

MULTIPLE SCLEROSIS AND OTHER CNS INFLAMMATORY DEMYELINATING DISEASES

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, HTLV I, SSPE, tropical spastic paraparesis/HTLV-1-ass. myelopathy
Congenital		Adrenoleukodystrophy, Alexander dz, Canavan dz, Krabbe dz, metachromatic leukodystrophy Adrenoleukodystrophy Adrenomyeloneuropathy
Toxic metabolic, radiation	Central pontine myelinolysis (CPM), toxic leukoencephalopathy CO poisoning	Subacute combined degeneration (B ₁₂ & IF deficiency), NO poisoning, Marchiafava-Bignami dz 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 contrast-enhancing lesion (CEL): rate of new MRI abnls in first few months ~80%–90%. After CIS repeat brain/spine MRI @ 3 & 6 mo, then annually. If new lesions, initiate Rx.
2. **Radiologically isolated syndrome (RIS)**: 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, B₁₂, 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 sent 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 ax.

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)	None; clinical evidence will suffice (additional evidence desirable but must be consistent w/ MS)
2 or more objective clinical lesions	
2 or more attacks 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 2 or more objective clinical lesions	Dissemination in space and time, demonstrated by: 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 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
1 attack 1 objective clinical lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For 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 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: 1. Evidence for DIS in the brain based on ≥ 1 T2 lesions in the MS characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord 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 mm³, + 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 (dd: cervical stenosis, spinal cavernous angioma or tumor; ↓ B₁₂); **(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 IVlg 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 3x/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 3x/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 Rx 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 μ g 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 x 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 long-term 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 w/ky. 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; non-sedating 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/lu:* 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)** Phospiasis (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.

Fundoscopy 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.

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 cecentral 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 B₁, B₁₂, 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.* IVlg & 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.