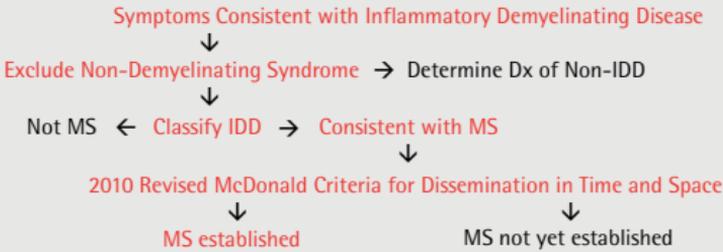


Diagnosing Multiple Sclerosis

A diagnosis of MS requires evidence of

- 1) Signs and symptoms that are consistent with inflammatory demyelinating disease
- 2) Dissemination in time
- 3) Dissemination in space
- 4) No other explanation for the clinical and paraclinical findings

Diagnostic Algorithm (Miller et al., 2008)



Signs and Symptoms Consistent with Inflammatory Demyelinating Disease

Visual	Blurred vision, unilateral loss of vision, oscillopsia, diplopia
Motor	Limb weakness, spasticity, hyperreflexia
Sensory	Numbness, paresthesias, dysesthesias, Lhermitte's sign, "MS hug", trigeminal neuralgia, allodynia, hyperpathia
Cerebellar	Tremor, ataxia, incoordination
Genitourinary	Urgency/frequency/retention, incontinence, frequent UTI, constipation, impotence, anorgasmia, dyspareunia
Neuropsychiatric	Impairment of memory, attention, and/or processing speed, depression, irritability <i>Prominent, intractable fatigue with no other explanation</i>

Differential Diagnoses

Common Differentials (Marshall and Mayer, 2001)

V Vascular	Multiple lacunar infarcts, CADASIL, spinal arteriovenous malformation
I Infectious	Lyme disease, syphilis, HIV myelopathy, PML, HTLV-I myelopathy
T Traumatic	Spondylitic myelopathy
A Autoimmune	NMO, acute disseminated encephalomyelitis, CNS vasculitis, Behcet syndrome, sarcoidosis, SLE
M Metabolic/toxic	Central pontine myelinolysis, vitamin B12 deficiency, vitamin B6 deficiency, radiation, hypoxia
I Idiopathic/genetic	Spinocerebellar degeneration, Friedreich ataxia, Arnold-Chiari malformation, adrenoleukodystrophy, metachromatic dystrophy
N Neoplastic	CNS lymphoma, glioma, paraneoplastic encephalomyelitis, metastatic cord compress.
S Psychiatric	Conversion disorder

Neuroinflammatory Disorders

Acute disseminated encephalomyelitis (ADEM)	Features	<ul style="list-style-type: none"> • Isolated postinfectious or postvaccinal autoimmune attack on the CNS • Diffuse demyelination, occasionally with fulminant hemorrhagic component (acute hemorrhagic encephalomyelitis or leukoencephalitis)
	Symptoms	<ul style="list-style-type: none"> • Encephalopathy: confusion, irritability, AMS (somnia to coma) • Multifocal deficits, fever, meningismus (headache, photophobia, stiff neck)
	Imaging	<ul style="list-style-type: none"> • Large (> 1 to 2 cm) multifocal, hyperintense, bilateral, asymmetric lesions in the supra-/infratentorial white matter on T2-weighted or MRI FLAIR images • Gray matter, especially basal ganglia and thalamus, may be involved
Optic neuritis	Features	Usually a clinically isolated syndrome (CIS) caused by an inflammatory condition or idiopathic, but may be associated with MS or ADEM
	Symptoms	<ul style="list-style-type: none"> • Headache and painful eye movements followed by vision loss, pupillary defect (Marcus Gunn pupil), or visual field defects • Usually unilateral in adults but may be bilateral in children < 12 yo
	Imaging	Gadolinium MRI shows acute demyelination confined to optic nerve
Transverse myelitis	Features	<ul style="list-style-type: none"> • Spinal cord dysfunction typically owing to inflammatory lesion • Usually presents as a CIS, but may be associated with MS or ADEM
	Symptoms	Unilateral or bilateral motor or sensory deficits such as paresthesias, weakness, sphincter dysfunction; can occasionally be more severe, including paraplegia and urinary retention
	Imaging	Gadolinium-enhancing lesions on MRI spreading over 1 or more segments
Neuromyelitis optica	Features	<ul style="list-style-type: none"> • Dx requires ON, myelitis, and 2 out of the following 3: longitudinally extensive spinal cord lesion ≥ 3 segments in length; brain MRI nondiagnostic for MS; NMO-IgG seropositivity (Wingerchuk et al., 2007). • More common in non-Caucasians, especially Asians • Rule out sarcoid, SLE, Sjogren's or other vasculitis
	Symptoms	Combination of concurrent or sequential bilateral optic neuropathy and transverse myelitis

Features Suggestive of MS	Red Flags for Other Diagnoses
<ul style="list-style-type: none"> • Relapses and remissions • Onset between ages 15 and 50 • Optic neuritis • Lhermitte sign • Internuclear ophthalmoplegia • Fatigue • Uhthoff phenomenon 	<ul style="list-style-type: none"> • Steady progression • Rigidity, sustained dystonia • Seizures • Early dementia • Onset before age 10 or after age 50 • Absence of sensory or genitourinary symptoms • Deficit developing within minutes • Cortical deficits (aphasia, apraxia, alexia, neglect)

2010 Revised McDonald Diagnostic Criteria for MS



National Multiple Sclerosis Society

2010 Revised McDonald MS Diagnostic Criteria¹



EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space (DIS) and time (DIT)*

CLINICAL (ATTACKS)	LESIONS	ADDITIONAL CRITERIA TO MAKE DX
2 or more	Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	DIS; OR await further clinical attack implicating a different CNS site
1	Objective clinical evidence of ≥ 2 lesions	DIT; OR await a second clinical attack
1	Objective clinical evidence of 1 lesion	DIS OR await further clinical attack implicating a different CNS site AND DIT; OR await a second clinical attack
0 (progression from onset)		One year of disease progression (retrospective or prospective) AND at least two of: DIS in the brain based on ≥ 1 T2 lesion in periventricular, juxtacortical or infratentorial regions; DIS in the spinal cord based on ≥ 2 T2 lesions; or positive CSF

1. Polman et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald Criteria. *Ann Neurol* 2011;69:292-302. * See reverse for DIS and DIT



National Multiple Sclerosis Society

Paraclinical Evidence in MS Diagnosis



EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Evidence for Dissemination of Lesions in Space (DIS) ²	Evidence for Dissemination of Lesions in Time (DIT) ³
<p>≥ 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord</p> <ul style="list-style-type: none"> • Gadolinium enhancement of lesions is not required for DIS • If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count 	<ul style="list-style-type: none"> • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI or • Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time
Evidence for Positive CSF	
Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index	<p>² Swanton KL et al. <i>Lancet Neurology</i> 2007;6:677-686 / Swanton KL et al. <i>J Neurol Neurosurg Psychiatry</i> 2006;77:830-833</p> <p>³ Montalban X, et al. <i>Neurology</i> 2010;74:427-434</p>

These diagnostic criteria were developed through the consensus of the International Panel on the Diagnosis of MS. See cited articles for details. Funding through National Multiple Sclerosis Society (USA) and European Committee for Treatment and Research in MS; additional support from the Multiple Sclerosis International Federation and MS Ireland

National Multiple Sclerosis Society (USA) Professional Resource Center. 733 Third Avenue. New York, NY 10017-3288
<http://www.nationalMSsociety.org/PRC>. MD_info@nmss.org
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Diagnostic Workup

Evoked Potentials

Visual evoked potential (VEP) Particularly useful in patients who lack clear clinical evidence of dysfunction above the level of the foramen magnum

Somatosensory evoked potentials (SSEP) Can be helpful in establishing spinal cord involvement

Blood Tests

B12 and folate to rule out nutritional deficiencies, ANA, ESR, and RF to rule out other autoimmune disease, Lyme disease, HIV, and HTL-1 titers to rule out some infectious causes, thyroid functions, anticardiolipin antibody testing to rule out other white matter disease, angiotensin converting enzyme to rule out sarcoidosis

Cerebrospinal Fluid Analysis

CSF oligoclonal banding 85% to 95% abnormal A qualitative CSF assessment for IgG oligoclonal bands is considered the gold standard analysis

CSF IgG index 90% abnormal

- $IgG\ index = \frac{[IgG_{CSF}/albumin_{CSF}]}{[IgG_{serum}/albumin_{serum}]}$
- Index is elevated in most MS patients (nl is < 0.7)

Other CSF Findings and Differentials

	Normal	Inflammatory CNS disease
Cell count/μL	< 5	Normal or < 50
Cells	Lymphocytes/monocytes	Lymphocytes/monocytes
Total protein mg/L	< 50	Normal to slightly elevated (protein > 100 is not consistent with MS)
Glucose ratio (CSF/plasma)	Typically > 0.5	Normal
Lactate mmol/L	< 2.1	Normal
Other	ICP: 6-22 cm H ₂ O	ICP generally within normal limits

Most Common Clinically Isolated Syndrome Presentations (Miller et al., 2008)

Optic Neuritis

Typical for MS:

Unilateral visual loss, orbital pain, afferent pupillary defect, retrobulbar or mild disc swelling, visual loss does not progress beyond two weeks

↓
Brain & Spinal MRI



Brainstem

Typical for MS:

Internuclear ophthalmoplegia, 6th nerve palsy, multifocal signs (e.g. facial sensory loss, vertigo, hearing loss, ataxia, dysarthria)

↓
Brain & Spinal MRI



Spinal Cord

Typical for MS:

Evolution over hours to days, partial myelitis, Lhermitte's sign, partial Brown-Sequard, spontaneous remission

↓
Brain & Spinal MRI



Within 5 years:

Normal brain MRI → 20% risk of conversion to clinically definite MS (CDMS)

Abnormal brain MRI (≥2 lesions consistent with demyelination) → ~90% risk of conversion to CDMS

Imaging Studies

Brain MRI findings are abnormal in 95% of MS patients

Brain MRI

Location

- Plaques typically in the periventricular region, corpus callosum, centrum semiovale, and occasionally in deep white matter structures and basal ganglia
- Most common infratentorial plaque locations: surface of the pons, cerebellar peduncles, and white matter regions adjacent to the fourth ventricle.

Appearance

- Ovoid lesions, typically radiating at right angles from the corpus callosum (Dawson's fingers)
- Hyperintense on proton density and T2-weighted studies, and hypointense (or not visible) on T1-weighted images.

Acute vs chronic lesions

- Acute lesions are gadolinium enhancing owing to the inflammatory response and BBB disruption (a transient effect that disappears after 30 to 40 days)
- Concentric ring-enhancing lesions may be indicative of more extensive tissue damage and more aggressive disease

Note: Lesions caused by other conditions - ischemia, SLE, Behcet disease, or other vasculitides - may appear similar, particularly in patients over 50

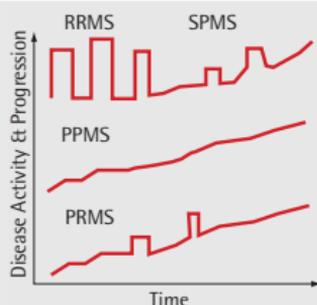
Spinal MRI

- Little or no spinal cord swelling
- Unequivocal hyperintensity on T2-weighted sequences
- Size at least 3 mm but < 2 vertebral segments in length
- Usually occupy only part of the cord in cross-section
- Focal (ie, clearly delineated and circumscribed on T2-weighted sequences)

Describing Multiple Sclerosis

MS Disease Types (Lublin and Reingold, 1996)

Relapsing remitting (RRMS)	Characterized by acute attacks followed by periods of remission (85%)
Primary progressive (PPMS)	Steadily progressive course from onset with no acute attacks (10%-15%)
Secondary progressive (SPMS)	Of those diagnosed with RRMS, 75%-85% will transition to a steadily progressive course with or without acute relapses
Progressive relapsing (PRMS)	Progressive from onset with occasional attacks along the way (< 5%)



Treating Multiple Sclerosis (more extensive and up-to-date information is available at nationalMSSociety.org/treatments)

Disease Modification

FDA-approved as first-line therapies for relapsing MS

IFN - β 1a (Avonex)	30 mcg IM once weekly
IFN - β 1a (Rebif)	22-44 mcg SC 3 times per week
IFN - β 1b (Betaseron; Extavia)	Begin 62.5 mcg SC qod; 62.5 q 2 wks to 250 mcg qod
Glatiramer acetate (Copaxone)	20 mg SC qd
Fingolimod (Gilenya)	0.5 mg tablet qd

Other approved options

Natalizumab (Tysabri) - as a monotherapy for relapsing MS	300 mg IV over 1 h every 4 weeks; risk of PML
Mitoxantrone (Novantrone) - for SPMS, PRMS, and worsening RRMS	12mg/m ² IV q 3 mo; max lifetime cumulative dose: 140 mg/m ² ; requires ongoing LVEF monitoring; risk of cardiac toxicity and secondary AML

Off-label use of chemotherapies

Azathioprine	Consult oncologist
Cyclophosphamide	
Methotrexate	

Relapse Management

(relapse = sudden new or worsening symptom(s) lasting at least 24 hours); to be differentiated from a pseudoexacerbation caused by temporary elevation in core body temperature (infection (eg, UTI) fever, exercise, ambient temperature)

- IV methylprednisolone - 1gm/day for 3-7 days with or without taper
- Oral prednisone - 500-1250mg daily/divided for 3-7 days
- Dexamethasone - 160-200mg po/IV daily/divided for 3-7 days
- Tapering regimens - optional:
 - prednisone - 200mg x 4 days; 100mg x 4 days
 - methylprednisolone dose pack
 - dexamethasone - 20mg x 4 days; 16mg x 4 days
- ACTH (Acthar Gel) - 80-120 units daily IM/SQ for up to 2-3 weeks
- If steroids ineffective or not medically feasible: consider IVIg (400 mg/kg daily for up to 5 days); plasmapheresis (total 5-7 exchanges)

Symptom Management

Interdisciplinary strategies involving medication management, rehabilitation, and mental health interventions. (more extensive information re: symptoms and their treatment is available at nationalMSSociety.org/symptoms)

Psychosocial Interventions

- Education and emotional support for individuals and families
- Prompt diagnosis and treatment of depression (affecting at least 50%) and other mood changes
- Prompt diagnosis and management of cognitive symptoms (along with the fatigue, the primary cause of early departure from the workforce)

Kurtzke Functional Systems Scores (FSS)

Each graded on a scale from 0 (normal) through 5 or 6 (severe dysfunction)

Pyramidal functions
Cerebellar functions
Brainstem functions
Sensory function
Bowel and bladder function
Visual function
Cerebral (mental) functions

Kurtzke Expanded Disability Status Scale (EDSS)

0.0	Normal neurological exam (all grade 0 in all Functional System (FS) scores)
1.0	No disability, minimal signs in one FS* (i.e., grade 1)
1.5	No disability, minimal signs in more than one FS* (more than 1 FS grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+)
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+)
7.0	Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems)
8.5	Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems)
9.0	Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+)
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+)
10.0	Death due to MS

*Scoring forms are available at nationalMSSociety.org/EDSS

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983 Nov;33(11):1444-52. Haber A, LaRocca NG. eds. *Minimal Record of Disability for Multiple Sclerosis*. New York: National Multiple Sclerosis Society; 1985

Bladder Control Scale

During the past 4 weeks, how often have you...	Not at all	Once	2-4 times	More than weekly; less than daily	Daily						
	0	1	2	3	4						
Lost control of your bladder or had an accident											
Almost lost control of your bladder or had an accident											
Altered your activities											
During the past 4 weeks, how much have bladder problems restricted your overall lifestyle?	Not at all				Severely						
	0	1	2	3	4	5	6	7	8	9	10

Summed scores range from 0-22, with higher scores indicating greater bladder control problems.

Source: *Multiple Sclerosis Quality of Life Inventory*. National Multiple Sclerosis Society, 1997

Two-Question Screening Tool for Depression in MS

An affirmative response on either or both questions reliably identifies 98.5 of patients with major depressive disorder

1. During the past two weeks, have you often been bothered by feeling down, depressed, or hopeless?

2. During the past two weeks, have you often been bothered by little interest or pleasure in doing things?

Source: Mohr DC, Hart SL, Julian L, Tasch ES. *Mult Scler*. 2007 Mar;13(2):215-9. Reprinted by Permission of SAGE.

National MS Society Resources

For clinicians

The Professional Resource Center (PRC) is a resource for healthcare professionals and researchers, providing information, clinical consultations, library services, Society slide decks, professional publications

- PRC: nationalMSSociety.org/PRC
- MD-on-Call (for clinical consultations): MD_info@nmss.org
- National MS Society Resource Guide for Clinicians: nationalMSSociety.org/ResourceGuide
- Clinical Measures: nationalMSSociety.org/ClinicalStudyMeasures
- Health Insurance Appeals Tool Kit: nationalMSSociety.org/HealthInsuranceAppeals
- SSDI Guidebook for Professionals: nationalMSSociety.org/SSDI
- Research Information: nationalMSSociety.org/Research
- Clinical Trials Information and Listings: nationalMSSociety.org/ClinicalTrials
- Research Funding: nationalMSSociety.org/ResearchFunding
- Fellowships and Grants: nationalMSSociety.org/FellowshipsGrants

For patients

MS Navigator Program for patients (1-800-344-4867; generalmailbox@nmss.org)
Information, support, referrals, financial assistance, educational programs, self-help groups, publications

- *Knowledge is Power* (learn-at-home program for the newly-diagnosed): nationalMSSociety.org/Knowledge
- Financial Planning Resources: nationalMSSociety.org/FinancialPlanning
- Workplace Disclosure Tool: nationalMSSociety.org/DisclosureTool
- National MS Society Financial Assistance Program: nationalMSSociety.org/FinancialAssistance
- Social Security Disability: nationalMSSociety.org/SocialSecurityDisability

About the National Multiple Sclerosis Society

Vision: A world free of MS

Mission: We mobilize people and resources to drive research for a cure and to address the challenges of everyone affected by MS

2011–2015 Strategic Response

- We are a driving force of MS research and treatment to stop disease progression, restore function, and end MS forever
- We develop, deliver and leverage resources to enhance care for people with MS and quality of life for those affected by the disease
- We are leaders in the worldwide MS movement, mobilizing millions of people to do something about MS now
- We are activists
- We develop and align human, business and financial resources to achieve breakthrough results

Please let us know if you have any comments, questions or feedback related to the content of this piece or other National MS Society resources at MD_info@nmss.org



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