International Organization of MS Nurses

The Nature of MS

Supported by Novartis Pharmaceuticals Corporation

Objectives

- Define multiple sclerosis (MS) and its presentation to facilitate optimal nursing care
- Discuss the diagnostic process in MS to enhance patient education
- Review the MS phenotypes in order to explain treatment options to patients and families
- Discuss need for proper diagnosis to start treatment early to reduce sequelae of MS

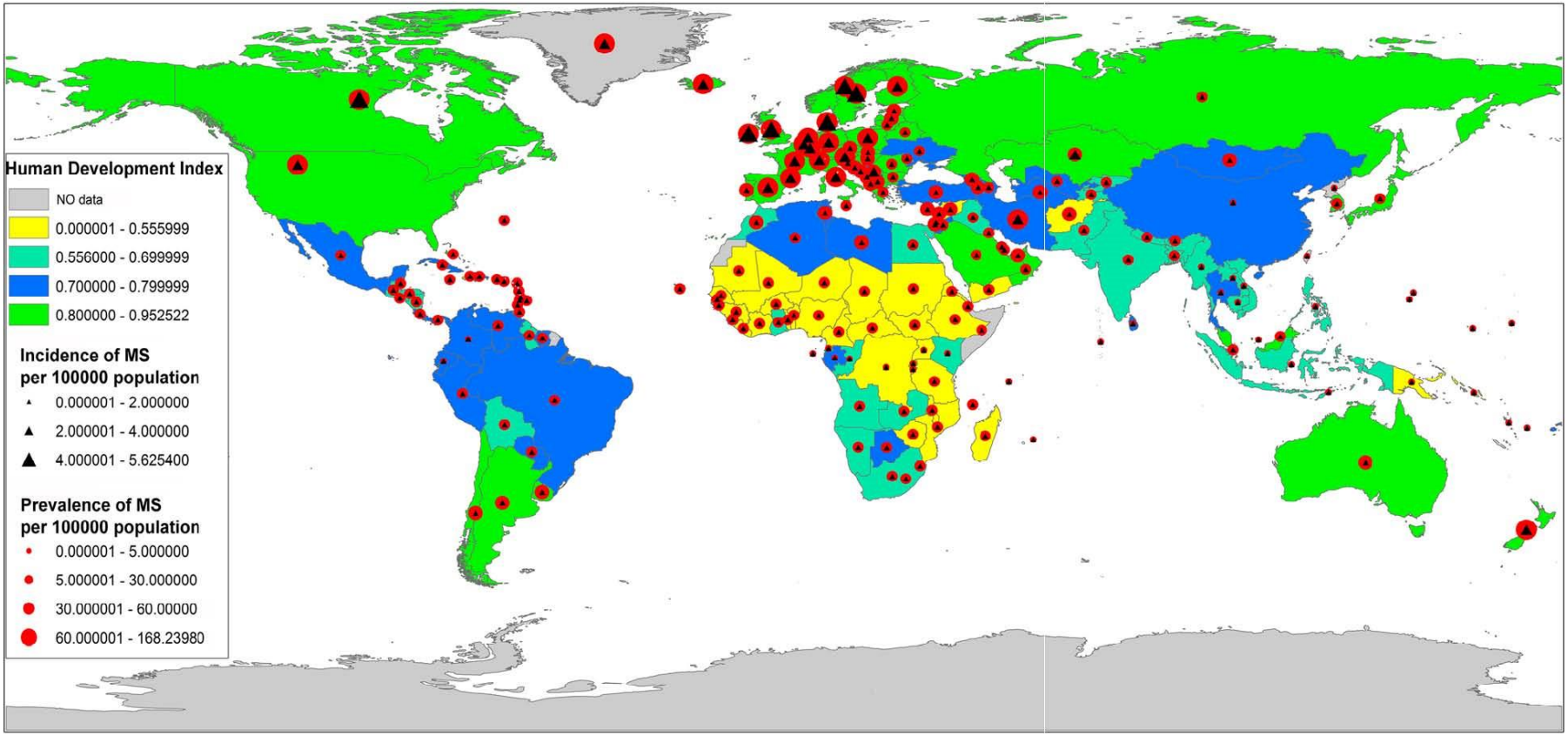
Multiple Sclerosis Is…

- An unpredictable, immune-mediated, chronic, inflammatory, degenerative disease striking in prime of life
  - Inflammatory, demyelinating lesions (plaques) and axonal loss in CNS
  - Lesions attributed to autoimmune attacks directed against myelin, oligodendrocytes, and axons often causing clinical symptoms
  - White and gray matter involvement
- Most often characterized by relapses and remissions of neurological symptoms, residual worsening and/or steady progression of disability over time

CNS=central nervous system.

Giovannoni G et al. *Mult Scler Relat Disord.* 2016;9:S5-S48. 43:1430-1438; Gross HJ, Watson C. *Neuropsychiatr Dis Treat.* 2017;13:1349-1357; Kappos L et al. *JAMA Neurology.* 2020;77:1132-1140.

Worldwide Prevalence of MS



Moghaddam VK et al. Global burden of disease data. *BMC Neurol.* 2021;21:145.

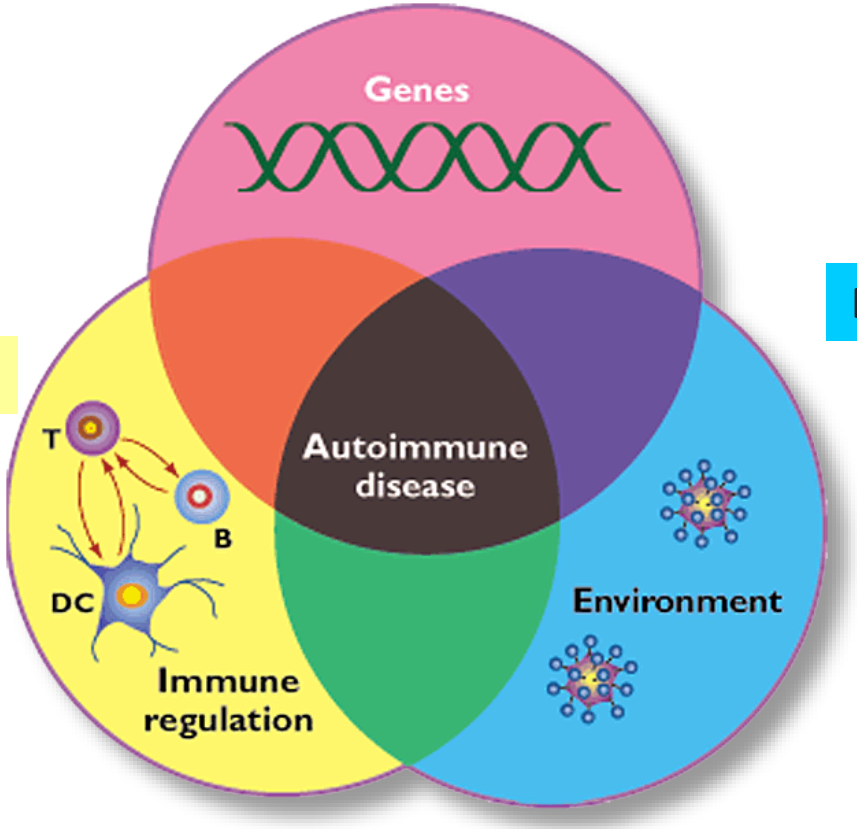
Etiology of MS Is Not Clear

Genetic Predisposition

>200 immune genes implicated in risk for MS: HLA-DRB1*15, IL-2 and IL=7 receptors

Immune Dysregulation

Th1/Th 17
CD4/CD8
B-cells
IgG



Environmental Factors

Viruses (EBV)
Vitamin D
Latitude
Smoking
Obesity
Diet (salt?)
Gut microbiome

EBV=Epstein-Barr virus.

Cree BA. Multiple sclerosis genetics. In: Goodin DS, ed. *Handbook of Clinical Neurology: Multiple Sclerosis and Related Disorders.* 2014;122;193-209; Kim W, Patsopoulos NA. *Semin Immunopathol.* 2022;44:63-79; Bjornevik K et al. *Science.* 2022;375:296-301.

Risk Factors for MS

- Cigarette smoking
  - Active smokers have 40% increased risk of developing MS
  - Smoking causes increased progression if smoking continued after diagnosis
- Obesity
  - In girls, associated with 60%-95% increased risk
  - In boys, 30%-80% increased risk
  - In women age 18 with BMI >30 kg/m^2, 2-fold increased risk
- Epstein-Barr virus
  - Late adolescent infection 10x risk vs those with no infection
- Low serum vitamin D
  - Higher vitamin D levels seem to be protective against MS

BMI=body mass index.

Ascherio A, Munger K. *Semin Neurol.* 2016;36:103-114.

MS Symptoms

- Symptoms are unpredictable and may be mild, moderate, or severe
- Symptoms may appear as acute attack or may become chronic, with clinical and functional deterioration defining disease progression
- Each patient differs in the types and intensity of symptoms, depending on the areas of the CNS that are affected

National MS Society.

PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS

Pathophysiology of MS

- Immune system triggered to target the CNS
  - Breakdown of blood-brain barrier
  - Multifocal areas of inflammation
  - Demyelination and oligodendrocyte loss
  - Gliosis
  - Axonal degeneration
- Major cause of neurologic disability is axonal loss
- CNS damage occurs early in disease process
- Peripheral immune response targeting the CNS appears to drive early disease process, while immune reactions within CNS drive progressive phase

BBB=blood-brain barrier.

Halper J et al. *Nursing Practice in Multiple Sclerosis: A Core Curriculum.* 4th ed. 2016; Hemmer B et al. *Lancet Neurol.* 2015;14:406-419; Absinta M et al. *Curr Opin Neurol.* 2020;33:277-285; Mahad DH et al. *Lancet Neurol.* 2015;14:183-193; Stankiewicz JM, Weiner HL. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e636; Giovannoni G et al. *Mult Scler Relat Disord.* 2016;9:S5-S48.

Pathophysiology of MS: Demyelination

- MS plaques / lesions are:
  - Areas of demyelination
  - Followed by partial remyelination and gliotic scarring
  - Demyelination can also cause black holes, which equates to poorer prognosis

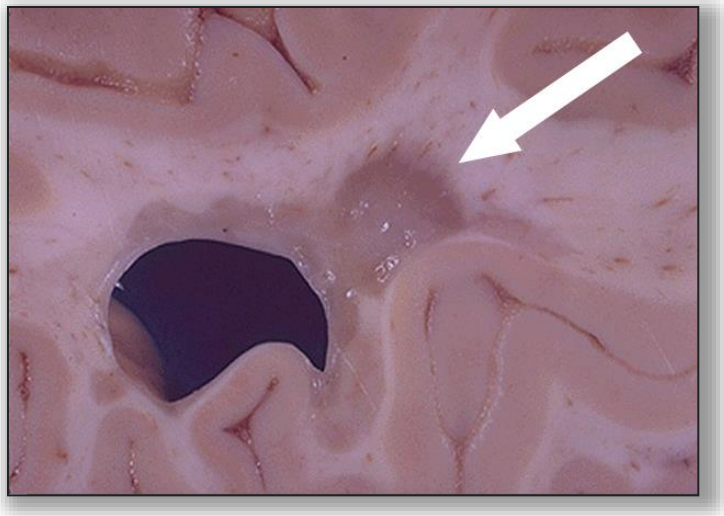
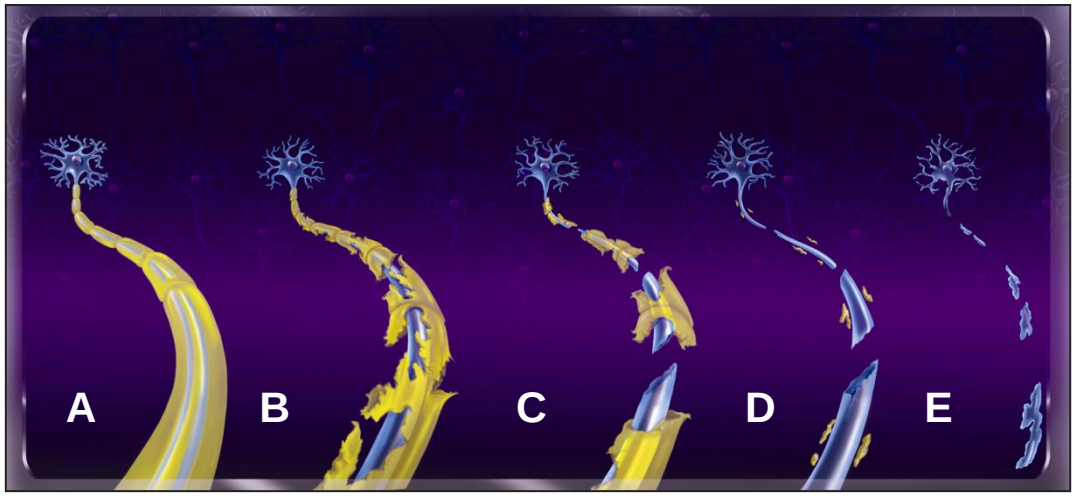


Photo credit: Spencer S. Eccles Health Sciences Library.

Compston A, Coles A. *Lancet*. 2002;359:1221-1231; Lassmann H. *Clin Neurol Neurosurg*. 2002;104:168-171; Lucchinetti C et al. *Ann Neurol*. 2000;47:707-717.

Nerve Damage and Myelin Loss

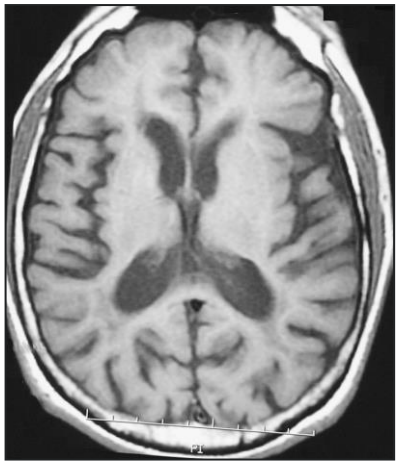


A. Normally, axons have a protective myelin coating that is necessary for normal conduction of electrical impulses
B. In MS, the immune system destroys myelin, resulting in slowed conduction and exposure of axons
C. Exposed axons may then be severed…
D. …leading to permanent loss of the axon
E. Result is permanent loss of nerve function

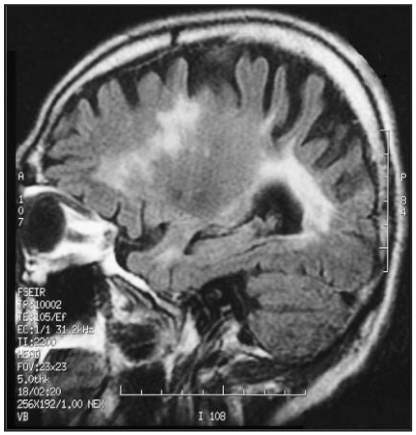
Adapted from Trapp BD et al. *The Neuroscientist.*1999;5:48-57.

Brain Atrophy in MS

- Atrophy may occur early in the disease
- Represents cumulative effect of:
  - Demyelination and axonal loss, black holes
  - Diffuse, non-focal tissue damage
- Brain tissue decreases at an approximate mean rate of:
  - 0.7% to – 2.0% per year in patients with MS
  - 0.1% to – 0.32% per year in normal controls



T1



FLAIR

Cagol A et al. *JAMA Neurol.* 2022;79:682-692;
Kalkers NF et al. *Arch Neurol*. 2002;59:1572-1576;
Rovaris M et al. *J Neurol.* 2000;247:960-965;
Scahill RI et al. *Arch Neurol.* 2003;60:989-994.

DISEASE COURSES (PHENOTYPES) IN MULTIPLE SCLEROSIS

Disease Courses (Phenotypes)

- Clinically isolated syndrome (CIS)
- Relapsing MS (RMS)
  - About 85% of people are diagnosed with RRMS
- Secondary-progressive (SPMS)
  - Some people diagnosed with RRMS will eventually transition to SPMS
- Primary-progressive MS (PPMS)
  - About 10%-20% of people experience this course

Lublin FD et al. *Neurology.* 2014;83:278-286.

Clinically Isolated Syndrome (CIS)

- First neurologic episode, lasting at least 24 hours
- Caused by inflammation/demyelination in one or more sites in the CNS
- Monofocal attack: Single neurologic sign or symptom (eg, attack of optic neuritis caused by single lesion)
- Multifocal attack: ≥1 sign or symptom caused by multiple lesions (eg, attack of optic neuritis accompanied by weakness on one side)
- May or may not develop clinically definite MS (CDMS)
  - When clinical symptoms are accompanied by positive MRI scan, 60%-80% of people with CIS will go on to develop MS within a few years

National MS Society; Lublin FD et al. *Neurology.* 2014;83:278-286.

Radiographically Isolated Syndrome (RIS)

Not considered to be a disease course or phenotype

- MS-like lesions detected when brain MRI is performed for another reason (eg, headache, post trauma)
- *Absence* of clinical symptoms referable to MS
- Recent study of 457 patients with RIS found 51% experience a first clinical event within 10 years
- Presents ethical and diagnostic challenges
- Patient requires careful follow-up and discussion to treat or not
- Careful medical history needs to be taken

Lublin FD et al. *Neurology.* 2014;83:278-286; Lebrun-Frenay C et al. *Ann Neurol.* 2020;88:407-417.

Definitions Related to MS Phenotypes

- Active disease
  - **Clinical:** relapses, acute or sub-acute episodes of new or increasing neurologic dysfunction followed by full or partial recovery in the absence of fever or infection
  - **Imaging (MRI):** occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions

- Progressive disease
  - **Clinical:** steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)
  - **Imaging (MRI):** Measures of progression not established or standardized and not useful as phenotype descriptors. Under consideration are increasing number and volume of T1-hypointense lesions, brain volume loss, and changes in magnetic transfer imaging and diffusion tensor imaging

Lublin FD et al. *Neurology.* 2014;83:278-286.

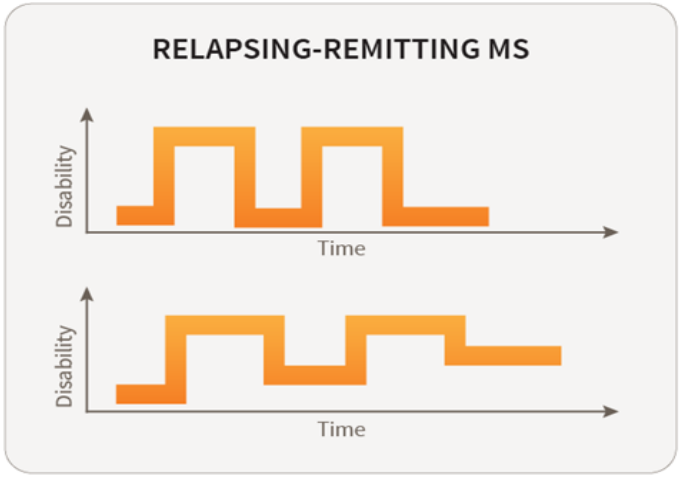
Definitions Related to MS Phenotypes (cont.)

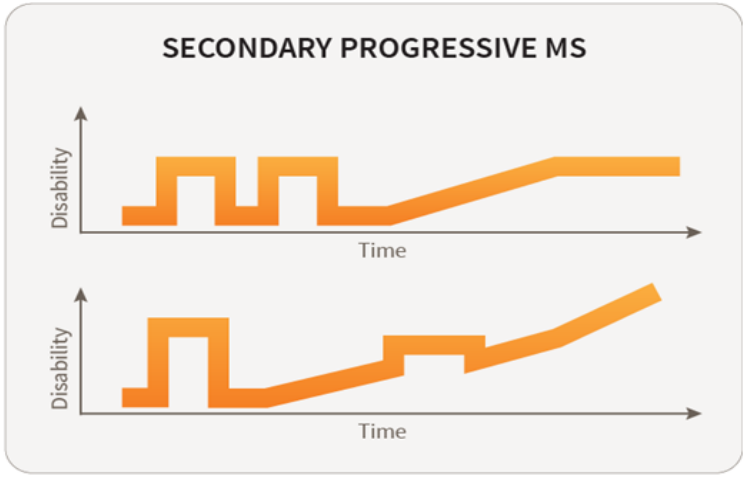
- Worsening disease
  - Documented increase in neurologic dysfunction/disability as result of relapse or progressive disease, reserving term “disease progression” for those solely in progressive phase of the illness

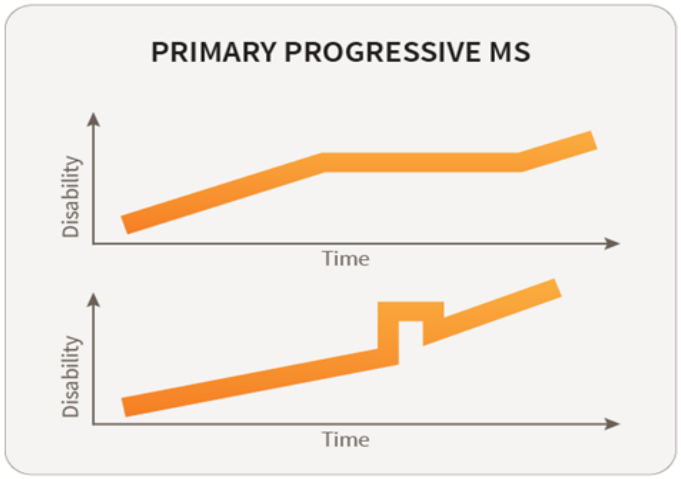
- Confirmed progression or worsening
  - Increase of neurologic dysfunction confirmed throughout defined time interval (eg, 3, 6, or 12 months)
  - Because neurologic dysfunction may still improve, even if progression is confirmed over 6 or 12 months, it’s recommended abandoning the term “sustained”

Lublin FD et al. *Neurology.* 2014;83:278-286.

What Happens in MS Over Time?







Relapsing course can be:
- Active or inactive
- Worsening or not worsening

Progressive courses can be:
- Active with or without progression
- Not active with or without progression

Klineova S, Lublin FD. *Cold Spring Harb Perspect Med.* 2018;8:a028928.

DIAGNOSING THE DISEASE: DIAGNOSTIC CRITERIA

Diagnosing MS

Requires 2 or more neurological events referable to CNS, with objective findings and disseminated in space and time

- History of symptoms referable to the CNS
- Neurological exam
- Para-clinical testing
- Exclusion of other potential MS mimics

Poser CM et al. *Ann Neurol*. 1983;13:227-231; Miller DH et al. *Mult Scler.* 2008;14:1157-1174; Polman CH et al. *Ann Neurol.* 2011;69:292-302; Thompson AJ et al. *Lancet.* 2018;17:162-173.

Diagnostic Criteria for MS: 2017 Revisions to McDonald Criteria

- Dissemination in Time (DIT): Criteria can be met with CSF-specific oligoclonal bands in CIS pt already meeting Dissemination in Space criteria
- Dissemination in Space (DIS): Cortical lesions can be used to demonstrate this
- Symptomatic and asymptomatic lesions can be used to demonstrate DIS or DIT in pts with supratentorial, infratentorial, or spinal cord syndrome
- NMOSD should be considered in the differential diagnosis of patients presenting with symptoms indicative of MS especially those with optic neuritis or spinal cord predominant disease
- MOG should also be considered

CSF=cerebrospinal fluid; MOG=myelin oligodendrocyte glycoprotein; NMOSD=neuromyelitis optica spectrum disorder.

Thompson AJ et al. *Lancet.* 2018;17:162-173.

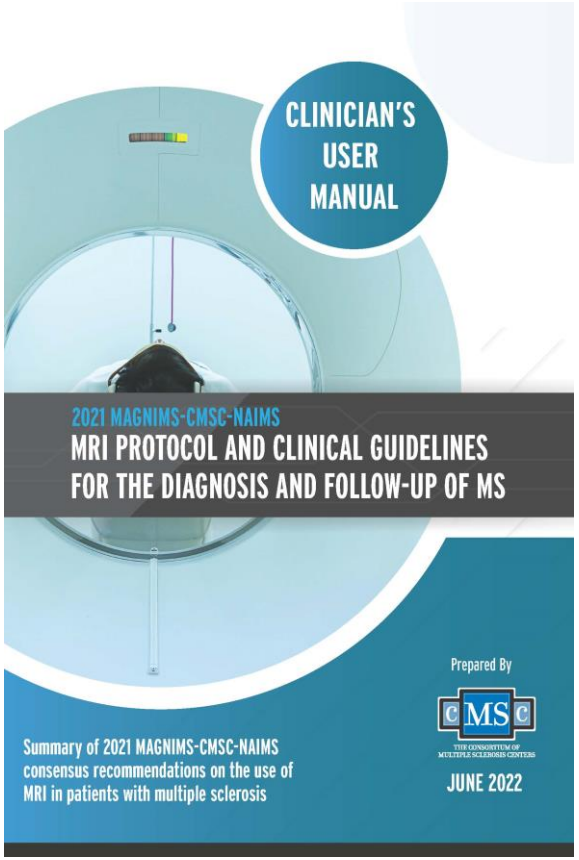
2017 McDonald Diagnostic MS Criteria

Clinical Attacks	Number of Lesions with Objective Clinical Evidence of MS	Additional Information Needed to Make Diagnosis
2 or more	2 or more	None
2 or more	1—plus clear-cut historical evidence of previous attack involving lesion in a distinct anatomical location	None
2 or more	1	DIS demonstrated by additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	2 or more	DIT demonstrated by additional clinical attack or by MRI or CSF-specific oligoclonal bands
1 clinical attack	1	DIS demonstrated by additional clinical attack implicating a different CNS site or by MRI AND DIT demonstrated by additional clinical attack or by MRI or CSF-specific oligoclonal bands

DIS=dissemination in space; DIT=dissemination in time.

Thompson AJ et al. *Lancet.* 2018;17:162-173.

MRI International Guidelines Circa 2021



- New MRI international guidelines for MS were published in August 2021 as a collaboration among The Consortium of Multiple Sclerosis Centers (CMSC), the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) study group, and the North American Imaging in Multiple Sclerosis (NAIMS) Cooperative
- These guidelines were developed in an attempt to standardize imaging protocols for MS to avoid misdiagnosis and allow comparison of sequential scans

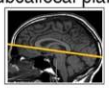
Wattjes MP et al. *Lancet Neurol.* 2021;20:P653-P670.

MRI Standardized Protocol Card to Download

2021 MAGNIMS-CMSC-NAIMS STANDARDIZED MRI PROTOCOL

Lancet Neurology 2021 Aug;20(8):653-670

Magnims | CMSC THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS | NAIMS North American Imaging in MS Cooperative

	BRAIN	SPINAL CORD	OPTIC NERVE
FIELD STRENGTH	≥1.5 T (preferably 3T)	≥1.5 T	≥1.5 T
ACQUISITION	3D (preferred) or 2D	2D or 3D	2D or 3D
SLICE THICKNESS	3D: 1mm isotropic[1] 2D: ≤3mm, no gap[2]	Sagittal ≤3mm, no gap Axial ≤5mm, no gap	≤2-3mm, no gap
IN-PLANE RESOLUTION	≤1mm x 1mm	≤1mm x 1mm	≤1mm x 1mm
COVERAGE	Whole brain (include as much of cervical cord as possible)	Whole cord (cervical, thoracolumbar including conus)	Optic nerve & chiasm
AXIAL SCAN ORIENTATION (2D ACQUISITION OR 3D RECONSTRUCTION)	Subcallosal plane 	Perpendicular to sagittal axis of cord	Align to optic nerve/ chiasm orientation

T = tesla; 3D = 3 dimensional; 2D = 2 dimensional

[1] Isotropic preferred; if over-contiguous (through-plane and in-plane), not > 1.5 mm with 0.75 mm overlap

[2] Diffusion-weighted imaging: slice thickness should be ≤ 5mm with no more than a 10–30% slice gap

Brain	Dx	Fm	Sm
Axial T_2		±	±
Sagittal & axial FLAIR (or 3D)			
Post-Gd axial (or 3D) T_1			
Diffusion-weighted imaging		DDx	
DIR or PSIR			
High-resolution 3D T_1 (brain volume assessment)			
Susceptibility-weighted imaging			
Optic Nerve	**Dx**	**Fm**	**Sm**
Axial & coronal fat-suppressed T_2 or STIR			
Post-Gd[3] axial & coronal fat-suppressed T_1			
Spinal Cord	**Dx**	**Fm**	**Sm**
Sagittal at least 2 of T_2, PD or STIR			
Sagittal 3D T_1 (PSIR, MPRAGE)[4] cervical only			
Axial T_2 or T_2^*			
Pre-Gd Sagittal T_1			
Post-Gd[3] Sagittal T_1			
Post-Gd[3] axial T_1			

Recommended Core | Optional | Not Required

[3] No additional Gd necessary if immediately following Post-Gd brain examination

[4] Could substitute for one of T_2, PD or STIR

Dx Diagnosis of MS

Fm Follow-up monitoring of disease activity and effectiveness of disease modifying treatment (DMT)

Sm Safety monitoring for DMT e.g., screening for risk of progressive multifocal encephalopathy (PML)

T_2 (TSE/FSE, turbo/fast spin echo)

± Axial T_2 optional if 3D FLAIR with sagittal/axial reconstructions are available

Gd macrocyclic agent, 0.1mm/kg body weight, minimum delay 5-10 minutes

T_1 (TSE/FSE)

DDx For differential diagnosis

FLAIR (fluid-attenuated inversion recovery), with optional fat suppression

DIR (double inversion recovery)

PSIR (phase-sensitive inversion recovery)

High resolution 3D T_1 (e.g. MPRAGE/MP2RAGE magnetization-prepared rapid acquisition of gradient echoes; IR-SPGR, inversion recovery prepared spoiled gradient; TFE, turbo field-echo)

STIR (short tau inversion recovery)

PD (proton-density, TSE/FSE)

T_2^* (T_2 gradient recalled echo)

Download at: https://mscare.org/ page/MRI_protocol

PARA-CLINICAL TESTING ASSESSMENT TOOLS

Assessment Tools to Diagnose MS

- Medical history
  - Age/gender/ethnicity
  - Identify any events that might be indicative of MS-related symptoms
  - Complete differential diagnosis
- Neurologic examination
  - Mental status and affect, cranial nerves, motor, sensory, balance and coordination, gait
- MRI changes should support diagnosis
  - Clinical attacks/relapses/exacerbations
  - Brain and spinal cord imaging
  - Detect subclinical lesions in some people
  - Identify active inflammation with gadolinium (Gd) contrast enhancement

National MS Society; Thompson AJ et al. *Lancet Neurol.* 2018;17:162-173.

Assessment Tools to Diagnose MS (cont.)

- Lumbar puncture with CSF analysis
  - IgG elevation, oligoclonal bands, mild leukocytosis
- Serum neurofilament light chain (sNfL)
  - Possible prodromal marker of MS activity
- Laboratory studies: Exclude disease mimics
  - Metabolic illness, infections, other inflammatory illnesses
- Evoked potential testing
  - Visual Evoked Potentials (VEP)
  - Brainstem Auditory Evoked Potentials (BAEP)
  - Sensory Evoked Potentials (SEP)
- Central vein sign

National MS Society; Thompson AJ et al. *Lancet Neurol.* 2018;17:162-173;
Bjornevik K et al. *JAMA Neurol.* 2020;77(1):58-64;
Sinnecker T et al. *JAMA Neurol*. 2019;76:1446-1456.

MRI BASICS

MRI Basics

- Magnetic field and radiofrequency pulse to differentiate normal and abnormal tissue
- No radiation involved
- Intensity of MRI signal
  - 7T usually only available for clinical research. Most centers with 3T
  - Varies based on water content of tissues, magnitude and timing of RF pulses, use of enhancing agent

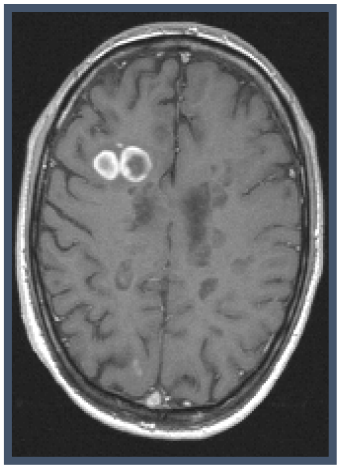
Boesch C. *Mol Aspects Med.* 1999;20:185-318;
CMSC. MRI protocol and clinical guidelines for the diagnosis and follow-up of MS. 2018.

2018 Revised CMSC MRI Protocol for Diagnosis and Follow-up of Patients with MS

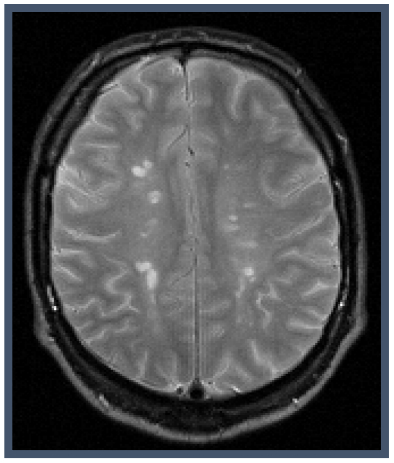
- Brain MRI with gadolinium recommended for diagnosis
- Spinal cord MRI recommended if brain MRI is non-diagnostic or if presenting symptoms are referable to spinal cord
- Follow-up brain MRI is recommended to:
    - Demonstrate dissemination in time for diagnosis
    - Detect clinically silent disease activity while on treatment
    - Safety monitoring including PML surveillance while on treatment
    - Evaluate unexpected clinical worsening
    - Reassess the original diagnosis
    - As a new baseline MRI before starting or modifying therapy
    - Every 6 months to 2 years for patients with relapsing MS
- Prudent use of gadolinium for diagnosing MS, but not necessarily for routine monitoring

CMSC. MRI protocol and clinical guidelines for the diagnosis and follow-up of MS. 2018.

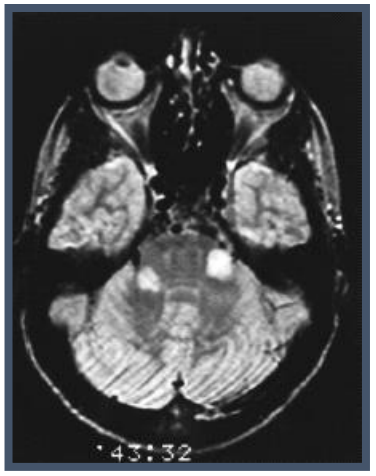
Typical MRI Lesions



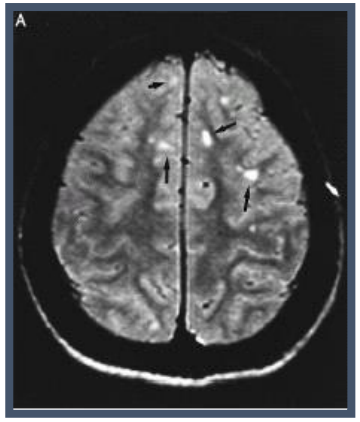
Gd-enhancing



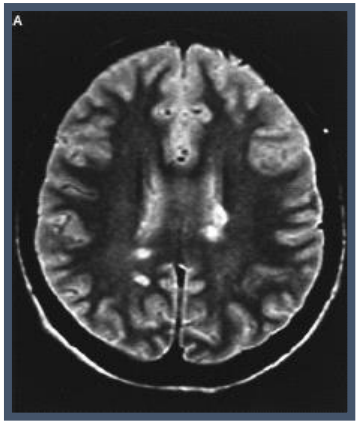
T2-hyperintense



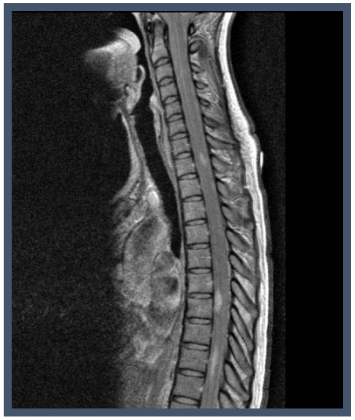
Infratentorial



Juxtacortical



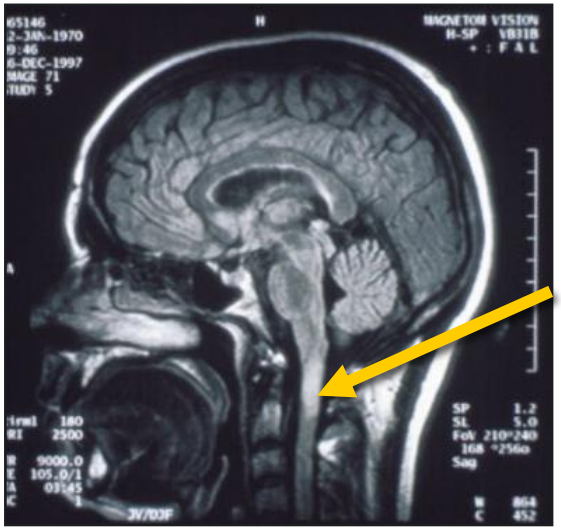
Periventricular



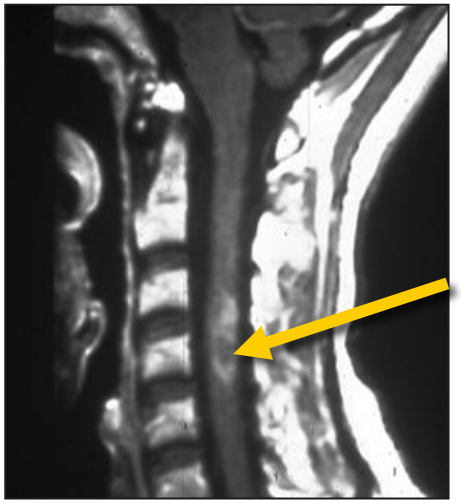
Spinal Cord

Spinal Imaging

- Spinal lesions occur in ~75% of patients with MS, primarily in cervical spine
  - Less likely to enhance or cause cord swelling
  - More likely to cause progressive disease



- Lesions seen on T2 scan are less predictive of disability than atrophy

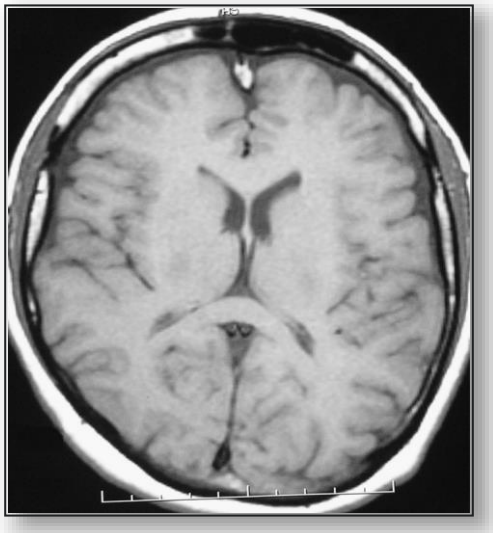


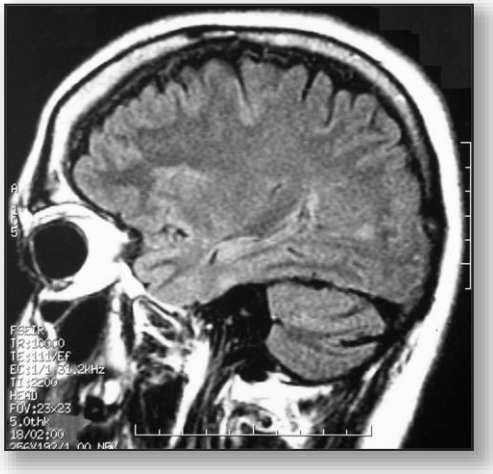
Used with permission of Kathy Costello, ANP, and Patricia Kennedy, ANP. *A Comprehensive Overview of MS Nursing.* 2nd edition. 2010.

Brain Atrophy: MRI Findings

(Represents cumulative effect of demyelination, axonal loss, and diffuse, nonfocal damage)

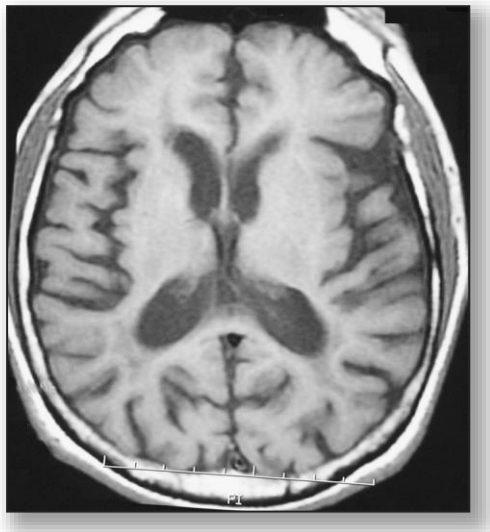
33-year-old man with RRMS for 2 years

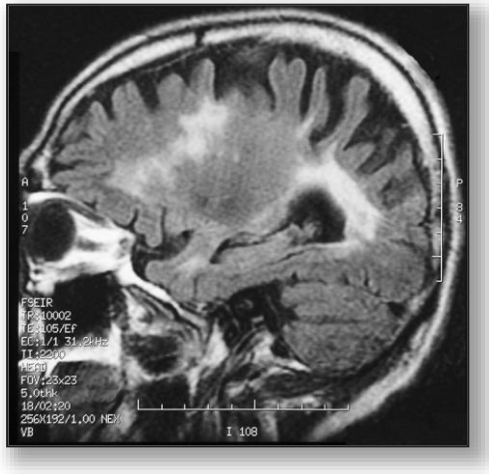




T1

FLAIR





47-year-old man with RRMS for 20 years

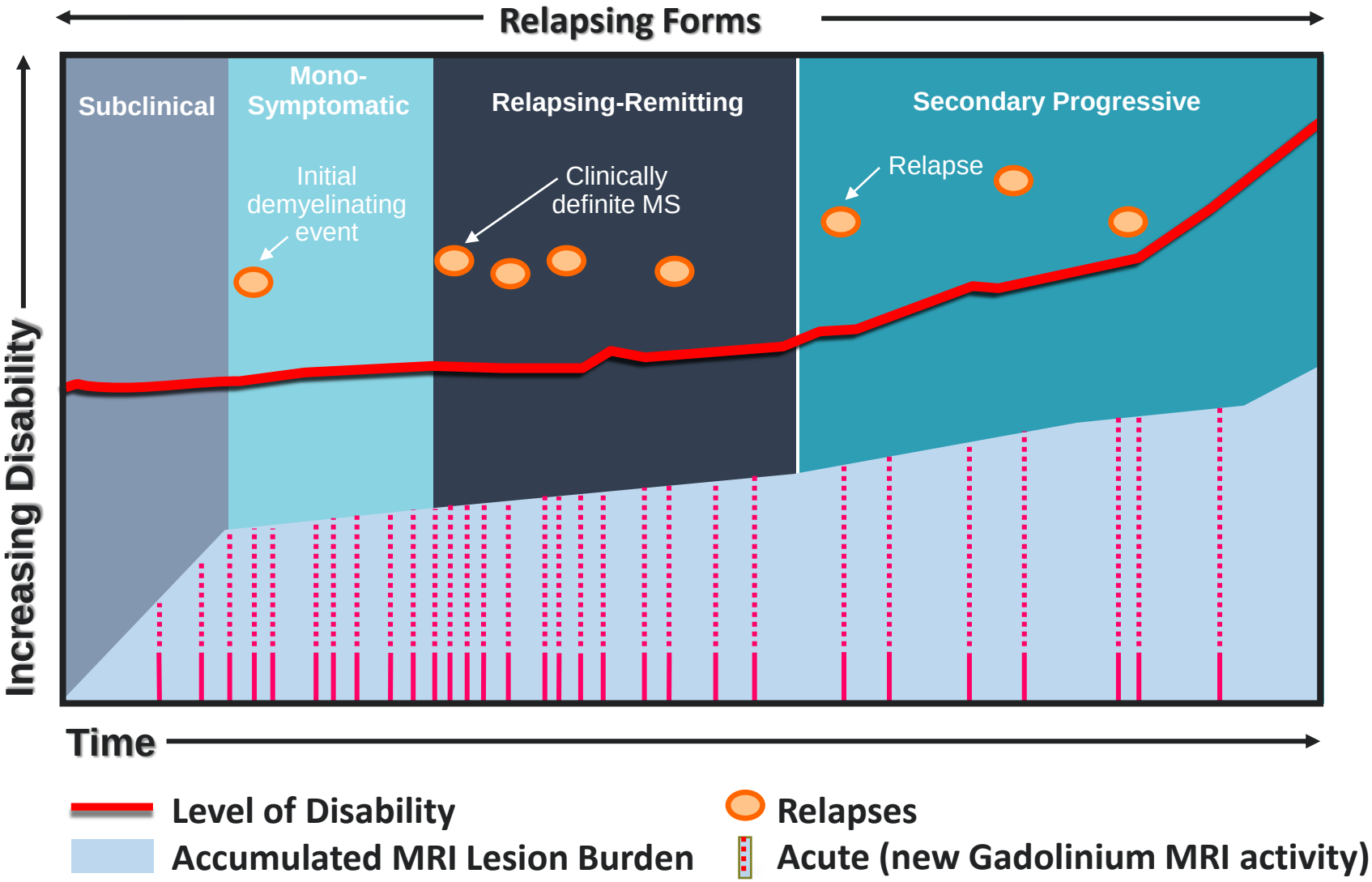
Courtesy of Dr. D. Mikol.

Case for Early Treatment with DMTs

- Relapses and impairment have been shown to parallel MRI burden of disease
- Axonal damage occurs early
  - May cause permanent neurological dysfunction
- Number of MRI lesions may be predictive of future disability
- Preventing development of lesions may delay progression of disability and conversion to SPMS
- Preventing early relapses may delay long-term disability

DMTs=disease-modifying therapies; SPMS=secondary-progressive MS.
MS Coalition, 2019; American Academy of Neurology, 2018;
Brown JWL et al. *JAMA Neurol.* 2019;321:175-187.

Progression of Untreated MS



Summary

- MS is a complex, immune-mediated disease affecting CNS
  - Causes inflammation, demyelination, axonal damage
- MS remains a clinical diagnosis supported by paraclinical evidence
  - MRI, CSF analysis, lab studies, and evoked potential testing
- MS phenotypes may provide clarity and consistency in defining and treating patient groups
- Majority of individuals will start with relapsing MS
  - Will develop progression of disability if untreated

Nursing Implications

- MS is a dynamic chronic illness requiring nursing professionals with experience in identifying, diagnosing, and treating patients with MS
- Planning of care for patients with MS should be flexible and nimble to meet individualized needs of patients and families
- International Organization of MS Nurses (IOMSN) is a comprehensive source of continuing education, skill development, and support for nursing professionals engaged in field of patient care in MS