fugax) or non-ischemic. Pt's perception of monocular might be misleading (e.g., pts often localize homonymous hemianopia to the eye of the temporal field deficit). **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/common carotid or ICA atheroembolism or less frequently severe carotid stenosis causing retinal or choroidal hypoperfusion, ±other lateralizing TIA symptoms (transient language changes, c/l wkness/numbness); GCA usually elderly, with jaw claudication and temporal tenderness, ± PMR. (2) *Nonischemic*: Unlike ischemic, sx may be more vague; wide DDx, but common/notable dxs: blurring, ↓ w/blinking/artificial tears → dry eyes; “positive” visual sx (flashing lights) → migraine; visual obscurations w/bending forward → optic disc swelling; Uhthoff phenomenon (old demyelination); eye pain → angle-closure glaucoma; ↓vision w/eye mvmts→ orbital tumor; HA; APD (retinal artery vasospasm, demyelination, often 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/vasculitis via impending anterior ischemic optic neuropathy (AION) (can be 2/2 GCA, which is a treatable *vascular emergency*). **(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. hx & vascular risk factors (including carotid & cardiac dz). **(2)** Eye exam: *Nonischemic TMVL*: Routine eye exam (r/o anterior segment dz & ↑intraocular pressure). *Ischemic TMVL*, may see refractile emboli w/in retinal arteries on funduscopy (Hollenhorst plaques). **(3)** Eval for GCA (ophthalmologic emergency) via CBC, ESR, & CRP (none has good specificity). **(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; CEA if due to symptomatic ICA stenosis. **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; *Neuro Clin* 2010;28:619).

## RETINAL AND OPTIC NERVE ISCHEMIA

**CRAO and BRAO**: Vascular urgency since cerebral infarction may ensue. Central retinal and branch retinal artery occlusions ≥ acute monocular visual loss, usually painless. Permanent loss, but might be preceded by one or more (stuttering) episodes of TMVL or cerebral TIA. Since ocular vascular supply is through ICA branches, ocular ischemic symptoms can be secondary to distal (ophthalmic artery) or proximal (cardiac) processes. If ICA severe stenosis/occlusion ≥ retinal blood supply may be from ECA, and steal retrograde flow from eye (ophthalmic a.) to brain. **P/w**: *CRAO*: acute, monocular, severe visual loss (may be far peripheral visual field sparing); RAPD common; fundus w/attenuated retinal arteries, sometimes emboli can be visualized, retinal edema (whitening) after a few hours from retinal thickening/lost of transparency & cherry red spot (at fovea, where retina is most thin and red choroid still visible); *BRAO*: acute, monocular, partial visual loss; variable RAPD; fundus w/altitudinal (superior or inferior) retinal thickening/whitening w/corresponding field defect (superior BRAO causes inferior visual field defect).

**Ophthalmic artery occlusion:** similarly to CRAO; ICA large emboli vs. in-situ thrombosis/plaque. **DDx**: retinal vein occlusion (subacute over days). **Dx:** Similar to cerebral ischemia work up; exclude GCA in pts >50 yo and other GCA risk factors. Association of BRAO/CRAO + AION highly suggestive of GCA; recurrent BRAO is part of Susac syndrome (rare vasculopathy of small retinal, cochlear and cerebral arteries). **Rx:** No clear treatments. IA thrombolysis (catheterization of ophthalmic artery) or IV tPA with limited evidence of benefit. Focus on prevention of subsequent vascular events. Pts admitted for secondary stroke prevention (*Am J Ophthalmol* 2014;157(6):1119).

**Optic Nerve ischemia—Def:** ↓ blood supply to any portion of ON— short posterior ciliary arteries to ON head w/anterior ON ischemia & long posterior ciliary arteries (from ophthalmic artery) and pial vasculature w/posterior ON ischemia. Classified based on **(1)** location: **AION,** anterior optic dz; posterior ischemic optic neuropathy **(PION),** posterior or retrobulbar (i.e., behind lamina cribosa) ON. **(2)** Underlying cause: “arteritic” or “non-arteritic.” “Arteritic” synonymous w/GCA-related ischemia. Emboli not believed to obstruct posterior ciliary

arteries.

**Epid:** AION much more common (90%). **(1)** *Nonarteritic AION* (*NA-AION*): Typically >50 yo (but can occur at any age). A/w small optic cups (cup-to-disc ratio < 0.3), hypotension, anemia, cardiac or spinal surgeries, hypercoagulable disorders, acute ↑ intraocular pressure, radiation. Controversial risk factors: vascular risk factors/dz, amiodarone, sildenafil; since dz of small vessels, not related to ipsilateral ICA stenosis or emboli; rare cases 2/2 ON head drusen or papilledema (from "vascular crowding"). (2) *Arteritic AION* (*A-AION*): Age >50 yo, a/w GCA; often +PMR. (3)



*PION*: Typically in setting of severe blood loss (cardiac or lengthy spine surgery in prone position) or prolonged ↓ BP; pts >50 yo; rarely from GCA or fungal infxn (e.g., mucor).

**P/w:** Disc edema present in AION. **(1)** *NA-AION*: Acute monocular vision (mild to severe); worst at onset, but nadir may take days (to weeks); pt 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; optic discs show pallor 4-6 wks after event.

**Dx:** **(1)** Si/sx of optic neuropathy—↓ acuity, dyschromatopsia, APD, edematous hyperemic optic disc (pallor w/edema in A-AION), inf. altitudinal field defect common (but can be superior or global); 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 for GCA eval. **(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 neoplastic-related.

**Rx:** *NA-AION*: no proven Rx. *A-AION*: Immediate IV methylprednisolone (250 mg every 6 h for 3-5 days), then PO prednisone (1 mg/kg/d) to protect fellow eye; rx started immediately on presumed dx (don't wait for ESR or temporal artery bx). *PION*: No proven Rx; 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 rx are exceedingly rare; poor visual recovery. *PION*: Poor visual recovery.

| | **A-AION** | **NA-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 | Nl | Small | Nl |
| Visual field defect | Any ON type defect | Altitudinal or arcuate, typically inferiorly | Any ON-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; <5% recurrences same eye, but 15% fellow eye involvement in 5 yr | Most recover; risk of developing MS |

## OPTIC NEURITIS & DEMYELINATING OPTIC NEUROPATHIES

See Optic Neuritis section in *Multiple Sclerosis and Other CNS Inflammatory Demyelinating Diseases* chapter.



## HEREDITARY, TOXIC, & METABOLIC OPTIC NEUROPATHIES

**Def:** Various ON dzs, most often affect central vision (via maculopapillary bundle).

**P/w:** Insidious, usually painless, bilateral and symmetric 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; vision loss may precede anemia and other neurological sx**. Epid:** Pernicious anemia (most common in developed countries), 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.

**Thiamine deficiency:** Rare; vitamin $B_1$ is cofactor for several mitochondrial enzymes. ON may occur w/Wernicke encephalopathy (alcohol abuse, malnutrition). P/w: acute/subacute visual loss, disc swelling. Dx: serum thiamine has low Se and Sp, so supplementation should be done empirically. Prog: complete recovery.

**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.

**Linezolid:** antibiotic designed for MRSA and VRE, disrupts protein synthesis in mitochondria. Dose dependent optic and peripheral neuropathy. Dx: clinical. Rx: discontinuation. Prog: some recover from ON, peripheral neuropathy usually permanent.

**Cyclosporine and Tacrolimus:** immunosuppressants used to prevent rejection after organ transplant. Both cause PRES and more rarely, optic neuropathy. Likely 2/2 elevated ICP and papilledema. Case reports w/o improvement after discontinuing drug, but visual loss stabilized.

**Leber hereditary optic neuropathy (LHON):** mitochondrial DNA mutation, affects mostly men 15-35 yo; +/- maternal Fhx. Painless subacute visual loss in one eye, followed by contralateral eye in weeks to months; final acuity 20/200 OU. Dx: visual fields with central and cecocentral deficits; lack of leakage on retinal angiography (pseudoedema); genetic test. No proven rx.

**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); monocular or binocular; may be sequential visual loss. **Epid:** Prior radiation exposure of at least 50 Gy. **Dx:** Exam w/retrobulbar optic neuropathy or retinopathy, more common in pts with underlying vascular dz; 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).

**Other etiologies:** Ethambutol, ?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 & brain MRI w/gado | Coronal STIR images aid in ONs evaluation evaluate 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 help 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, pituitary-hypothalamic involvement); chest CT; serum ACE; ↑ protein & WBC (mild) in CSF; "tissue is the issue" biopsy of skin, lacrimal glands, 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** (*Autoimmune Dis* 2012;290898): **Def:** Myriad ocular manifestations due to 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 (sens), anti-dsDNA, and anti-Smith (higher spec), 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, earlier steroids are associated w/better prognosis.

### 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; Dx: rheumatoid factor (50% pts), Ro and La. Rx: Consider corticosteroids and immunosuppressive therapy.

**Behcet dz-related optic neuropathy**—Visual loss can occur from optic neuritis, neuroretinitis, or↑ ICP w/papilledema; retinal vasculitis affecting veins, and anterior chamber inflammation; systemic si/sx of Behcet's (genital & oral ulcers, lymphadenopathy). Rx: Immunomodulatory (& acetazolamide if ICP culprit).

**Chronic relapsing inflammatory optic neuropathy (CRION)** (*Brain* 2003;126:276-284)—Recurrent, acute/subacute painful visual loss (i.e., recurrent optic neuritis). Vision loss may manifest during steroid taper. Unclear pathogenesis, but elevated ANA (79%) and anticardiolipin are common (82%) (*Am J Ophthalmol* 1982;94:11).

## INFECTIOUS OPTIC NEUROPATHIES

**Lyme-related optic neuropathy** (*J Neuro-ophth* 1997;17:108): **Def:** ON dysfn 2/2 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. Lymerelated 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 Lymerelated 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 western blot. and abnormal CSF. 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 as part of active neurosyphylis. **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:** variable, depending on meningeal inflammation, perineuritis, or ON. *Funduscopy for ON*: Acute: disc swelling + splinter hemorrhages; chronic disc pallor; variable neuroretinitis; disc may appear normal if retrobulbar. *Serum* FTA-ABS and abnormal CSF (↑ WBC & TP, CSF VDRL, but not required). High incidence of concurrent HIV. *Orbital & brain MRI* w/gado (enhancement & enlargement of ON; meningeal thickening & enhancement in chronic dz). **DDx:** AION, idiopathic optic neuritis, optic perineuritis, sarcoidosis. **Rx:** IV penicillin for 2 wks +/- steroids. **Prog:** Variable improvement in early-stage dz; stability w/Rx in late stage dz.

**Bartonella-related optic neuropathy:** Typically neuroretinitis; rare isolated optic neuropathy (*Neurology* 2015;84;e204-e205). **Def:** ON/retina infxn w/*Bartonella henselae* (part of cat scratch dz) **P/w:** Acute/subacute monocular visual loss; variable fever, malaise, & lymphadenopathy; ± encephalitis, sz. **Epid:** Kitten scratches. **Dx:** *Funduscopy (*neuroretinitis): disc swelling, subretinal fluid from disc to macula, “macular star” (exudates around fovea); centrocecal & central scotomas; uveitis & vitritis may coexist. Confirmed by *Bartonella serologies*; *CSF*: (variable lymphocytic pleocytosis & TP, CSF Bartonella antibodies). **Ddx:** Other causes of neuroretinitis (postviral, Lyme, syphilis, TB, toxoplasmosis, SLE). **Rx:** Doxycycline and Rifampin or Azithromycin; may be self-limited, treatment may be optional. **Prog:** 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 (V1-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; optic neuritis-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.

***Mycoplasma 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** (*J Clin Neurosci* 2013;20:1045): **Def:** Proliferation of arachnoid cap cells of ON sheath (and not ON itself); meningiomas from olfactory groove & planum sphenoidale can → optic neuropathy (& frontal & olfactory dysfxn). **P/w:** Insidious monocular visual loss; proptosis 60%; transient & gaze-evoked visual sx. Neoplastic compressive optic neuropathies. **Epid:** Second most common primary ON tumors; F > M, NF-2. **DDx:** Sarcoidosis, lymphoma, metastasis, optic perineuritis. **Dx:** Funduscopy w/disc pallor >> disc swelling, may see optociliary shunt vessels on disc (if orbital) and optic disc cupping (i.e., non-glaucomatous cupping); homogenously enhancing linear mass of ON sheath by MRI; ±intralesional calcifications; small lesions at orbital apex easily missed by MRI (even w/marked sx). Biopsy rarely indicated as carries increased risk of damaging ON. **Rx:** Observation (serial exams and MRIs); 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; 85% of pts prog vision loss.

**Low-grade ON glioma** (*Br J Ophthalmol* 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 first 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, risk of developmental delay. **Prog:** Depends on location, size of tumor and associated deficits. 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:** Rare; adults; typically w/o NF-1 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 Ophthalmol* 2000;118:217): **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:** Rare; 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** (*Surv Ophthalmol* 2013;58:430): **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, metastatic infiltration, carcinomatous meningitis or treatment-related injury. **Dx:** *Funduscopy*: Variable disc swelling & hemorrhage, retinitis, & vitritis (constellation seen in anti-CRMP-5 syndrome, typically related to SCLC); *anti-CRMP-5 Ab*; *LP*; *imaging* search for systemic cancer. Neuroimaging: patchy T2-signal changes and ON enhancement; nearly always a/w multifocal neurological deficits; may co-exist w/myelopathy and mimic NMO. **Rx:** Steroids, Rx underlying cancer, IVIg. **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 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; *JAMA Neurol* 2014;13:1641.

**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; compressed/small transverse venous sinuses common. **(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:** weight loss, nutrition counseling, and acetazolamide (IIH trial); 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 (unilateral might provide bilateral benefits, but risk of permanent visual loss due to lesion of central retinal artery). HAs refractory: consider other common primary HA d/o's (e.g., migraine) & Rx. Treat systemic HTN (untreated may increase risk of visual loss). **(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:** 15% of all intracranial tumors. Low-grade (hormone secretory or non-fxning). **P/w:** Slow-onset visual loss (often unnoticed, incidentally found on imaging), usually macroadenomas (>10 mm) to cause visual symptoms); 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 can decrease size in up to 80% of the pts), others monitored w/exam (visual fields) & MRI; if visual compromise: resection (transphenoidal). **Prog:** Good if Rx early; can recur—must have serial exams/MRIs. Optic disc pallor/compression at time of diagnosis will determine prognosis.

**Pituitary apoplexy:** Rapid enlargement of adenoma, true emergency. **P/w:** Lifethreatening condition w/acute binocular visual loss & diplopia w/HA or coma; typically postpartum or postprocedural (cardiac surgery) hemorrhage into infarcted & enlarged adenoma. **Dx:** Severe visual loss w/ocular motor palsies; panhypopituitarism; often overlooked on CT scan; more easily seen on MRI. **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 resection often subtotal due to risk of hemorrhage. Usually adjunct radiation.

**Aneurysms: Locations:** Supraclinoid & cavernous carotid, ophthalmic, ACA, or AComm. **P/w:** Carotid lateral compression, nasal or binasal field defects; ocular motor & trigeminal deficits. **Dx:** CTA, MRA. **Rx:** Both clipping and endovascular procedures carry risk of further vision loss and damage to other eloquent areas from vascular or direct injury, as well as thrombosis, inflammation, and 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 occipitoparietal 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 dz.

**Central dyschromatopsia:** Impaired ability to visualize color from occipitotemporal (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 visual pathway**. Cortical motor control of eye mvmts arises from the frontal eye fields (F), supplementary eye fields (S), & parietal eye fields (Pa). Descending projections fall upon relevant structures inferiorly for horizontal & vertical eye mvmts. Three brainstem sections at the levels of CN3,4,6 (upper midbrain, lower midbrain, & pons). Each relevant ocular motor nucleus is shown as a dark circle; the attached white circle represents the MLF. Slightly above CN3 nuclei in the upper midbrain, lies the riMLF. The cavernous sinus is shown CNVI, CNV2, ICA (I), optic chiasm (OC), & pituitary gland (P) depicted. As the ocular motor nerves enter & exit the cavernous sinus, the innervation pattern of the left CNIV & CNVI are shown of the ocular muscles: superior oblique (SO) & lateral rectus (LR), respectively. The remaining ocular muscles are innervated by CNIII: levator palpebrae (LR), superior rectus (SR), medial rectus (MR), inferior rectus (IR), & inferior oblique (IO).

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**Autonomic (sympathetic & parasympathetic) ocular pathways**. The **oculosympathetic pathway** originates in the autonomic cortical regions & hypothalamus (1: first-order neuron), descends through brainstem to synapse in the intermediolateral cell column of to the spinal cord from C8-T2 (2: second-order neuron). The pathway exits the cord, ascends to & synapses on the superior cervical ganglion (S; 3: third-order neuron) & then ascends along the carotid artery (C) through the cavernous sinus (CS), into the posterior orbit, & through the ciliary ganglion (CG) (without synapsing here) to the end organs: Muller muscle (M) & pupil dilator muscle in the iris (I). The **oculoparasympathetic pathway** is mainly activated by light stimulation to either retina, which in turn activates both Edinger-Westphal nuclei (E). The signals then travel with both CNIIIs to synapse in the ciliary ganglia (CG) & then innervate the iris sphincter muscles in the iris (I) & the ciliary muscles of the ocular lens (L).



## 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, thyroidassociated 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) & contralaterally (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 (49% pts, 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 (single subnucleus controlling levator), one or both pupils (rostral location of Edinger-Westphal nuclei), 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 first division, CN V second division, & CN VI involvement w/cavernous sinus involvement. **(4)** Variable ON involvement w/orbital apex dz (in addition to CN IV, CN V first 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. INO (e.g., 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 mo.

## 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; ipsilateral INO and 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 first division, CN V second division, & CN VI involvement w/cavernous sinus involvement. Variable ON involvement w/orbital apex dz (in addition to CN III, CN V first 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. Thyroideye 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 first division distribution pain or numbness, petrous apex lesion = *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 first division, & CN V second division involvement w/cavernous sinus involvement. Variable ON involvement w/orbital apex dz (in addition to CN III CN IV, & CN V first division involvement). W/pontine lesions, may see impaired horizontal gaze (due to innervation of contralateral medial rectus), 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, Gradenigo 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 or neuromuscular junction process.

**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, $T_4$, thyroid-stimulating Ab, antithyroid 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 Ophthalmol* 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 & postcommisure 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); post-sz (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 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 dz; ataxia telangiectasia syndrome; MSA; PSP; Niemann-Pick 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 comitant (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 horizontal-torsional. 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 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 changing directions 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; normal responses to pharmacologic agents. Differences in lid position also common (1-2 mm difference), so relatively small pupil w/relative ptosis ≠ Horner syndrome.

### THE LARGE PUPIL

**General:** Most cases are physiologic. The three common mechanisms are impaired oculoparasympathetic input

to iris constrictor (damage to the two-neuron pathway from Edinger-Westphal in ventral midbrain to ciliary ganglion); iris pathology (damage to the iris sphincter muscle) and pharmacologic effect.

**Presentation:** If isolated (e.g., tonic pupil), may c/o blurred vision (from large aperture & impaired lens accommodation), difficulty with near vision & 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/parasympathetic inhibitors or sympathomimetic)—unintended (albuterol or ipratropium nebulizers, scopolamine patch, insecticides) 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 (sectoral palsy visible on slit lamp exam), constricts to near & to dilute pilocarpine (larger pupil constricts more than normal pupil); when idiopathic termed Holmes-Adie pupil (full syndrome typically young women w/loss 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 of iris.

***Horner syndrome*:** Subdivided by pathology of three neuron pathways: *First order* (hypothal → C8-T2), *Second order* (C8-T2 → sup cervical ganglion (SCG)), & *Third order* (SCG → iris dilator).

**Presentation:** Horner syndrome overview—ptosis, miosis, lower eyelid elevation (may appear like enophthalmos), 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 first/second division, CN III/IV/VI palsies; (3) orbit—same as cav sinus but ON involved & CN V second 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** (blocks norepinephrine reuptake at the NMJ of the iris dilator muscle, normal reaction = dilation) —w/↓ dilation, confirms Horner; nl pupil dilates, increasing the anisocoria. **(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** (weak agonist action at postsynaptic 1-adrenergic receptors)—dilation in chronic Horner because of iris dilator denervation supersensitivity); no response in nl pupils or early Horner, decreases degree of anisocoria. **(5)** Consider brain & neck MRI/MRA (w/T1 fat-saturated images through the skull base to evaluate for dissection) & CTA. **(6)** Consider chest & shoulder imaging.