The Nature of Multiple Sclerosis :

Epidemiology, Diagnosis, Natural History & Clinical Course

IOMSN
International Organization of Multiple Sclerosis Nurses

Multiple Sclerosis

- **Immune-mediated, chronic, inflammatory disease**
  - precipitated by unknown environmental factors in genetically susceptible individuals
  - inflammation, demyelination, axonal loss in the CNS
- **Most common chronic neurological disease in young adults**
- **Characterized by relapses and remissions of neurological symptoms and progression of disability over time**

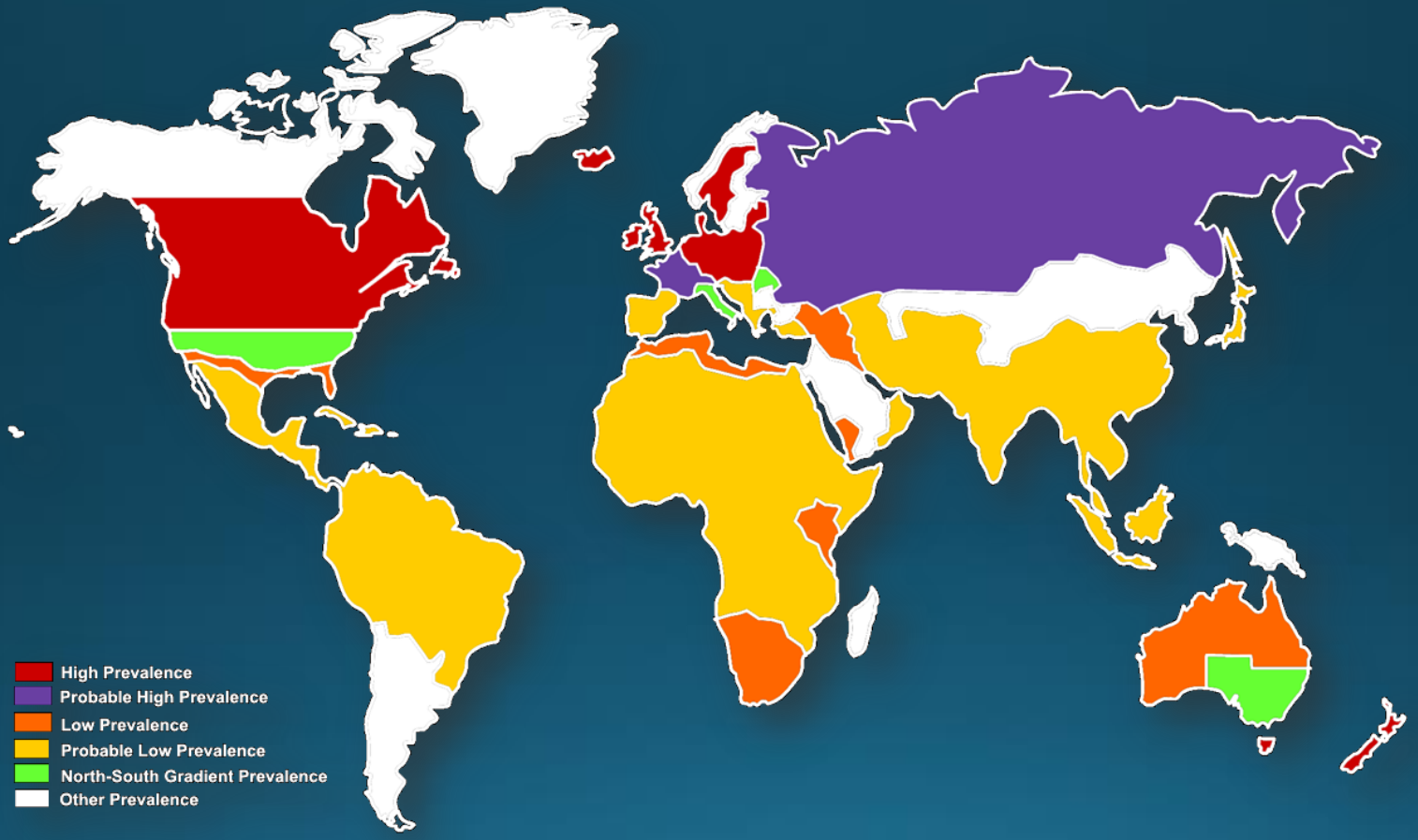
Compston A, Coles A. *Lancet*. 2002;359:1221-1231.
Fleming JO, Carrithers MS. *Neurology.* 2010;74:876-877.

Epidemiology of MS

- **Approximately 400,000 cases in the United States[1]**
  - (estimates range from 250,000–500,000)
- **Estimated 2.3 million cases worldwide[2]**
- **Higher prevalence with northern European ancestry[3]**
- **Highest incidence in Caucasians**
- **Higher incidence in women (≥3:1)[2,3]**
- **3/4 of cases present between ages of 15-45**

1. National MS Society Information Sourcebook. www.nationalmssociety.org/sourcebook. Accessed March 6, 2007.
2. National MS Society. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx. Accessed: February 1, 2014.
3. Hogancamp WE, et al. *Mayo Clin Proc.* 1997;72:871-878.

World Distribution of Multiple Sclerosis



MS varies geographically. High prevalence: Northern US, Canada, Most of Europe, Northern Australia, New Zealand, Northern Russia

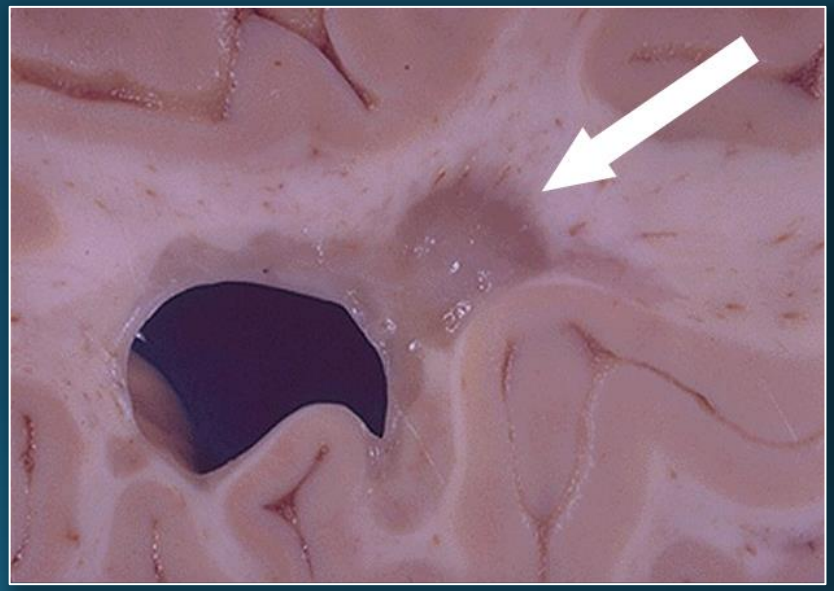
PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS

Pathophysiology of MS

- **Pathologic hallmarks of MS:**
  - breakdown of the blood brain barrier (BBB)
  - multifocal inflammation
  - demyelination and oligodendrocyte loss
  - gliosis
  - axonal degeneration
- **Major cause of neurologic disability is axonal loss**

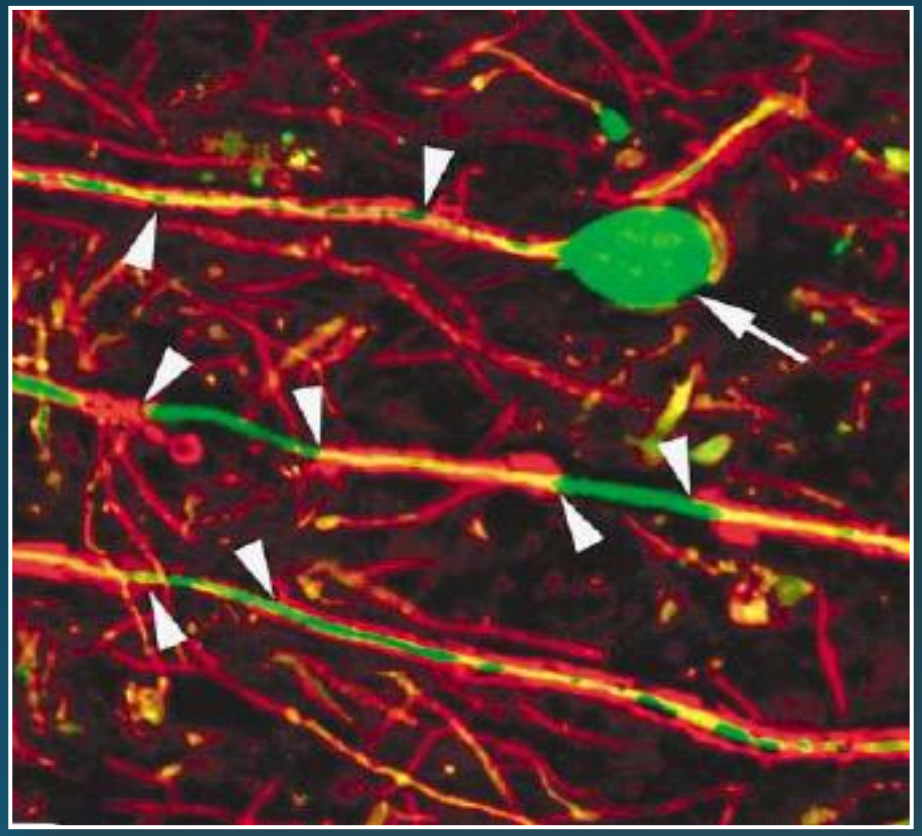
Pathophysiology of MS: Demyelination

- **MS plaques / lesions are:**
  - areas of demyelination
  - followed by partial remyelination and gliotic scarring



Spencer S. Eccles Health Sciences Library. http://www-medlib.med.utah.edu. Accessed March 6, 2007.

Pathophysiology: Axonal Loss



Arrowheads = areas of active demyelination.
Arrow = terminal axon ovoid.

Trapp BD, et al. *N Engl J Med*. 1998;338:278-285.

Brain Atrophy in MS

- **Atrophy may occur early in the disease**
- **Represents cumulative effect of:**
  - demyelination and axonal loss
  - diffuse, nonfocal tissue damage
- **Brain tissue decreases at an approximate mean rate of:**
  - 0.7% – 2.0% per year in patients with MS
  - 0.1% – 0.32% per year in normal controls

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.

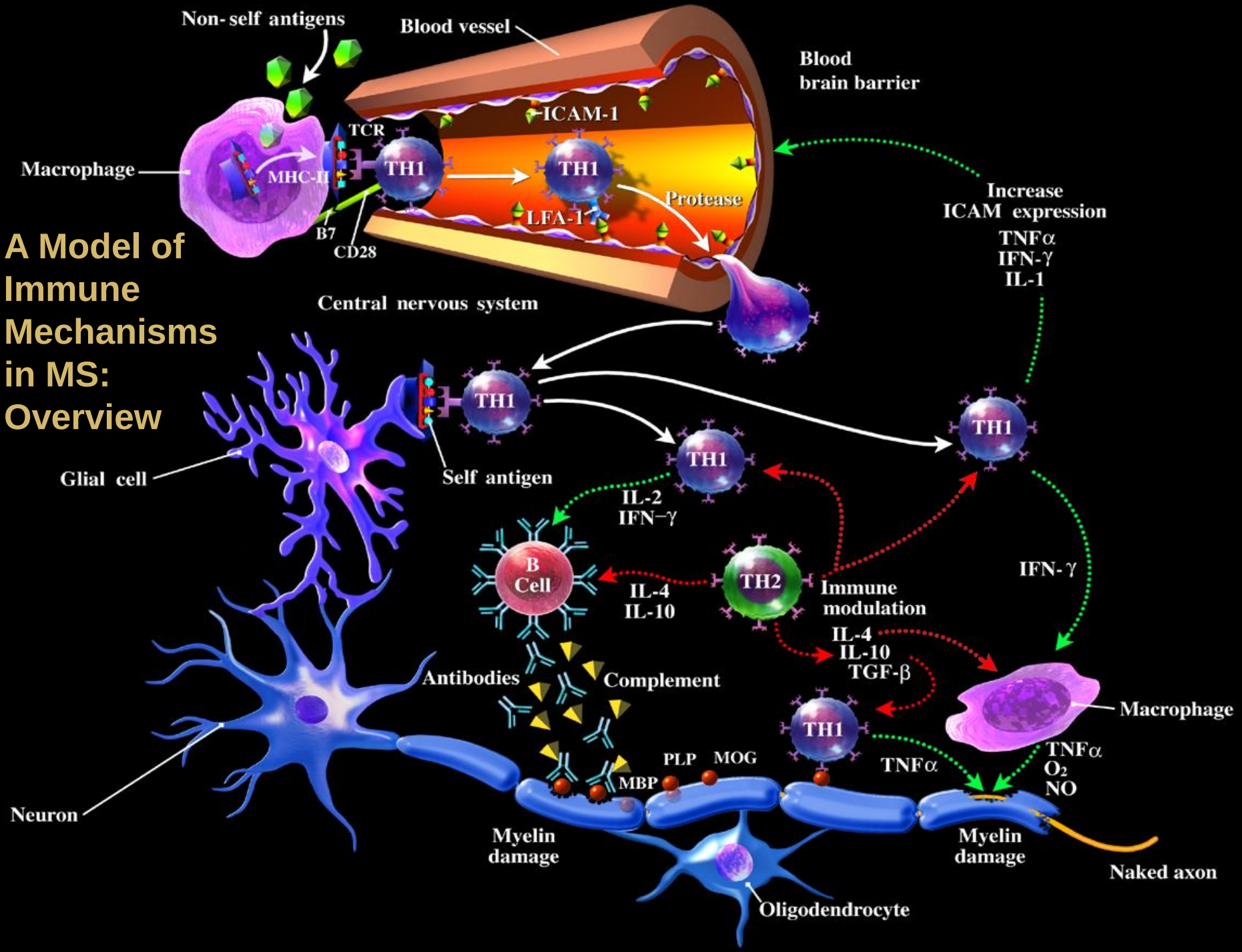
Immunology of MS

- **Autoimmune, neurodegenerative disease of CNS**
- **T-cell activated mediated inflammatory disorder**
  - overproduction of pro-inflammatory cytokines
- **B-cells also involved in inflammatory process**

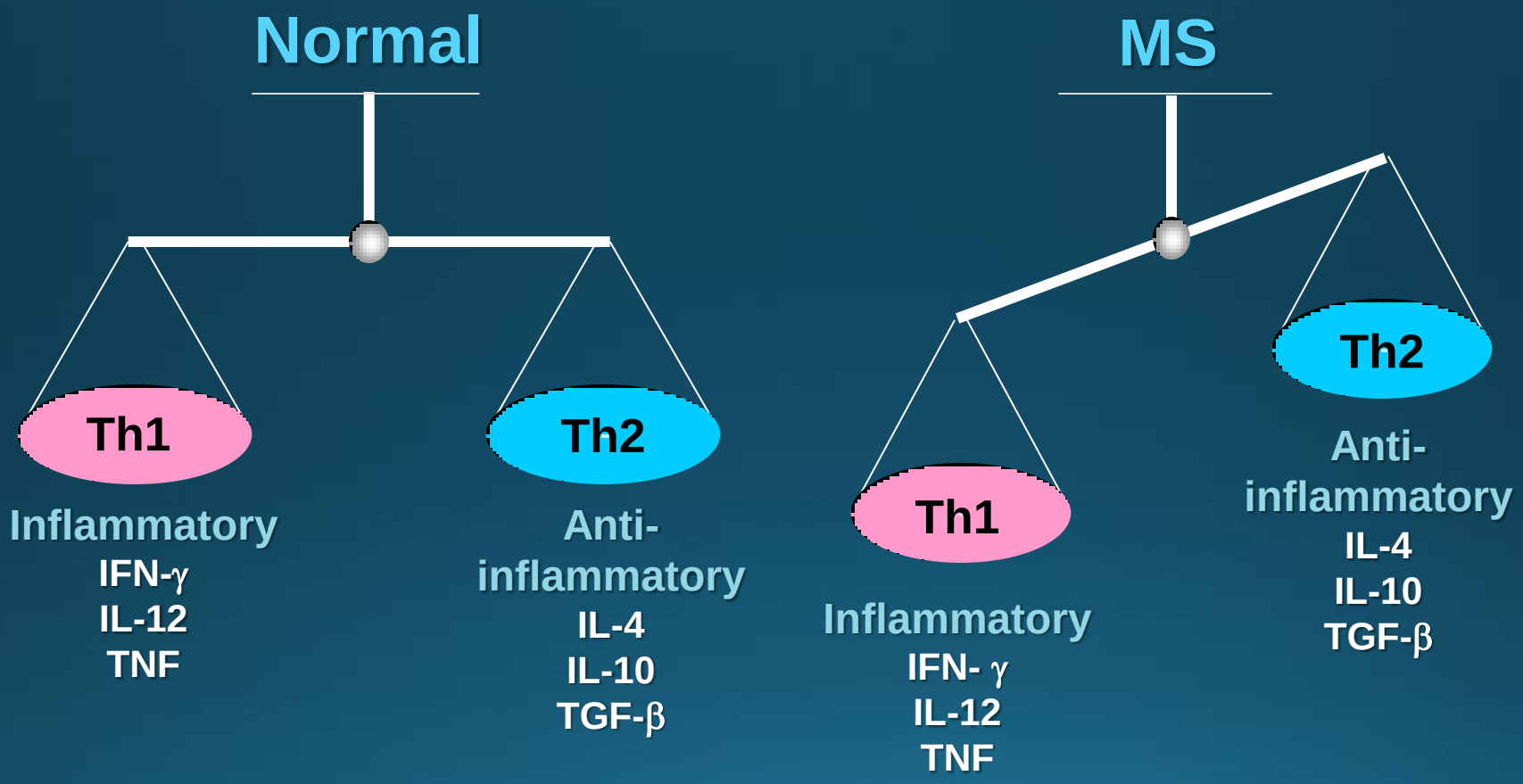
Immunology of MS

- **Lesions result from a highly selective, destructive process orchestrated by the immune system**
  - Old lesions: inactive, few immune cells, scaring
  - New lesions: activated immune cells
- **Immune system responses at the blood-brain-barrier**
  - Effects of the CNS responses on the biology of invading inflammatory cells

A Model of Immune Mechanisms in MS: Overview



Cytokine Imbalance in MS



Reference: Janeway CA Jr, et al. *Immuno Biology.* 5th ed. New York, NY: Garland Publishing; 2001.

PRESENTING SYMPTOMS

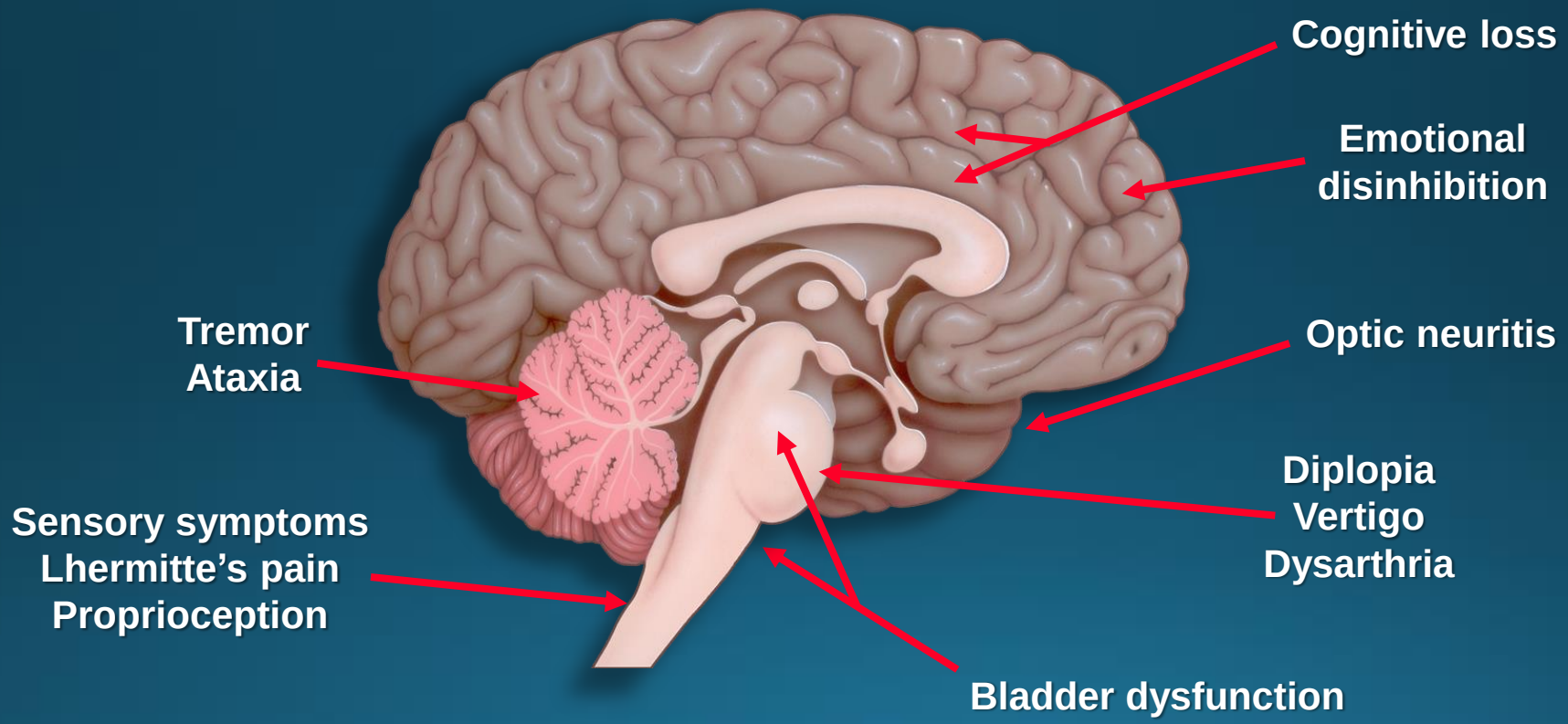
Symptom Overview

- **Motor, sensory, emotional, cognitive**
  - may remain, fluctuate, or progress
- **Symptoms:**
  - Primary (eg, fatigue, tremor)
  - Secondary (eg, falls, urinary tract infections)
  - Tertiary (eg, loss of job, divorce)
- **New onset of symptoms or worsening symptoms may indicate relapse or pseudo-relapse or progression**

Halper J, Harris C. In *Nursing Practice in Multiple Sclerosis.* 3rd ed. New York: Springer Publishing Company; 2012:53-54.
Schapiro RT, Schneider D. In *Comprehensive Nursing Care in Multiple Sclerosis*. 2002.

Symptoms of Multiple Sclerosis: Neurologic Origins

Symptom presentation depends on lesion location



Miller AE. In *Handbook of Multiple Sclerosis*. 2001:213-232.

DIAGNOSING THE DISEASE: DIAGNOSTIC CRITERIA

Diagnosis of MS: Basic Principles

- **Clinical profile and diagnosis**
  - no definitive laboratory test
- **Laboratory evaluation**
- **Evidence of dissemination of lesions in space and time**
- **Exclusion of other diagnoses**

Poser CM, et al. *Ann Neurol*. 1983;13:227-231.
Miller DH, Weinshenker BG, Filippi M, et al. *Mult Scler.* 2008;14:1157-1174.

Diagnostic Criteria for MS: 2010 Revisions to McDonald Criteria

- **Simplified dissemination in space (DIS) and dissemination in time (DIT)**
  - DIS and DIT can be shown in a single scan with asymptomatic gadolinium enhancing lesion
- **Allows for more rapid diagnosis of MS**
- **Requires fewer diagnostic MRI examinations**
- **Focus on application of criteria**
  - pediatric, Asian and Latin American populations

Polman CH, et al. *Ann Neurol.* 2011; 69:292-302

Summary of 2010 Revised McDonald Diagnostic MS Criteria

CLINICAL ATTACKS	MRI CHANGES	ADDITIONAL INFORMATION NEEDED TO MAKE THE DIAGNOSIS
2 or more	2 or more lesions on MRI or clinical evidence of one lesion with reasonable evidence of a prior attack	• Clinical evidence may be adequate but additional changes must be consistent with MS.
2 or more	Objective clinical evidence of one lesion	Dissemination in space: • One or more T2 lesion in typical MS locations in the CNS (central nervous system) (periventricular, juxtacortical, infratentorial, spinal cord Await further clinical attack(s) in a different area of the CNS
1	Objective clinical evidence or two or more lesions	Dissemination in time • Simultaneous, asymptomatic gadolinium enhancing or non-enhancing lesions • A new T2 and/or gadolinium enhancing lesion Await a second clinical attack

Polman, C. et al. Annals of Neurology (2011; 69:292-302)

Summary of 2010 Revised McDonald Diagnostic MS Criteria

CLINICAL ATTACKS	MRI CHANGES	ADDITIONAL INFORMATION NEEDED TO MAKE THE DIAGNOSIS
1	Objective clinical evidence of one lesion	Dissemination in space • One or more T2 lesions in at least two typical CNS locations Await further clinical attacks Dissemination in time • Simultaneous asymptomatic gadolinium enhancing or non-enhancing lesion at any time • A new T2 or gadolinium enhancing lesion(s) on follow-up MRI (no timing required) A second clinical attack
0 Progression from onset		One year of disease progression (retrospective or prospective and at least two out of three criteria • Dissemination in space in the brain based on one or more T2 lesions in areas typical of MS • Dissemination in space in spinal cord based on two or more T2 lesions • Positive CSF

Polman, C. et al. Annals of Neurology (2011; 69:292-302)

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

Assessment Tools to Diagnose MS

MRI

- **Clinical attacks**
- **MRI changes support diagnosis**
  - brain and spinal cord imaging
  - detect subclinical lesions in some people
  - identify active inflammation with gadolinium (Gd) contrast enhancement

Assessment Tools to Diagnose MS

- **Lumbar Puncture with CSF analysis**
  - IgG elevation, Oligiclonal bands, Mild leukocytosis
- **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)

MRI BASICS

MRI Basics

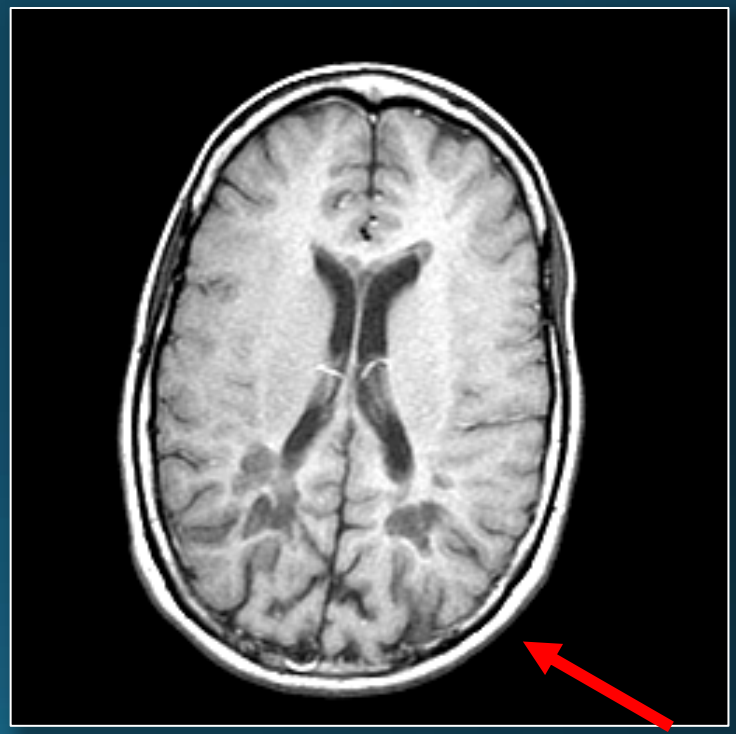
- **Magnetic fields and radiowaves**
  - cross-sectional views of the body
  - shows structural details of soft tissue
- **Intensity of MRI signal**
  - varies based on water content of tissues, magnitude and timing of RF pulses, use of enhancing agent
- **CMSC MRI Protocol for Diagnosis and Follow-up of patients with MS[1]**

1. http://c.ymcdn.com/sites/www.mscare.org/resource/collection/9C5F19B9-3489-48B0-A54B-623A1ECEE07B/mriprotocol2009.pdf

T1-weighted MR Image

Some lesions are dark (ie, hypointense) on T1-weighted MRI:

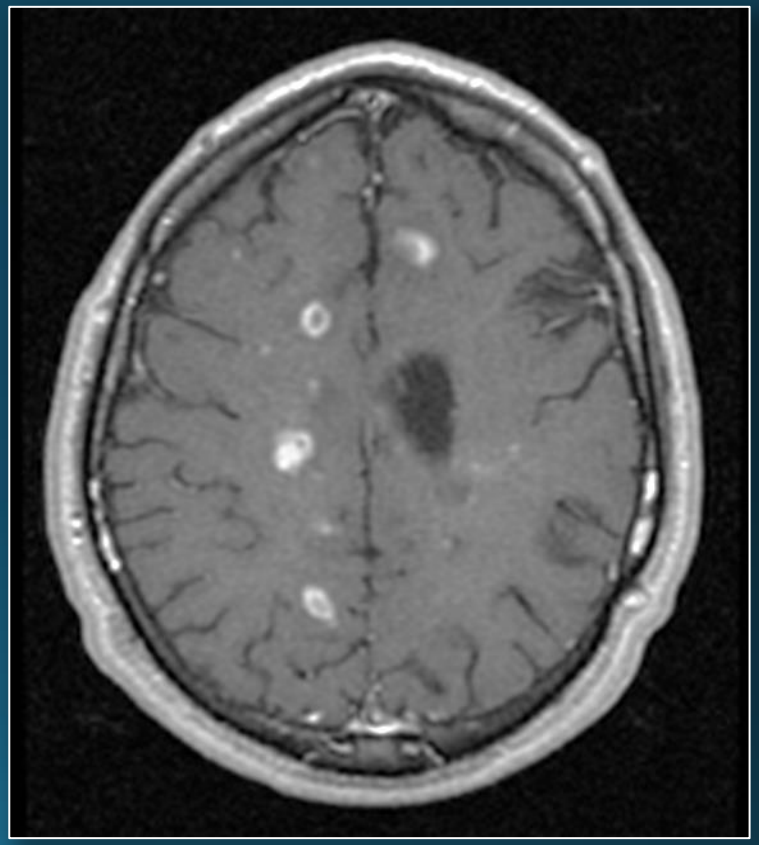
- **Acute lesions:**
  T1 hypointense due to local edema (may be reversible)
- **Chronic lesions:**
  the darker the image, the greater the tissue destruction
- **Severely hypointense areas:**
  referred to as "black holes"



The Whole Brain Atlas. http://www.med.harvard.edu/AANLIB/home.html. Accessed March 6, 2007.

T1-Weighted, Gadolinium-enhanced MR Image

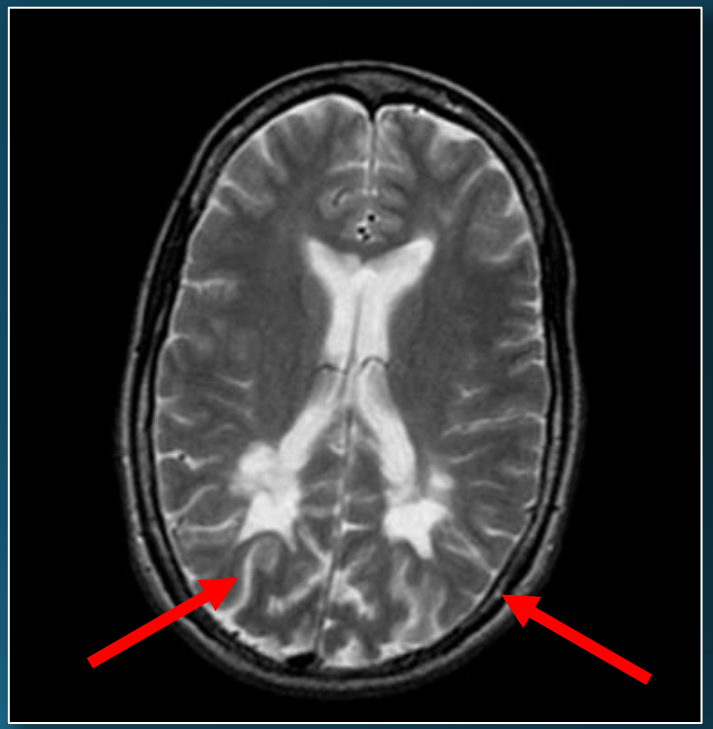
- **New and active lesions appear bright on gadolinium (Gd)-enhanced images, reflecting**
  - Areas of BBB disruption
  - Local edema (eg, T1-hypointensity)



T2-weighted MR Image

Lesions are bright (ie, hyperintense) on T2-weighted MRI:

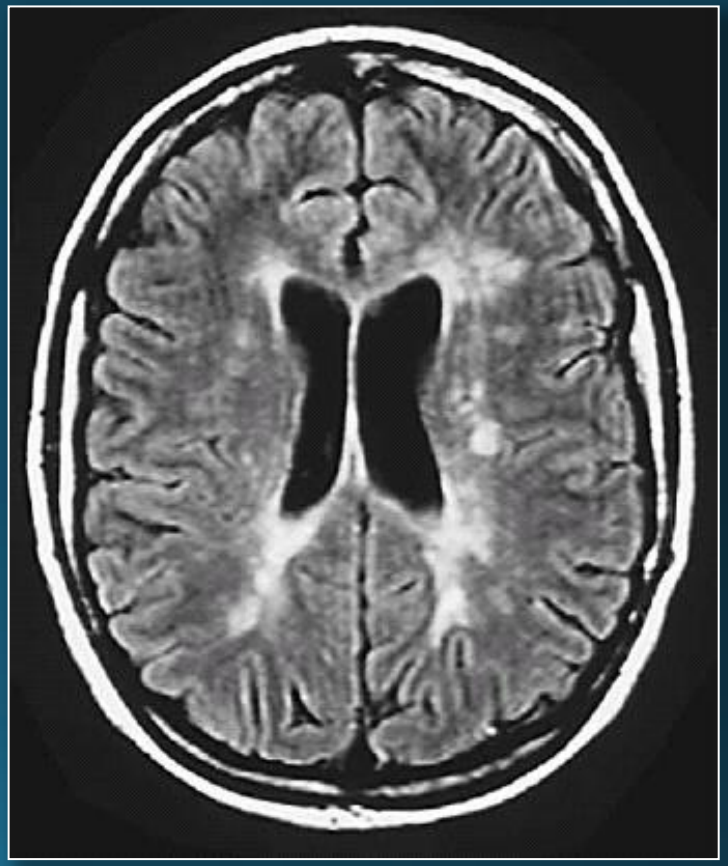
- T2-weighted scans are more sensitive than T1-weighted scans; a patient may have numerous T2 lesions and no T1 holes
- Limitation: inability to distinguish pathophysiologic heterogeneity of lesions
- May reflect demyelination, edema, gliosis, remyelination, or matrix destruction



The Whole Brain Atlas. http://www.med.harvard.edu/AANLIB/home.html. Accessed March 6, 2007.

T2 Fluid-Attenuated Inversion Recovery (FLAIR)

- Provides greater contrast between CSF and lesion

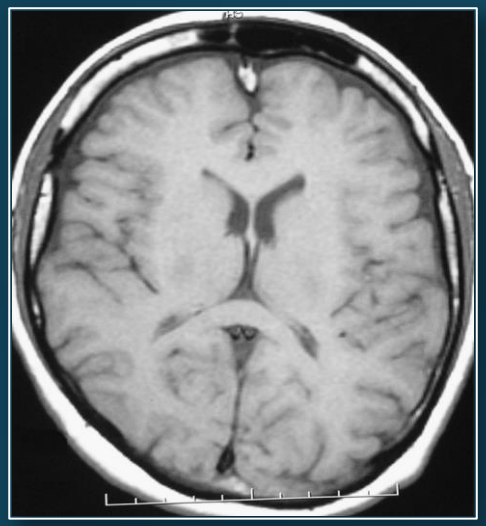


Noseworthy JH, et al. *N Engl J Med*. 2000;343:938-952.

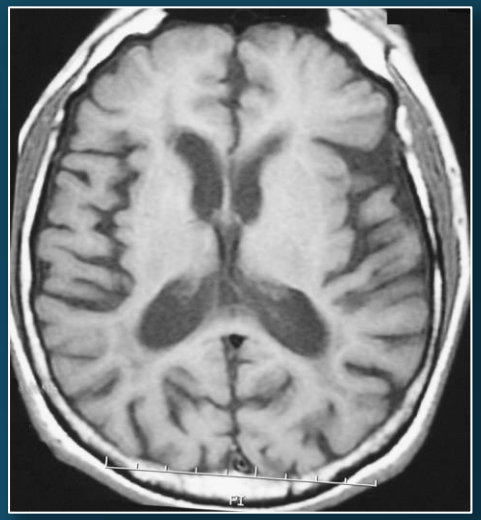
Brain Atrophy: MRI Findings

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

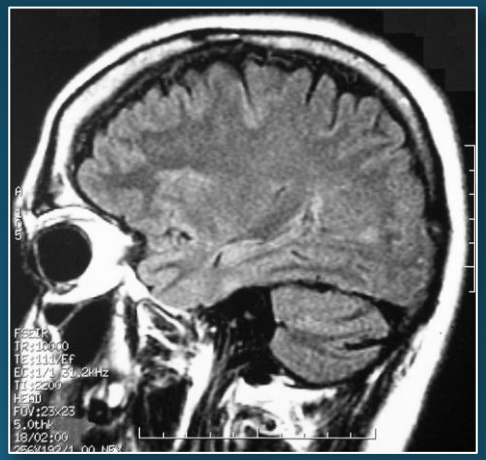
33-year-old man with RRMS for 2 years



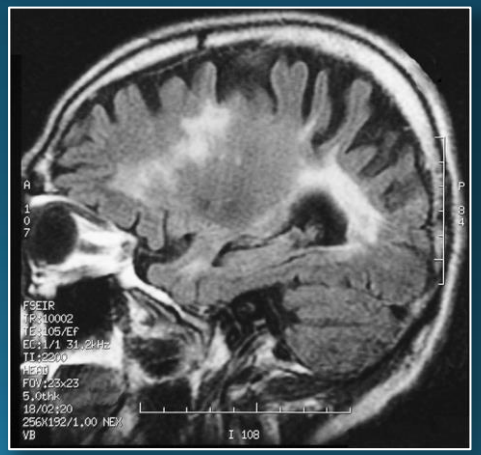
T1



47-year-old man with RRMS for 20 years



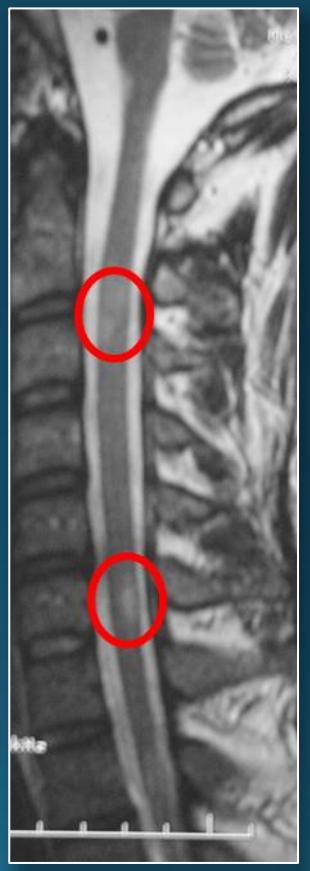
FLAIR



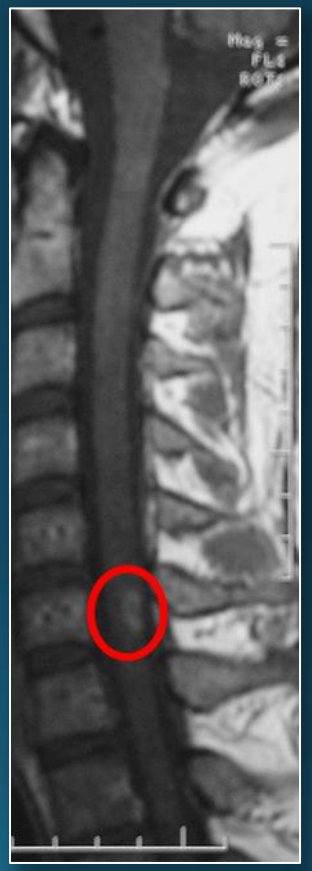
Courtesy of Dr. D. Mikol.

Role of Spinal Cord MRI

- **Spinal cord MRI may be used to support a diagnosis of MS in**
  - patients with normal brain MRI findings
  - older patients with age-related changes on T2-weighted brain MRI scans



T2



T1 + Gd

Courtesy of Dr. D. Mikol.

DIFFERENTIAL DIAGNOSIS OF MS

Diseases That Resemble MS

- ADEM
- Devic's disease or NMO
- CNS vasculitis
- Sarcoidosis
- Sjogren's
- CNS syphillis
- Vitamin B_{12} deficiency
- CADASIL
- CNS lymphoma
- Lyme disease

Hurwitz B, et al. Advances in Diagnosis of RRMS: Highlights of the Revised Guidelines. MS Update. 2006. Bourdette D. Conversations on MS: Diagnosing and Treatment Strategies in RRMS. 2006.

Clinical Features That May Suggest Misdiagnosis

- Normal neurological examination
- No dissemination over time and space
- Onset of symptoms before age 10 or after age 55
- Progressive course before age 35
- Localized disease

Coyle P. 7th Annual Review of Multiple Sclerosis. May 2004.

Clinical Features That May Suggest Misdiagnosis

- Atypical presentation
  - Fever
  - Headache
  - Abrupt hemiparesis
  - Abrupt hearing loss
  - Prominent pain
  - Normal optic exam
  - Normal sensory exam

Coyle P. 7th Annual Review of Multiple Sclerosis. May 2004.

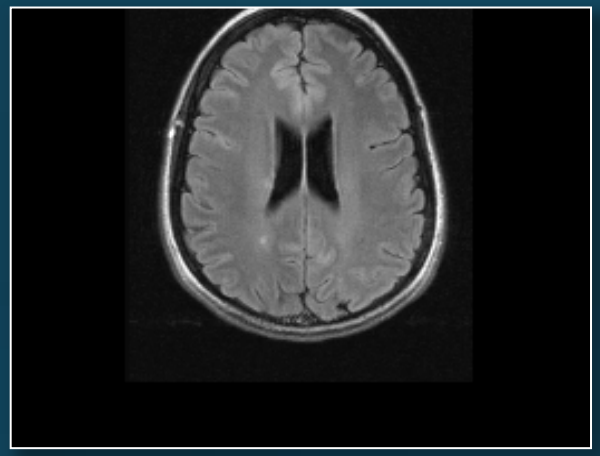
DISEASE COURSE

Types and Courses of MS

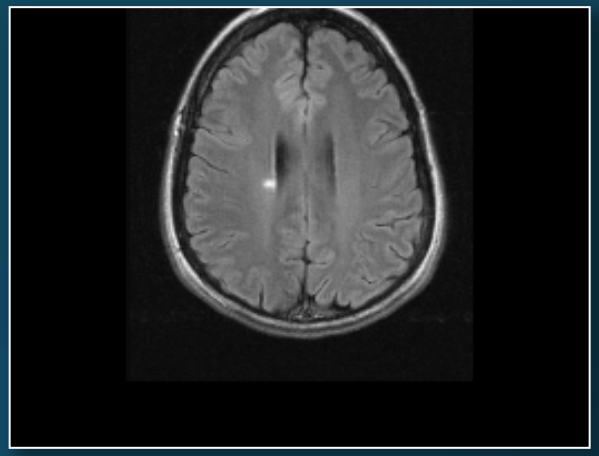
- **Radiologically Isolated Syndrome (RIS)**
- **Clinically Isolated syndrome (CIS)**
- **MS Clinical Subtypes**
  - Relapsing-remitting (RR)
  - Secondary progressive (SP)
  - Primary progressive (PP)
  - Progressive relapsing (PR)

Radiological Isolated Syndrome (RIS)

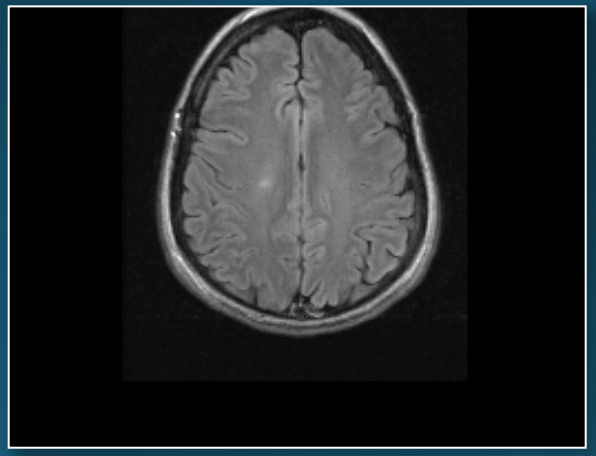
FLAIR T2 Axial



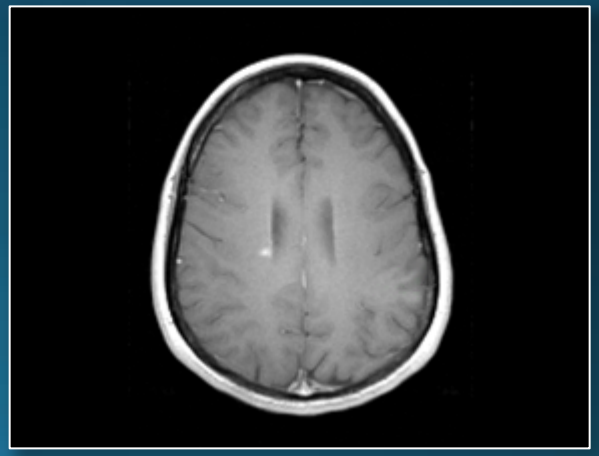
T2 FLAIR Axial



T2 FLAIR



T1 Post Gad



Images courtesy of Aliza Ben-Zacharia, DrNP, ANP-BC, MSCN

Clinically Isolated Syndrome (CIS)

- **First neurologic episode lasting at least 24 hours**
- **Caused by inflammation/demyelination in one or more sites in the CNS**
- **Can have a single neurologic sign or symptom:**
  - an attack of optic neuritis caused by a monofocal lesion
- **Or more than one sign or symptom**
  - an attack of optic neuritis accompanied by weakness on one side caused by multifocal lesions

National MS Society. Clinically Isolated Syndrome. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/diagnosing-ms/cis/index.aspx. Accessed: February 4, 2014. National MS Society: CIS. The MS Information Sourcebook. www.nationalmssociety.com. Accessed December 2006.

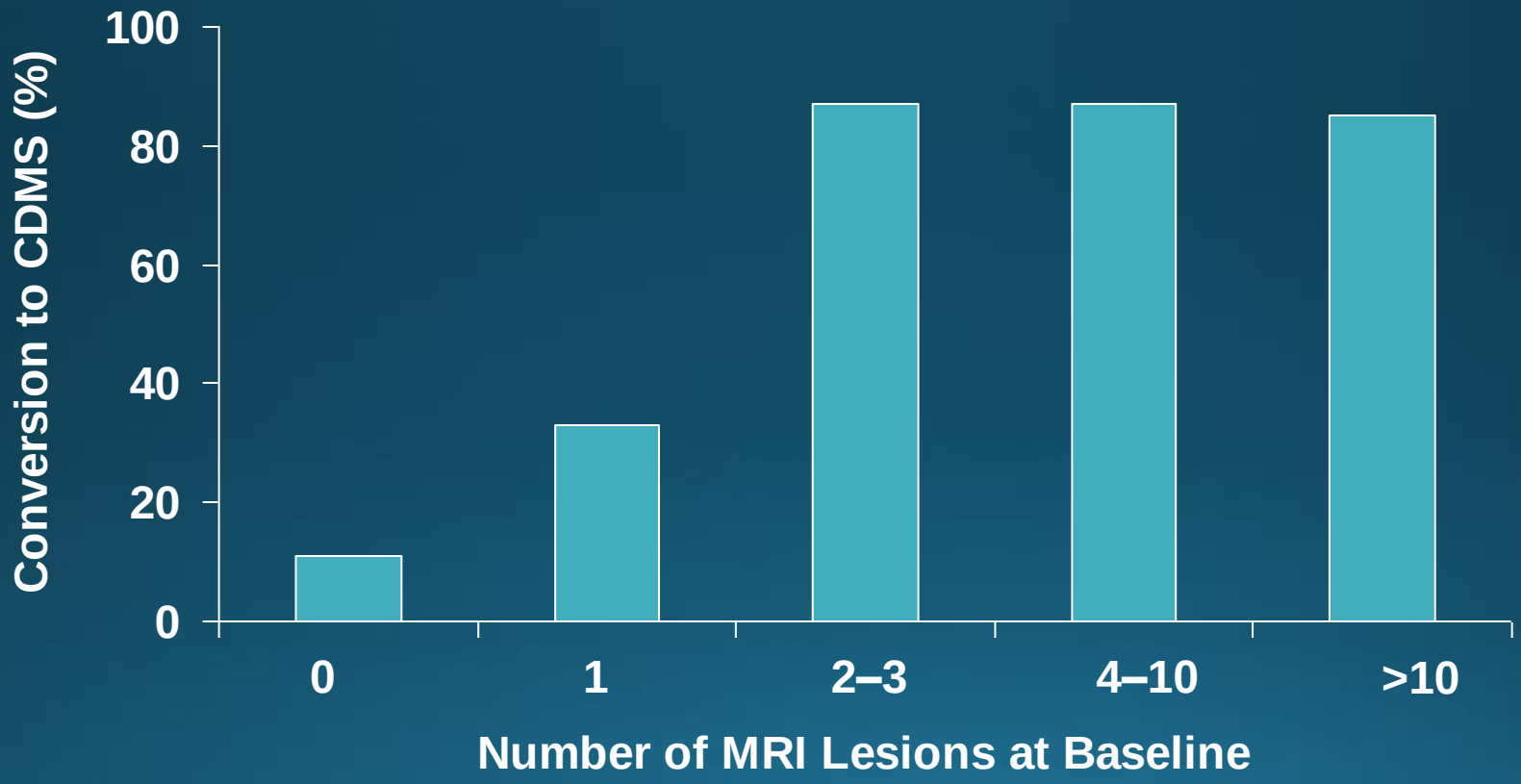
Clinically Isolated Syndrome (CIS)

- **CIS can consist of single or multiple neurologic signs or symptoms:**
  - an attack of optic neuritis caused by a monofocal lesion
  - an attack of optic neuritis accompanied by weakness on one side caused by multifocal lesions
- **May or may not develop clinically definite MS (CDMS)**

National MS Society. Clinically Isolated Syndrome. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/diagnosing-ms/cis/index.aspx. Accessed: February 4, 2014. National MS Society: CIS. The MS Information Sourcebook. www.nationalmssociety.com. Accessed December 2006.

CIS: Risk of Developing MS

Number of MRI lesions at baseline relates to risk of CDMS



O'Riordan JI, et al. *Brain*. 1998;121:495-503.

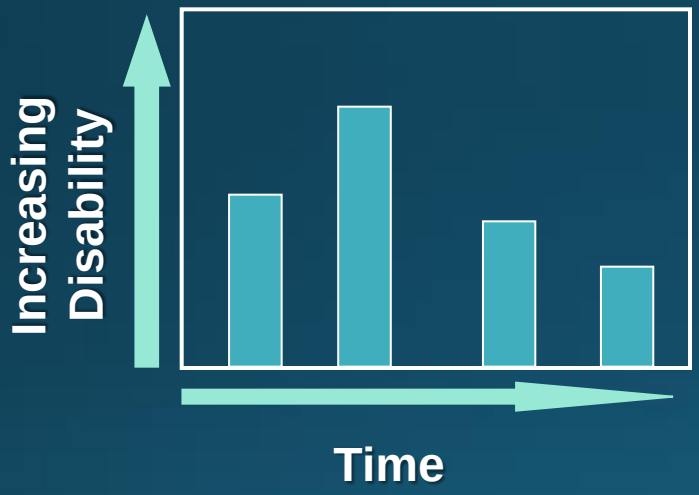
Why Treat Early ?

- **Relapses and impairment have been shown to parallel MRI burden of disease[1,2]**
- **Axonal damage occurs early**
  - may cause permanent neurological dysfunction[3]
- **Number of MRI lesions may be predictive of future disability[4]**
- **Preventing development of lesions may delay progression of disability[5]**
- **Preventing early relapses may delay long-term disability[6]**

1. Comi G. Curr Opin Neurol. 2000;13:235-240;
2. Munschauer FE 3rd et al. Clin Ther. 1997;19:868-882;
3. Trapp BD et al. N Engl J Med. 1998;338:278-285;
4. Brex PA. N Engl J Med. 2002;346:158-164;
5. O'Riordan JI. Brain. 1998;121:495-503;
6. Weinshenker BG et al. Brain. 1989;112:1419-1428

Relapsing-Remitting MS

No disease progression between relapses



Acute relapses with full recovery

Acute relapses with sequelae and residual deficit upon recovery

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

Secondary Progressive MS

Patients with an initial RRMS course convert to SPMS, which is characterized by continuous progression

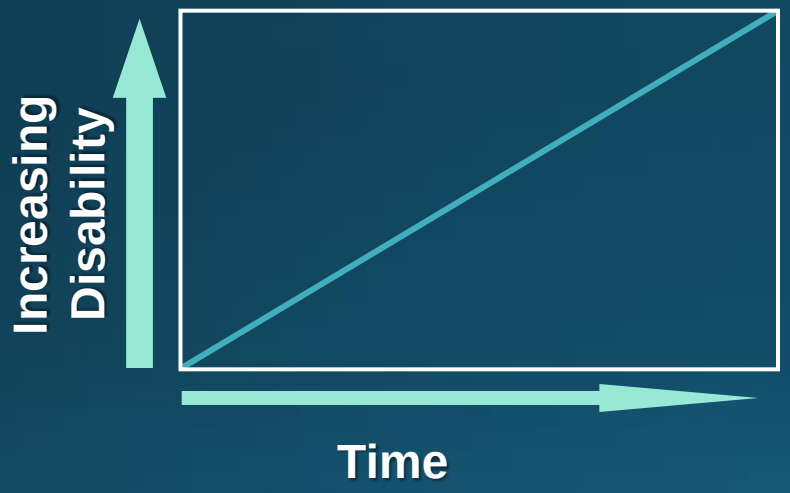
Without relapses

With relapses

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

Primary Progressive MS

PPMS is characterized by progression of disability from onset



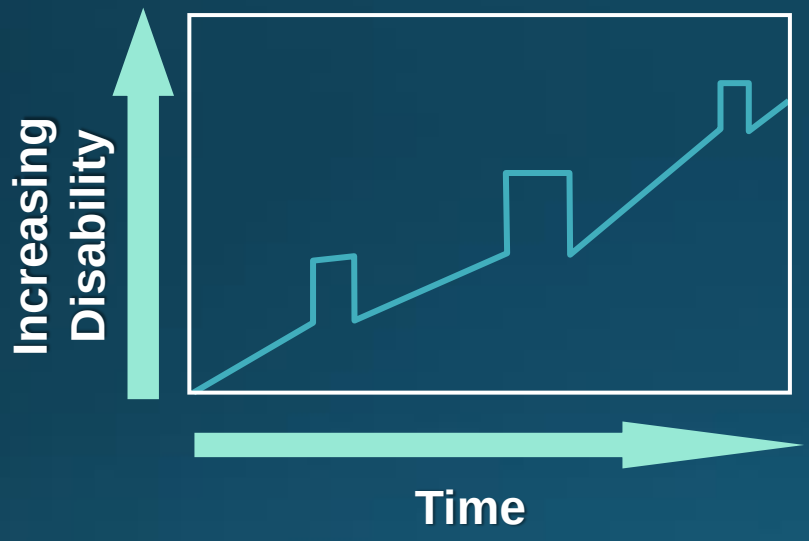
Without plateaus or remissions

With occasional plateaus and temporary minor improvements

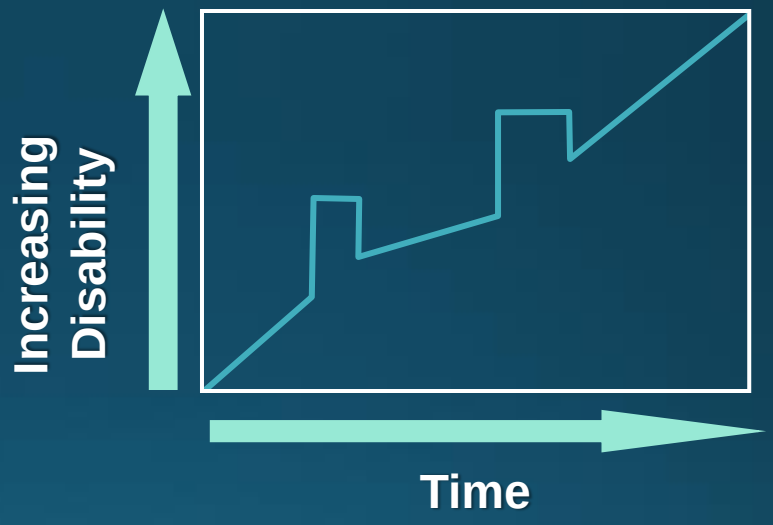
Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

Progressive Relapsing MS

PRMS is characterized by disease progression from onset with the occurrence of clear acute relapses



Full recovery following relapse with progression between relapses

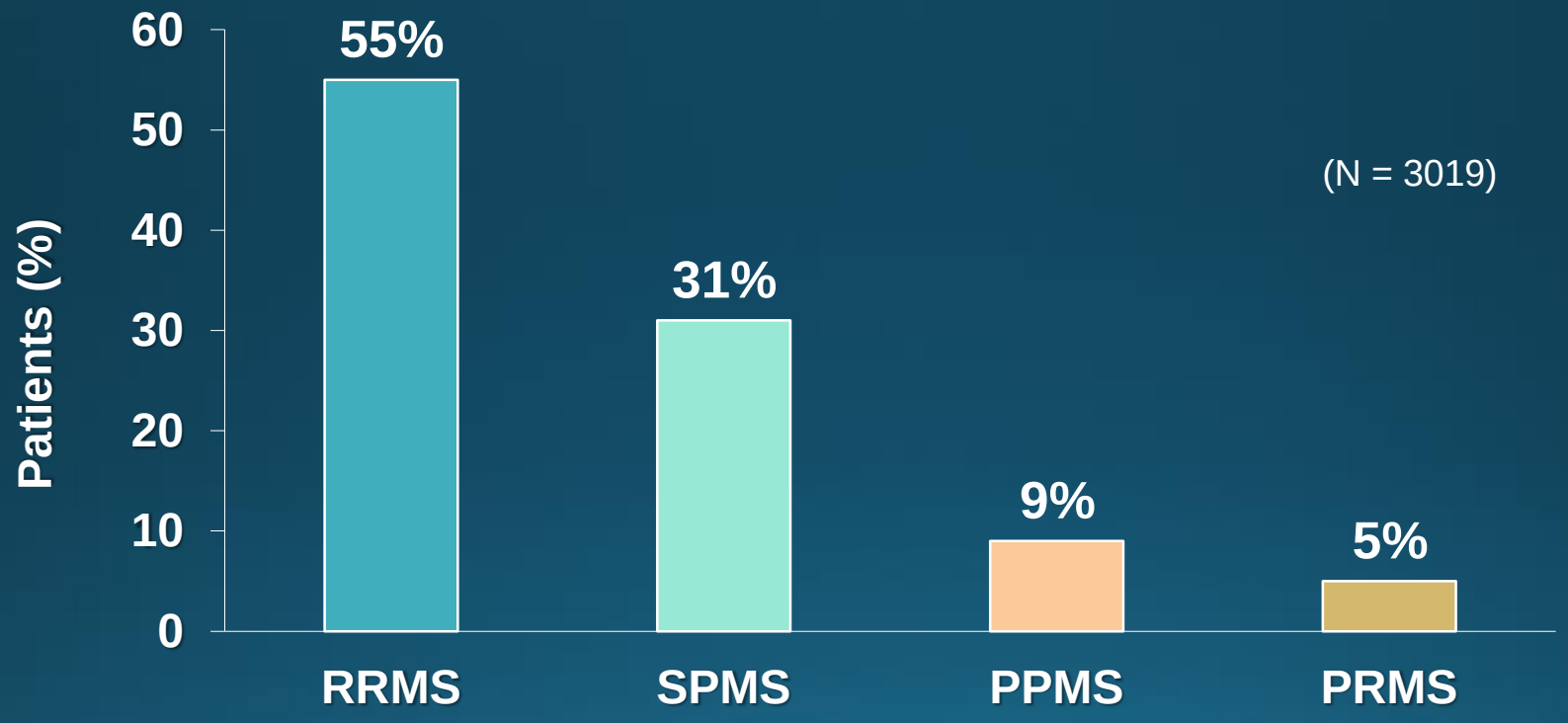


Without full recovery following relapse with progression between relapses

Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.

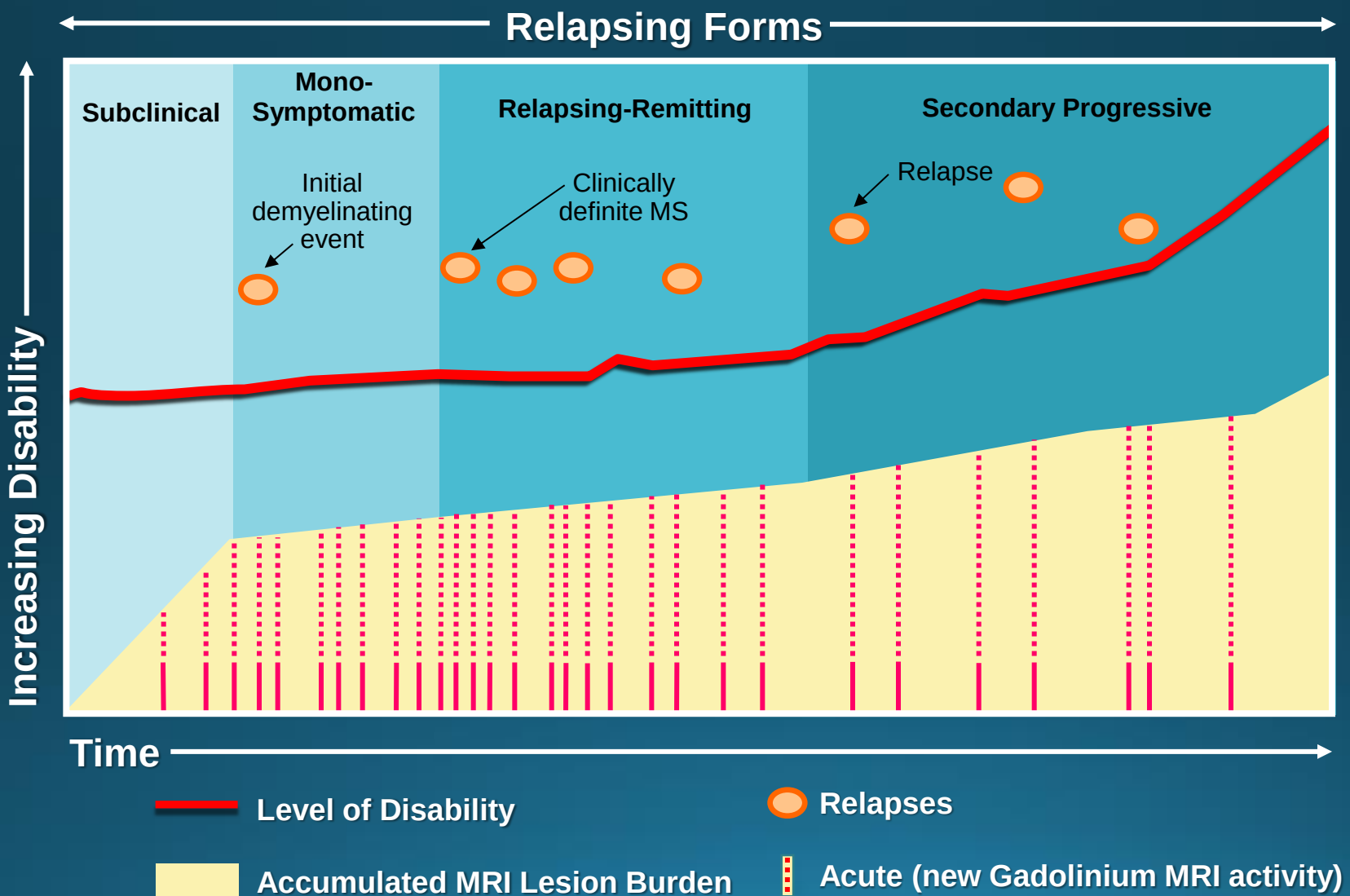
Clinical Subtypes (at Presentation)

About 80%–85% of all MS patients initially have RRMS; most will convert to SPMS in 6-10 years



Jacobs LD, et al. *Mult Scler.* 1999;5:369-376.

Progression of Untreated MS



PROGNOSTIC INDICATORS

Favorable Prognostic Indicators

- Early age of onset
- Female sex
- Monofocal onset
- Optic neuritis as presenting episode
- Sensory symptoms as presenting episode
- Acute onset of symptoms
- Residual disability after each exacerbation
- Long interexacerbation period

Lublin FD. *Neurol Clin*. 2005;23:1-15. Vukusic S, Confavreux C. Curr Opin Neurol. 2007;20:269-274.

Unfavorable Prognostic Indicators

- Later age of onset, multifocal onset, progressive course
- Male sex
- Frequent exacerbations, poor recovery
- Involvement of cerebellar or motor functions
- Burden of disease: MRI at diagnosis
  - ≥ 2 contrast lesions
  - ≥ 9 T2 lesions

Lublin FD. *Neurol Clin*. 2005;23:1-15. Vukusic S, Confavreux C. Curr Opin Neurol. 2007;20:269-274.

Summary

- **MS is a complex immune mediated disease that affects the central nervous system**
  - inflammation, demyelination and axonal damage.
- **MS remains a clinical diagnosis supported by paraclinical evidence**
  - MRI, CSF analysis, lab studies, and evoked potential testing
- **Majority of individuals will start with RRMS**
  - will develop progression of disability if untreated
- **Common symptoms include:**
  - fatigue, pain, muscle weakness, visual changes, depression, bowel and bladder dysfunction, spasticity, parasthesias.

Nursing Implications

- MS is a complex, 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 the individualized needs of patients and their families
- The International Organization of MS Nurses (IOMSN) is a comprehensive source of continuing education, skill development, and support for nursing professionals engaged in the field of patient care in MS

QUESTION-AND-ANSWER SESSION

Thank you for your participation!

- To receive credit for today's program, please complete the evaluation and post-test at: https://www.surveymonkey.com/s/CaringWebinarOneEvaluation
- For upcoming *Caring for the Patient with MS* Webinars, please visit our web page at: http://www.iomsn.org/component/content/article/239
- For additional IOMSN educational opportunities and future webinars programs, please visit IOMSN at: www.IOMSN.org
- We look forward to seeing you for our next CNE webinars:
  - Disease Management: Acute Relapses and DMTs on May 5th
  - Alternative Therapies and Wellness on June 16th