Overview of MS: Where We Are Today

Objectives

- Define multiple sclerosis (MS) and its presentation to facilitate optimal nursing care
- Review common symptoms of MS that will be treated throughout the course of the disease
- Discuss the diagnostic process in MS to enhance patient education
- Review the MS phenotypes in order to explain treatment options to patients and families

Multiple Sclerosis

- **Immune-mediated, chronic, inflammatory and degenerative disease**
  - Pathological hallmark is inflammatory, demyelinating lesions (plaques) and axonal loss in the CNS
  - Lesion formation attributed autoimmune attacks directed against myelin, oligodendrocytes and axons
  - White and gray matter involvement
- **Most often characterized by relapses and remissions of neurological symptoms and progression of disability over time**
- **Most common chronic neurologic disease of young adults**

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

Epidemiology of MS

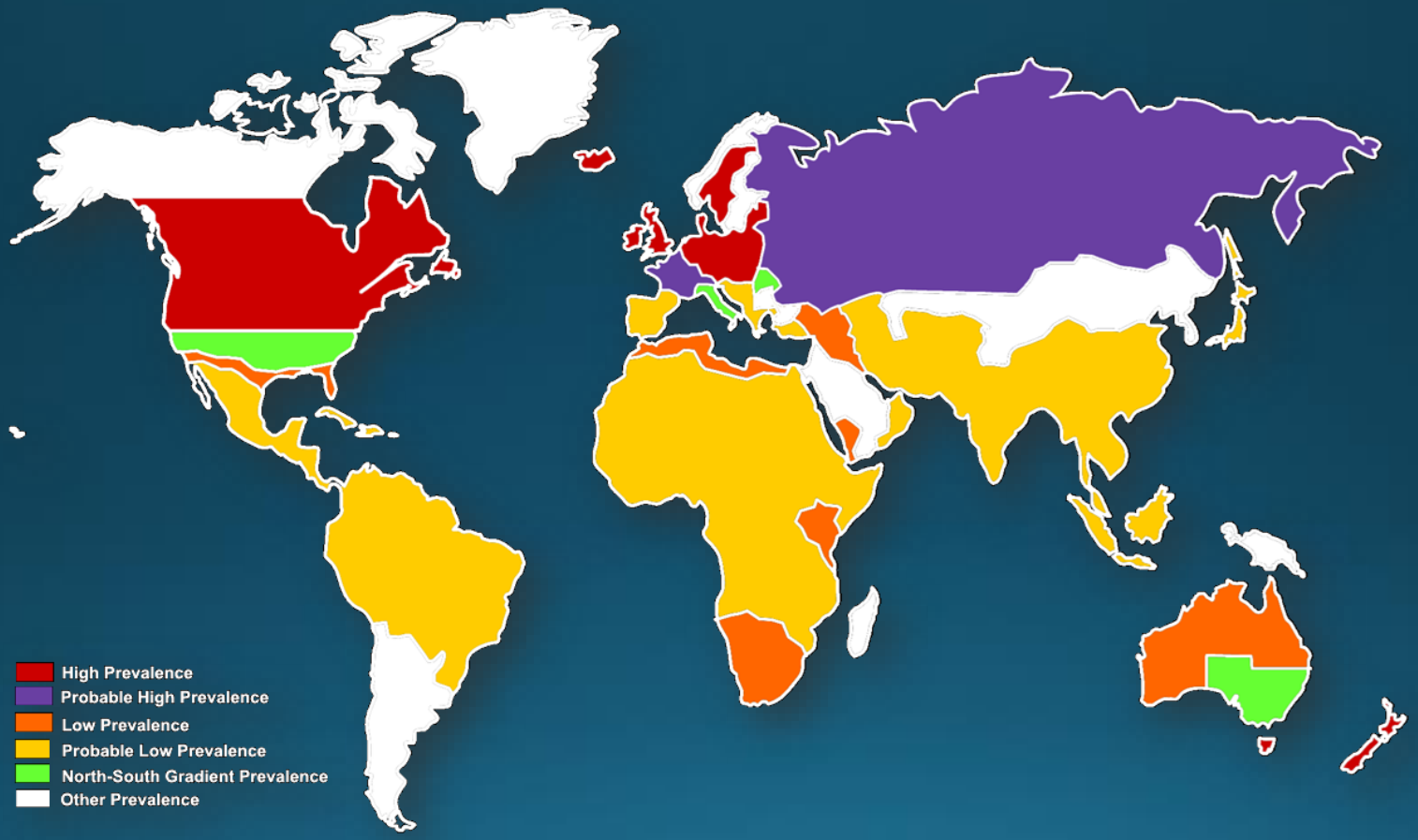
- **Approximately 950,000 cases in the United States[1]**

  (estimates range from 250,000–500,000)[1a]

- **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. Wallis MT, et al. The Prevalence of Multiple Sclerosis in the United States: A Population-Based Healthcare Database Approach. ECTRIMS 2017. 1a.National MS Society Information Sourcebook. www.nationalmssociety.org/sourcebook. Accessed March 6, 2007.
2. National MS Society. http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. Accessed: June 15, 2015.
3. Hogancamp WE, et al. *Mayo Clin Proc.* 1997;72:871-878.

World Distribution of Multiple Sclerosis

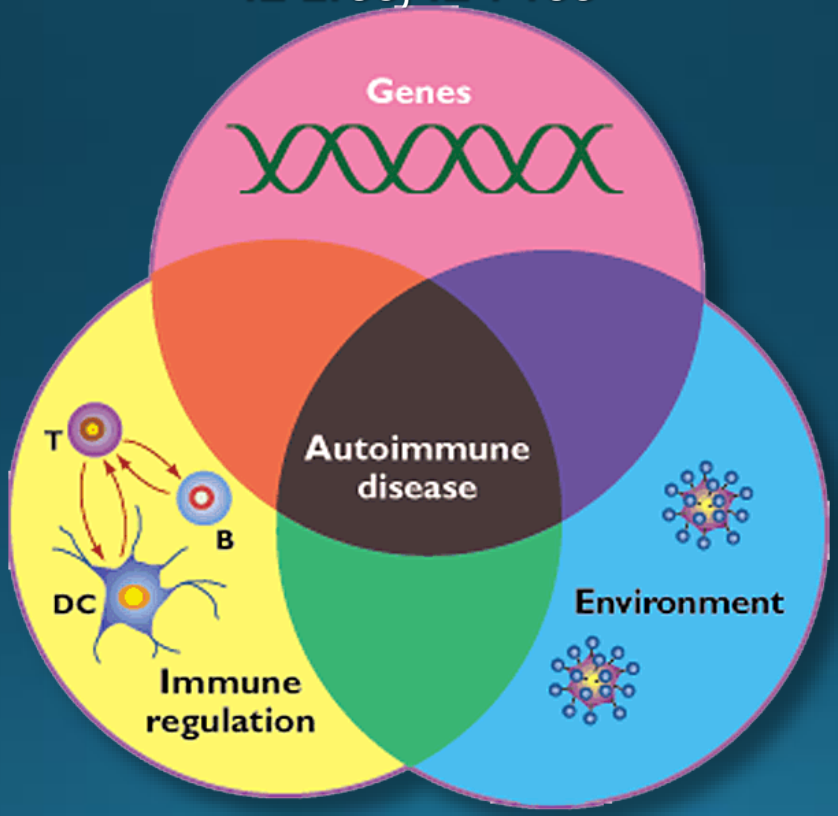


MS varies geographically. High prevalence: Northern US, Canada, Most of Europe, Northern Australia, New Zealand, Northern Russia

Etiology of MS - ??

Genetic Predisposition
Over 200 Immune Gene SNPs implicated in the risk of MS: HLADR2, IL-2rec, IL-7 rec

Immune Dysregulation
Th1/Th 17
CD4/CD8
B-cells
IgG



Environmental Factors
Viruses (EBV)
Vitamin D
Latitude
Smoking
Obesity
Diet (salt?)
Gut Microbiome

Cree, BA, Handbook of Clinical Neurology; 2014; 122-122:193-209. Libby, JE, Cusick, F. et al. Intl Rev of Immunology; Role of pathogens in MS; August 2014. Vol. 33, No. 4: 266-283

Modifiable Risk Factors for MS

- **Cigarette smoking**
  - Active smokers – 40% increased risk (40-60% dose dependent)
- **Obesity**
  - Obesity in girls associated with 60-95% increased risk
  - In boys 30-80% increased risk
  - In women age 18 with BMI >30 kg/m2 – 2 fold increase risk
- **Epstein Barr virus**
  - Late adolescent infection 10X risk vs those with no infection
- **Low serum Vitamin D**
  - Lower risk with increased 25(OH)D levels

Ascherio A and Munger K Seminars Neurology 2016;36:103-114

PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS

Pathophysiology of MS

- **Immune system targets the CNS**
  - Breakdown of the blood brain barrier (BBB)
  - Multifocal areas of inflammation
  - Demyelination and oligodendrocyte loss
  - Gliosis
  - Axonal degeneration
- **Major cause of neurologic disability is axonal loss**

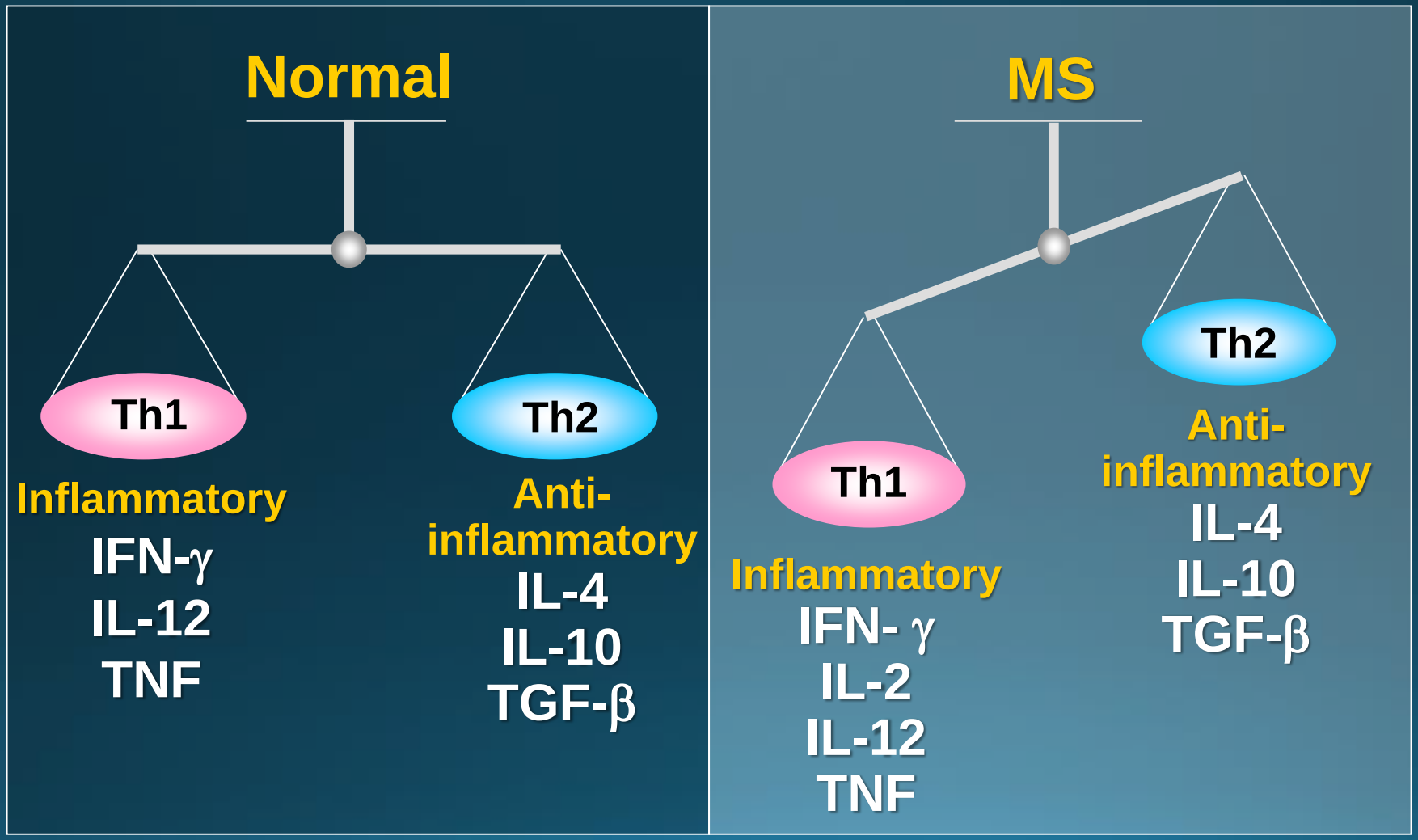
Immune Dysregulation in MS

- **Autoimmune, neurodegenerative disease of CNS**
  - Autoreactive immune cells usually deleted by the immune system
  - In MS loss of immune regulation, over abundance of inflammatory immune activity
- **T-cell activated mediated inflammatory disorder**
  - CD_4 T helper cells become activated in the in the periphery by unknown antigen
  - Misguided T cells mistake myelin protein for antigen
  - Overproduction of pro-inflammatory cytokines causing inflammation and damage to myelin and nerves
- **B-cells also involved in inflammatory process**
  - Found in CNS and plaques of MS patients
  - Travel with T cells through the BBB to the CNS
  - Produce myelin specific antibodies, activate complement

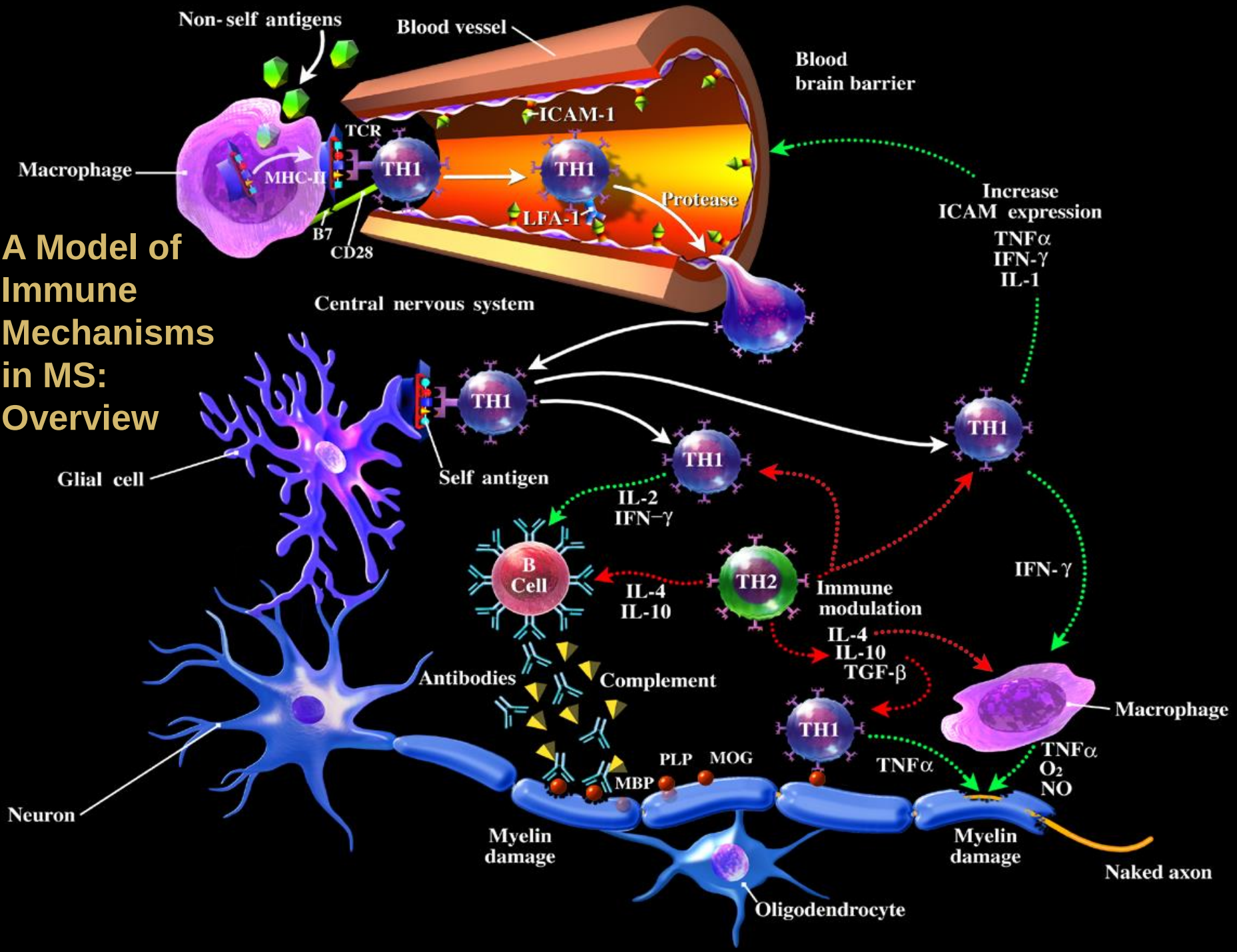
Immune Cells: Key Players

- **Antigen-presenting cells (APCs)**
  - Macrophages, microglia, etc.
- **T cells (T lymphocytes)**
  - Responsible for cell-mediated immune response
  - Th1, Th17
- **B cells (B lymphocytes)**
  - Responsible for the production of antibodies

Cytokine Imbalance in MS

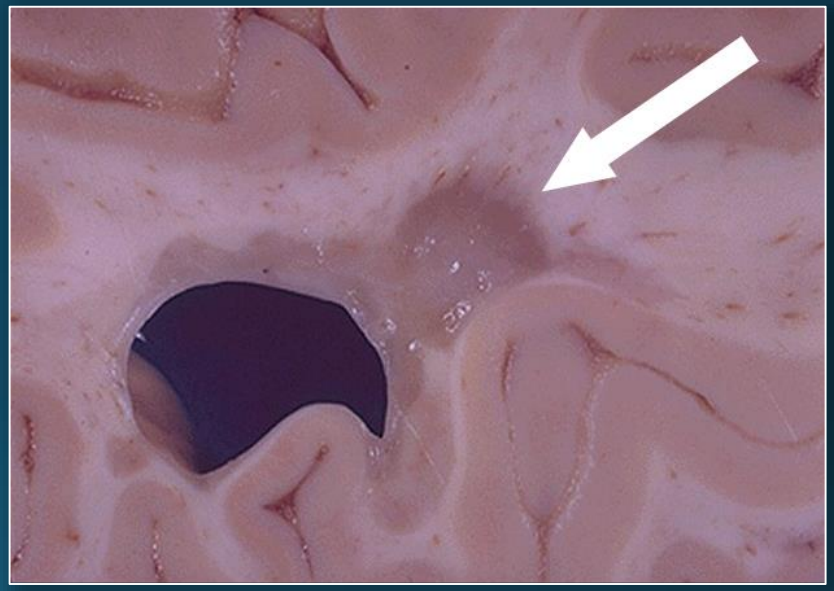


A Model of Immune Mechanisms in MS: Overview



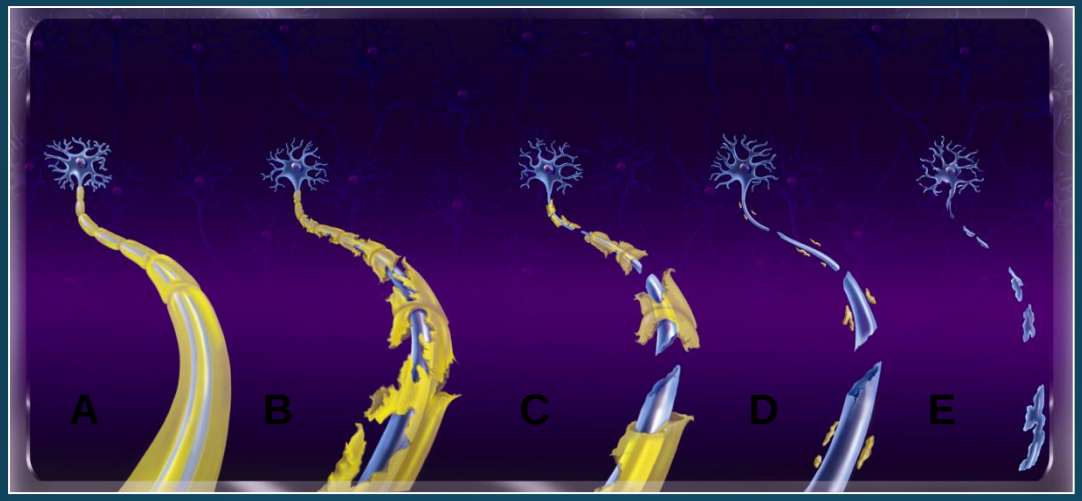
Pathophysiology of MS: Demyelination

- **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.

Nerve Damage and Myelin Loss

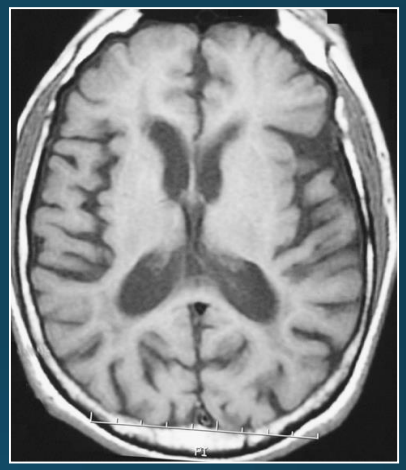


A. Normally, axons have a protective myelin coating that is necessary for normal conduction of electrical impulses
B. In MS, the immune system destroys myelin, resulting in slowed conduction and exposure of axons
C. Exposed axons may then be severed…
D. …leading to permanent loss of the axon
E. The result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

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

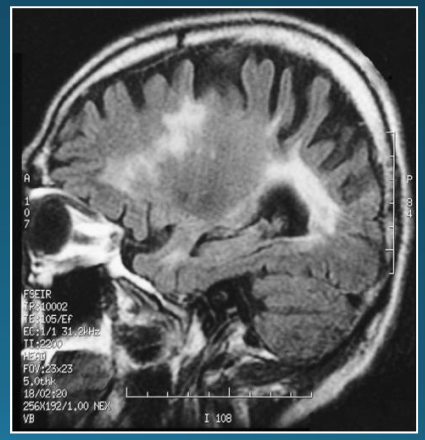
Brain Atrophy in MS

- **Atrophy may occur early in the disease**
- **Represents cumulative effect of:**
  - Demyelination and axonal loss
  - Diffuse, non-focal tissue damage



T1

- **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



FLAIR

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 Phenotypes

- **Clinically isolated syndrome (CIS)**
- **Relapsing-remitting MS (RRMS)**
  - About 85% of people are diagnosed with RRMS
- **Secondary progressive (SPMS)**
  - Most people diagnosed with RRMS will eventually transition to SPMS
- **Primary progressive MS (PPMS)**
  - About 15% of people experience this course

Lublin et al, 2014

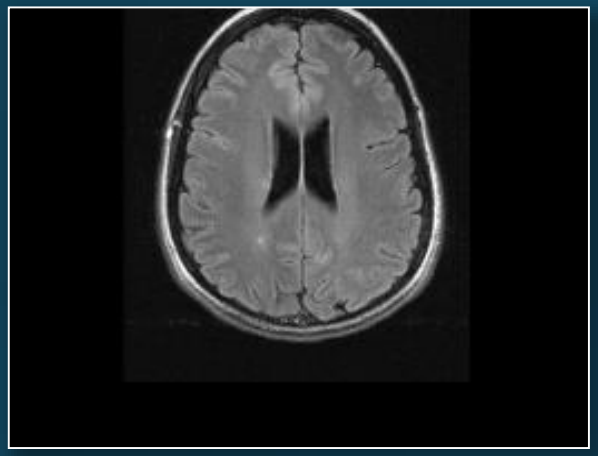
Clinically Isolated Syndrome (CIS)

- **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
- **May or may not develop clinically definite MS (CDMS)**

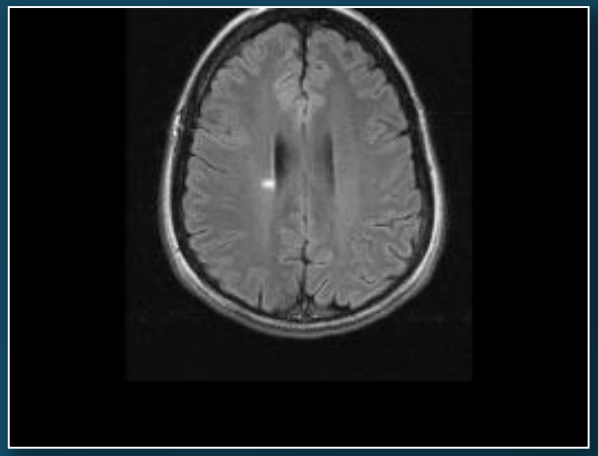
National MS Society. Clinically Isolated Syndrome. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/diagnosing-ms/cis/index.aspx. Accessed: February 4, 2014. National MS Society: CIS. The MS Information Sourcebook. www.nationalmssociety.com. Accessed December 2006.

Radiologically Isolated Syndrome (RIS)

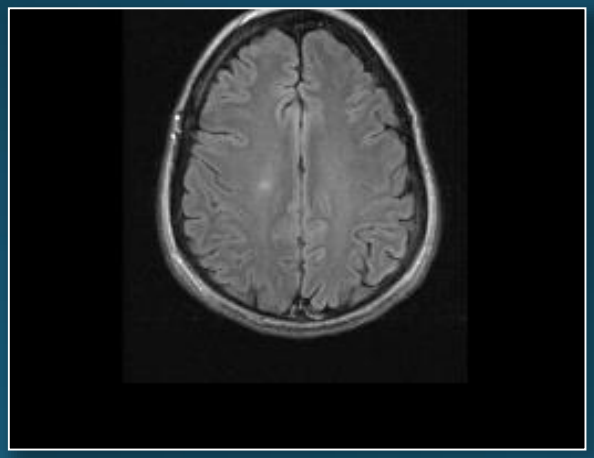
FLAIR T2 Axial



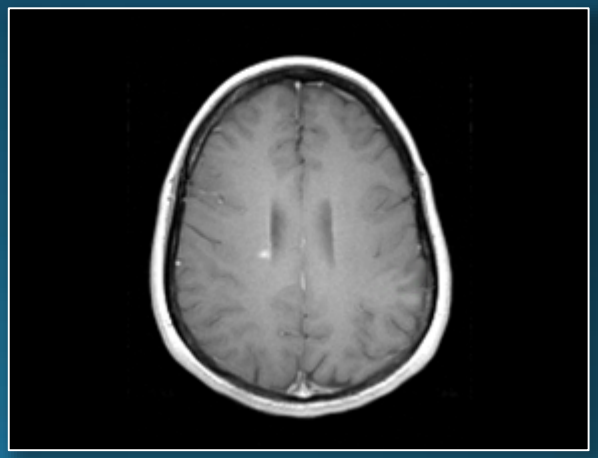
T2 FLAIR Axial



T2 FLAIR



T1 Post Gad



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

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 et al, 2014

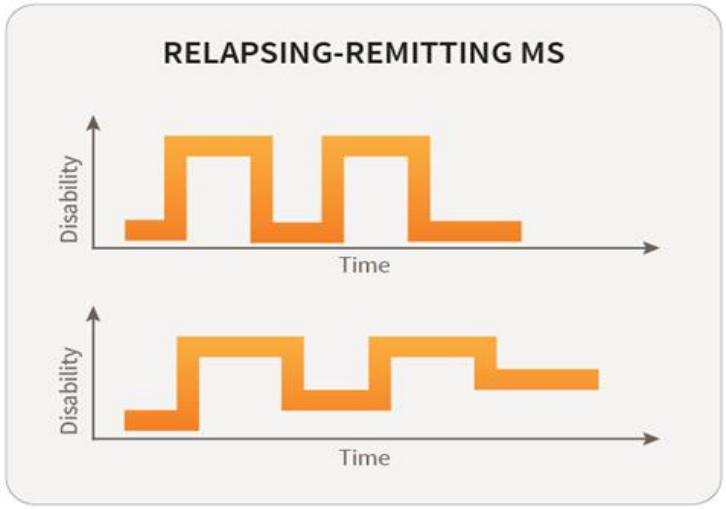
Definitions Related to MS Phenotypes

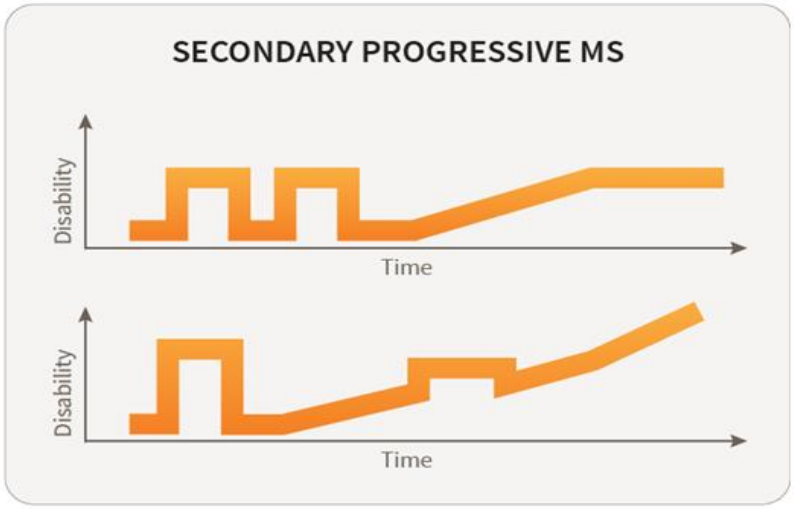
- **Worsening Disease**
  - Documented increase in neurologic dysfunction/disability as a result of relapse or progressive disease, reserving the term "disease progression" for those solely in a progressive phase of the illness

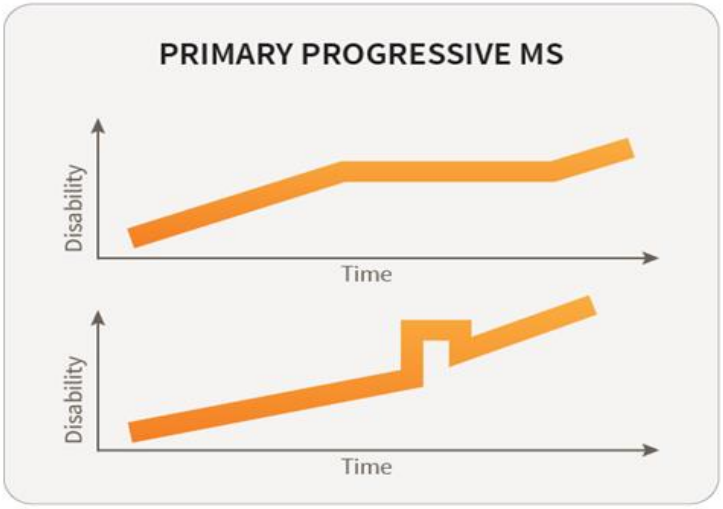
- **Confirmed Progression or Worsening**
  - Increase of neurologic dysfunction confirmed throughout a defined time interval (for example, 3, 6, or 12 months)
  - Because neurologic dysfunction may still improve, even if progression is confirmed over 6 or 12 months, it's recommended abandoning the term "sustained"

Lublin et al, 2014

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

Lublin et al, 2014

Benign and Malignant MS

- Not MS phenotype descriptors
- Recommended that clinicians use with caution particularly with patients and families
- Provide indication of disease severity over time for clinicians
- Apply to any MS phenotype depending on degree of severity or impairment over time

SYMPTOMS OF MS

Symptom Overview

- **Motor, sensory, emotional, cognitive**
  - Associated with exacerbation – complete or incomplete recovery possible
  - Often progressive over time – axonal degeneration over time may contribute to symptom worsening
- **Symptoms:**
  - Primary (e.g., fatigue, tremor)
  - Secondary (e.g., falls, urinary tract infections)
  - Tertiary (e.g., loss of job, divorce)
- **New onset of symptoms or worsening symptoms may indicate relapse or pseudo-relapse or progression**

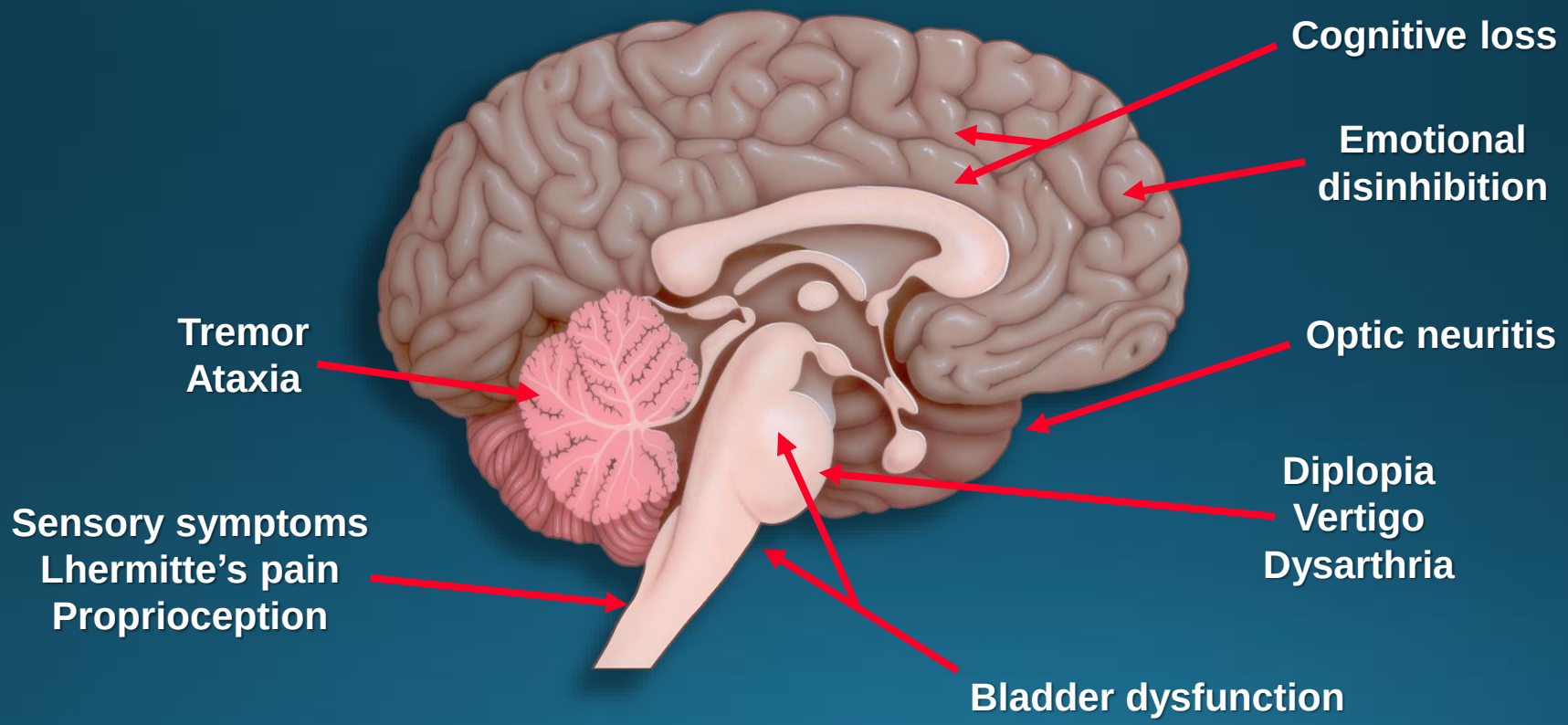
Halper J, Harris C. In *Nursing Practice in Multiple Sclerosis.* 3rd ed. New York: Springer Publishing Company; 2012:53-54.
Schapiro RT, Schneider D. In *Comprehensive Nursing Care in Multiple Sclerosis*. 2002.

Common MS Symptoms

- **Fatigue**
- **Visual**
  - Unilateral visual loss –
    - Optic neuritis (presenting symptom in 25%)
  - Diplopia
- **Motor**
  - Weakness
  - Spasticity
  - Impaired coordination
- **Emotional**
  - Depression
  - Anxiety
  - Pseudodbulbar affect
- **Sensory**
  - Numbness, tingling, pain
- **Cognitive**
  - Impaired recall
  - Learning difficulties
  - Slowed processing
- **Sexual**
  - Erectile dysfunction
  - Diminished libido
  - Dryness
- **Elimination**
  - Bladder urgency, hesitancy, incontinence
  - Bowel constipation, involuntary bowel

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

Diagnosing MS

2 or more neurological events referable to the 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, Weinshenker BG, Filippi M, et al. *Mult Scler.* 2008;14:1157-1174.
Polman CH, et al. *Ann Neurol.* 2011;69:292-302

Diagnostic Criteria for MS: 2017 Revisions to McDonald Criteria

- Dissemination in Time criteria can be met with CSF-specific oligoclonal bands in CIS pt already meeting Dissemination in Space criteria
- Symptomatic and asymptomatic lesions can be used to demonstrate DIS or DIT in pts with supratentorial, infratentorial or spinal cord syndrome
- Cortical lesions can be used to demonstrate dissemination in space
- NMOSD should be considered in the differential diagnosis of patients presenting with symptoms indicative of MS.

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

2017 McDonald Diagnostic MS Criteria

CLINICAL ATTACKS	Number of Lesions with objective clinical evidence	ADDITIONAL INFORMATION NEEDED TO MAKE THE DIAGNOSIS
2 or more	2 or more	none
2 or more	As well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location	none
2 or more	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI

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

Summary of 2010 Revised McDonald Diagnostic MS Criteria

CLINICAL ATTACKS	MRI CHANGES	ADDITIONAL INFORMATION NEEDED TO MAKE THE DIAGNOSIS
1	2 or more	Dissemination in time demonstrated by an additional clinical attack of by MRI or demonstration of CSF-specific oligoclonal bands.
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands.

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

National Multiple Sclerosis Society

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

ECTRIMS
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 the CNS in space and time. See Lancet Neurology paper* for details.

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset	(see KEY below for definitions)
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space (**DIS**) and dissemination in time (**DIT**) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS**: additional clinical attack implicating different CNS site – **DIS**: ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	**One** of these criteria: – **DIT**: additional clinical attack – **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT**: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**

CONTINUED ON REVERSE

Colored text= revisions compared to previous McDonald Criteria
KEY: CIS: clinically isolated syndrome **CNS**: central nervous system **CSF**: cerebrospinal fluid **DIS**: dissemination in space **DIT**: dissemination in time **T2 lesion**: hyperintense lesion on T2-weighted MRI
*Thompson AJ, et al. Lancet Neurol 2017; online Dec 21. http://dx.doi.org/10.1016/S1474-4422(17)30470-2.

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis (continued)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (continued)	(see KEY on reverse for definitions)
• 1 attack and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS**: additional attack implicating different CNS site – **DIS**: ≥1 MS-typical **symptomatic or asymptomatic** T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria: – **DIT**: additional clinical attack – **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT**: by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**
...in a person with progression of disability from onset	
• progression from onset	– 1 year of disability progression (retrospective or prospective) **AND** **Two** of these criteria: – ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxtacortical/cortical** or infratentorial) – ≥2 T2 spinal cord lesions – CSF-specific (i.e. not in serum) oligoclonal bands

The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the National MS Society and the European Committee for Treatment and Research in Multiple Sclerosis.

More resources for clinicians: https://www.nationalmssociety.org/For-Professionals/Physicians

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 support diagnosis**
  - Clinical attacks
  - 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, Oligoclonal bands, Mild leukocytosis
  - Neurofilament Light Chain (Kuhle, 2018) Possible 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)

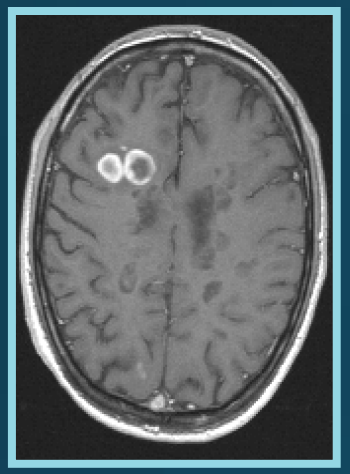
MRI BASICS

MRI Basics

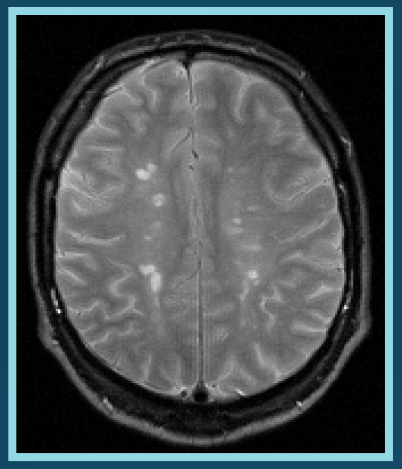
- **Magnetic field and radiofrequency pulse to differentiate normal and abnormal tissue**
- **Intensity of MRI signal**
  - Varies based on water content of tissues, magnitude and timing of RF pulses, use of enhancing agent
- **2015 Revised CMSC MRI Protocol for Diagnosis and Follow-up of patients with MS[1,2]**
- **Gadolinium is retained following repeated MRIs. No safety signal identified at this time**
  - Recommendations are for prudent use of gadolinium
    - Recommended for diagnosing MS, but not necessarily for routine monitoring

1. Traboulsee A, et al. AJNR 2015
2. http://www.mscare.org/?page=MRI_protocol

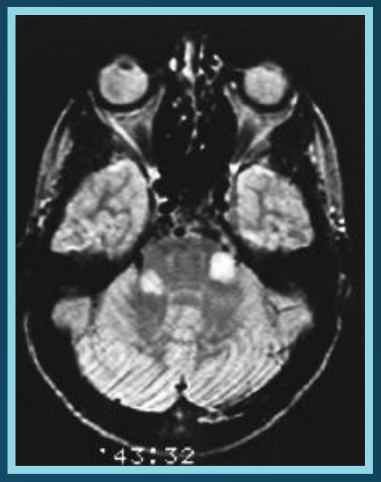
Typical MRI Lesions



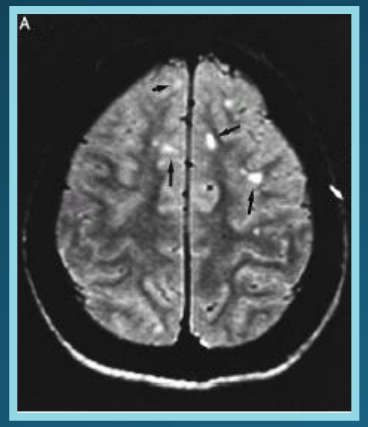
Gd-enhancing



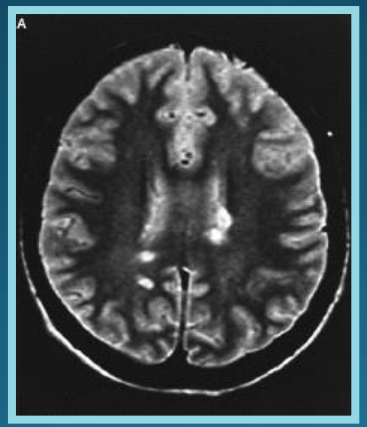
T2-hyperintense



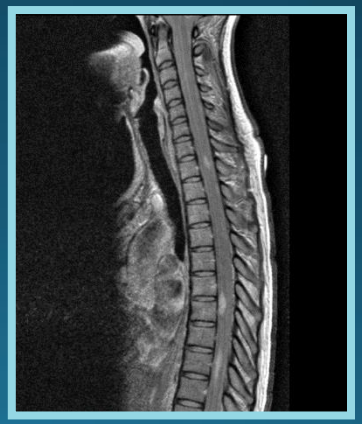
Infratentorial



Juxtacortical



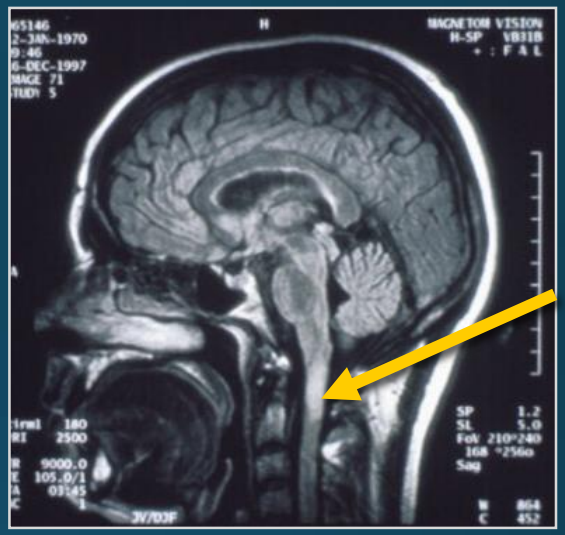
Periventricular



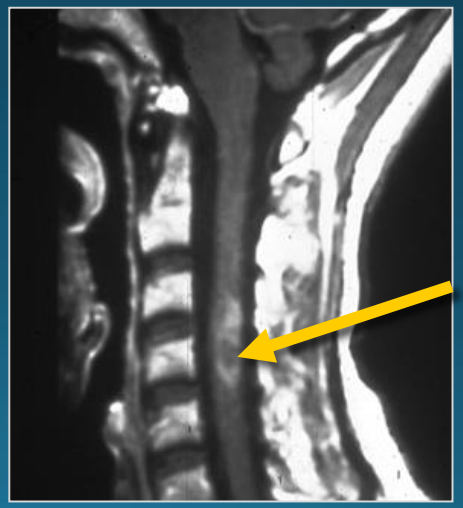
Spinal Cord

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**

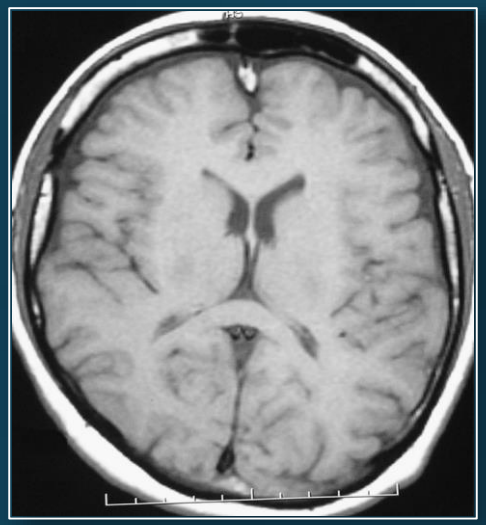


Used with permission of Kathy Costello, ANP and Patricia Kennedy, ANP.
A Comprehensive Overview of MS Nursing, 2nd Edition, 2010.

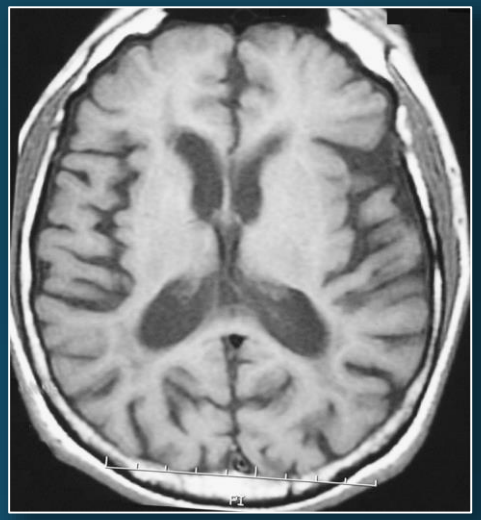
Brain Atrophy: MRI Findings

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

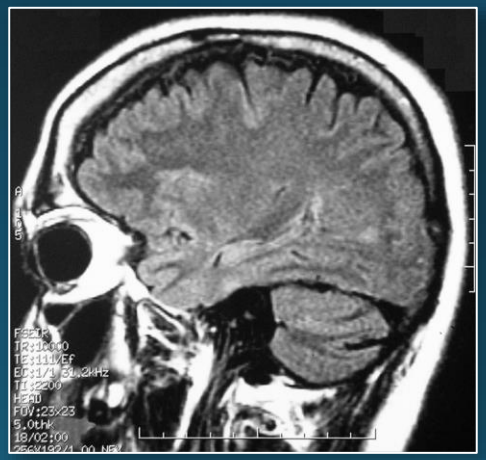
33-year-old man with RRMS for 2 years



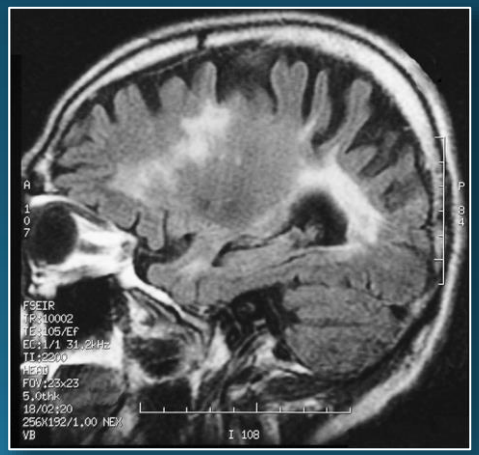
T1



47-year-old man with RRMS for 20 years



FLAIR



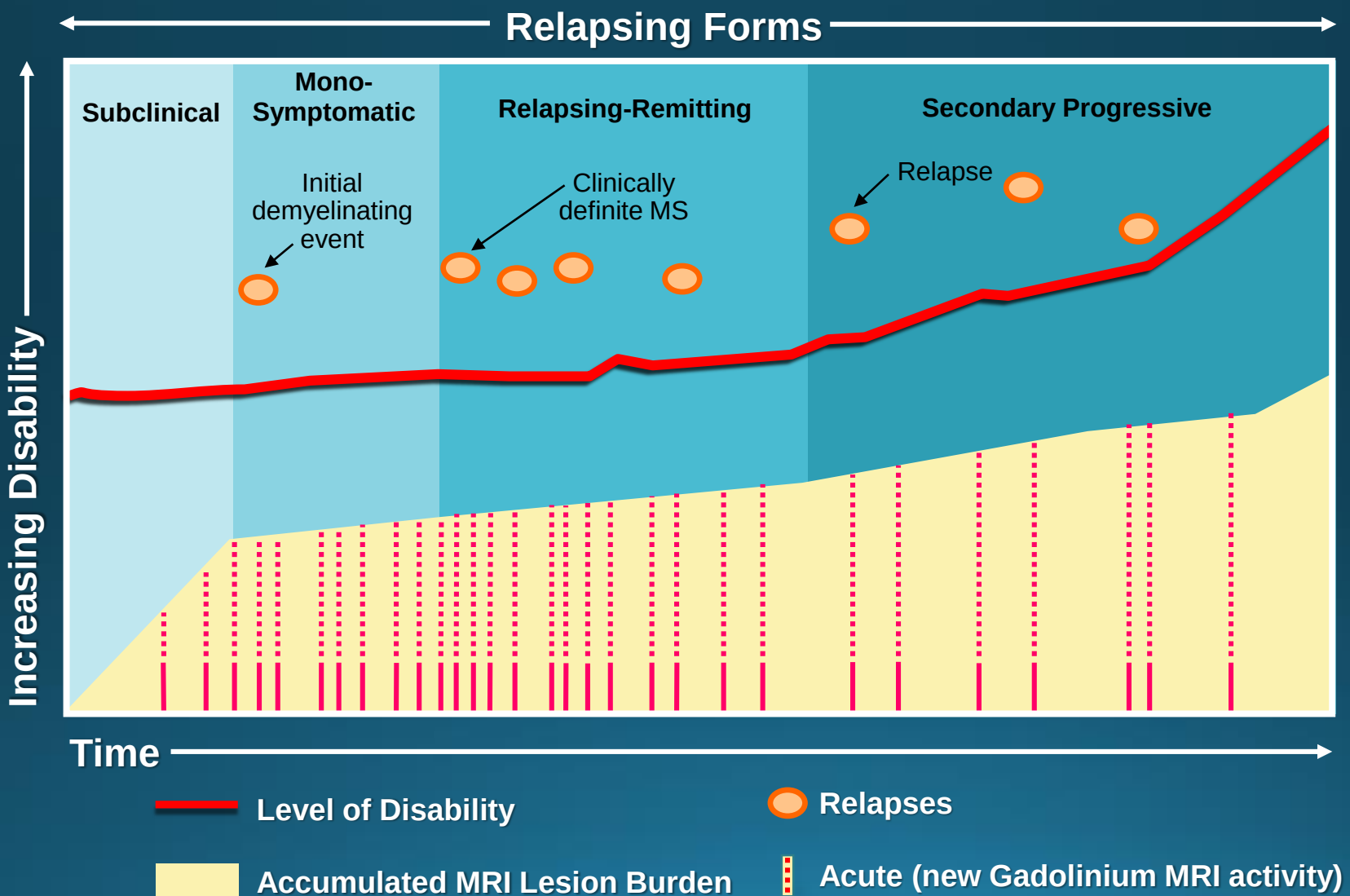
Courtesy of Dr. D. Mikol.

The Case for Early Treatment with DMTs

- **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

Progression of Untreated MS



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
- **MS phenotypes**
  - May provide clarity and consistency in defining and treating patient groups
- **Majority of individuals will start with RRMS**
  - Will develop progression of disability if untreated
- **Common symptoms include:**
  - Both visible and invisible symptoms

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