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

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

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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

Autoimmune disease

Environment

Immune regulation

Genes

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

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**
  - CD4 T helper cells become activated 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
  - Th\textsubscript{1}, Th\textsubscript{17}

- B cells (B lymphocytes)
  - Responsible for the production of antibodies
Cytokine Imbalance in MS

Normal

Inflammatory
IFN-γ
IL-12
TNF

Anti-inflammatory
IL-4
IL-10
TGF-β

Th1

Th2

MS

Anti-inflammatory
IL-4
IL-10
TGF-β

Inflammatory
IFN-γ
IL-2
IL-12
TNF

Th1

Th2
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

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

Brain Atrophy in MS

- Atrophy may occur early in the disease

- Represents cumulative effect of:
  - Demyelination and axonal loss
  - Diffuse, non-focal 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

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)

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-REMITTING MS**

**SECONDARY PROGRESSIVE MS**

**PRIMARY PROGRESSIVE MS**

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

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
  - Pseudodobulbar 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

- Sensory symptoms
  - Lhermitte’s pain
  - Proprioception
- Cognitive loss
- Emotional disinhibition
- Optic neuritis
- Diplopia
- Vertigo
- Dysarthria
- Tremor
- Ataxia
- Bladder dysfunction


Medical illustration © MCFlynn
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

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.

# 2017 McDonald Diagnostic MS Criteria

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

### Summary of 2010 Revised McDonald Diagnostic MS Criteria

<table>
<thead>
<tr>
<th>CLINICAL ATTACKS</th>
<th>MRI CHANGES</th>
<th>ADDITIONAL INFORMATION NEEDED TO MAKE THE DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 or more</td>
<td>Dissemination in time demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands.</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>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.</td>
</tr>
</tbody>
</table>

# 2017 McDonald Criteria for the Diagnosis of 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.**

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>...in a person with a typical attack/CIS at onset</td>
<td>(see KEY below for definitions)</td>
</tr>
<tr>
<td>• 2 attacks and objective clinical evidence of 2 lesions</td>
<td>None, dissemination in space (DIS) and dissemination in time (DIT) have been met.</td>
</tr>
<tr>
<td>• 3 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location</td>
<td>One of these criteria:</td>
</tr>
<tr>
<td></td>
<td>• DIS: additional clinical attack implicating different CNS site</td>
</tr>
<tr>
<td></td>
<td>• DIS: 1 symptomatonic or asymptomatic MS-typical T2 lesions in ≥2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial or spinal cord</td>
</tr>
<tr>
<td>• 1 attack and objective clinical evidence of 2 lesions</td>
<td>One of these criteria:</td>
</tr>
<tr>
<td></td>
<td>• DIT: additional clinical attack</td>
</tr>
<tr>
<td></td>
<td>• DIT: simultaneous presence of both enhancing and non-enhancing symptomatonic or asymptomatic MS-typical MRI lesions</td>
</tr>
<tr>
<td></td>
<td>• DIT: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan)</td>
</tr>
<tr>
<td></td>
<td>• CSF-specific (i.e. not in serum) oligoclonal bands</td>
</tr>
</tbody>
</table>

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**Continued on reverse**

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

| CLINICAL PRESENTATION | ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS (continued) | (see KEY on reverse for definitions) |
|-----------------------|----------------------------------------------------------|
| ...in a person with a typical attack/CIS at onset | One of these criteria: |
| • 1 attack and objective clinical evidence of 1 lesion | • DIS: additional clinical attack implicating different CNS site |
| | • DIT: additional clinical attack |
| | • DIS: 1 MS-typical symptomatonic 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 |
| | • DIS: simultaneous presence of both enhancing and non-enhancing symptomatonic 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 |

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...in a person with progression of disability from onset

<table>
<thead>
<tr>
<th>progression from onset</th>
<th>1 year of disability progression (retrospective or prospective) AND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two of these criteria:</td>
<td>1 symptomatonic or asymptomatic MS-typical T2 lesions (periventricular, juxtacortical/cortical or infratentorial)</td>
</tr>
<tr>
<td>2 T2 spinal cord lesions</td>
<td>CSF-specific (i.e. not in serum) oligoclonal bands</td>
</tr>
</tbody>
</table>

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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/ForProfessionals/Physicians

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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

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

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

47-year-old man with RRMS for 20 years

T1 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\(^6\)

5. O’Riordan JI. *Brain*. 1998;121:495-503;
Progression of Untreated MS

Subclinical

Mono-Symptomatic

Initial demyelinating event

Relapsing-Remitting

Clinically definite MS

Secondary Progressive

Increasing Disability

Relapsing Forms

Time

Level of Disability

Relapses

Accumulated MRI Lesion Burden

Acute (new Gadolinium MRI activity)
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