Multiple Sclerosis
2011 Update

Marie Namey, RN, MSN, MSCN
Mellen Center
Neurological Institute
Cleveland Clinic
Cleveland, Ohio

Mellen Center

• Opened February 8, 1985

• One of the largest and most comprehensive programs for Multiple Sclerosis care and research worldwide.

• Focus on addressing physical, emotional, cognitive and rehabilitation needs of the MS patient and their families

• Provide consultative services for neurologists and patients world-wide and ongoing care for approximately 8,000 MS patients annually, including approximately 1,600 new patient/consult visits.

• Emphasis on neurorehabilitation, imaging, therapeutics and clinical research.
Multiple Sclerosis (MS) Updates

- Definition
- Epidemiology
- Pathophysiology
- Diagnosis
- Treatments
- Monitoring Disease Activity
- Research

Multiple Sclerosis (MS)

- Multiple sclerosis is a chronic, often disabling disease that attacks the central nervous system (CNS), which is made up of the brain, spinal cord, and optic nerves.
- Symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision.
- The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to another.
- Today, new treatments and advances in research are giving new hope to people affected by the disease.
MS Triggers

- Gender
- Geography
- Virus
- Trauma
- Infection
- Genetics

Epidemiology of MS

- Most common disease of CNS in young adults
- Patient characteristics
  - 20 to 50 years of age\(^1\)
  - 70% are women\(^2\) - More women than men (ratio of 3:1)
- Incidence: 8,500 to 10,000 per year in US\(^3\)
- Prevalence: 400,000 in US
- Not directly hereditary, although genetic susceptibility plays part in development

Ethnicity and MS

• African Americans with MS have more severe disease course, older age at onset, more likely to have opticospinal symptoms, cerebellar dysfunction, more rapid accumulation of disabilities, than whites with MS.

• Asians with MS: characteristic findings—few brain lesions but extensive spinal cord lesions, severe optic nerve disease, associated with higher female: male ratio, frequent relapses, severe disability, absent oligoconal bands in CSF, different T cell responses in relapses and remission.
Paradigm Shift in View of MS

• MS is a continuous process
• Involving inflammatory myelin destruction
• Recognition of axonal destruction
• Recognition of activity of oligodendrocytes
• Monitored by MRI

Multiple Sclerosis

• Disease that affects the central nervous system (CNS)¹
• Occurs when myelin, the fatty tissue surrounding and protecting neurons, is destroyed by the body’s immune system¹
• Destruction of myelin results in formation of plaques and lesions (inflammation and sclerosis)¹
• MS is characterized by periodic loss of neurologic function and often progressive disability²

Classifications of MS

- Radiologically isolated syndrome (RIS)
- Clinically isolated syndrome (CIS)
- Clinically definite MS (CDMS)
- Four established clinical courses differ by the time course of relapse and progression
  - Relapsing-remitting MS (RRMS)
  - Secondary progressive MS (SPMS)
  - Primary progressive MS (PPMS)
  - Progressive relapsing MS (PRMS)


Radiologically Isolated Syndrome (RIS)

- Absence of MS symptoms
- MRI taken for reasons other than MS
- MRI findings highly suggestive of MS based on location and morphology in CNS
- Okuda study of 44 patients with RIS over 5 years
  - 10 patients developed a CIS or CDMS; 59% showed radiologic progression over time
- Question: When to treat?
  - Emotional/psychological repercussions for the patient of living with a radiological diagnosis, but not a clinical diagnosis; risk of patient developing fear of the clinical disease?

Clinically Isolated Syndrome (CIS)

- Episode of neurological symptom(s) consistent with inflammation and demyelination in the CNS
  - Characterized by MRI and lab data
  - Patient may or may not develop clinically definite MS
- Features of CIS suggestive of a first MS attack include
  - Appropriate age; female gender
  - Abnormal brain MRI
  - Optic neuritis
  - Brainstem/cerebellar dysfunction
  - Myelitis

CIS = clinically isolated syndrome; MRI = magnetic resonance imaging.


Disease Courses

Relapsing-remitting

Secondary-progressive

Primary-progressive

Progressive-relapsing

Therapeutic Interventions

• Relapse management
• Disease modifying agents
• Symptoms and symptom management
• Psychosocial issues

Philosophy of MS Care

• Acute, symptomatic and rehabilitative care remain the mainstays of care
• A wellness approach incorporates other systems of care (primary services, preventive measures, focus on education)
• The MS team may be found in centers, community practices, and in centers without walls
Sources of MS Symptoms

Symptoms vary widely in incidence and severity.

Signs and Symptoms

- Generalized weakness
- Visual changes
- Focal muscle weakness
- Fatigue
- Depression
- Bowel/bladder/sexual dysfunction
- Gait problems/spasticity
- Paresthesias
- Heat intolerance
- Dysarthria, scanning speech, dysphagia
- Lhermitte’s phenomenon*
- Neuritic pain
- Vertigo/ataxia
- Cognitive dysfunction
- Tremor/incoordination
- Sexual dysfunction
- Depression
- Pain

*Electric shock-like sensation down the spinal chord when flexing the neck
Pathology of MS

• An immune-mediated disease in genetically susceptible individuals
• Dual nature: inflammatory and neurodegenerative
• Demyelination leads to slower nerve conduction
• Axonal injury and destruction are associated with permanent neurological dysfunction
• Lesions occur in optic nerves, periventricular white matter, cerebral cortex, brainstem, cerebellum, and spinal cord

MS Triggers

• Initial target is myelin and the cells that make myelin
• Myelin is comprised of fat and protein
• Individual nerve fibers are wrapped in numerous layers of myelin
MS and the Central Nervous System (CNS)

- MS is thought to be an autoimmune disease
- The breakdown of the BBB permits entry of autoreactive T cells into the CNS
- Once within CNS, T cells activate the release of multiple cytokines which directly attack the myelin, oligodendrocytes, and neuron
- This attack on the myelin creates what is known as the MS lesion


Overview of Demyelination

Waxman SG. N Engl J Med. 1998;338(5):323-325. Copyright © 2004 Massachusetts Medical Society. All rights reserved
Axonal Loss in MS

- Axons may be or are transected during inflammatory demyelination
- Cortical demyelination causes axonal or dendritic transection which leads to neuronal death
- Chronic demyelination results in axonal degeneration

Axonal Damage in MS

- 50-80% axonal loss in chronic lesions (Lovas et al 2000)
- Immune-mediated inflammation is continuous, even during periods of apparent remission

What Causes Demyelination and Axonal Loss in MS

- Activation of T cells in the periphery
- Migration of T cells into the CNS
- Reactivation by autoantigens in the CNS (myelin proteins: myelin oligodendrocyte glycoprotein (MOG), Myelin associated glycoprotein (MAG), myelin basic protein (MBP), proteolipid protein (PLP))
- Release of inflammatory cytokines & other effectors (eg, nitric oxide, glutamate, matrix metalloprotease) in the CNS
- B cells & other leukocytes
- Pathology


Cytokine Imbalance

IFN=interferon; IL=interleukin; TNF=tumor necrosis factor; TGF=transforming growth factor

Disease modification—understanding pathogenesis

Immunopathogenesis of MS

Inflammatory Processes Occurring Early in MS Lead to Demyelination and Axonal Loss

Onset of Disease Time

Inflammation Demyelination Axonal loss

The exact relationship between MRI findings and the clinical status of patients is unknown.


**MS: Principles of Management**

- Delay progression to disability
  - Cognitive and physical disability
- Reduce frequency and severity of relapses
- Treat relapses when they occur
- Manage symptoms
- Maintain functional independence
- Improve and facilitate an acceptable quality of life and promote hope

**Relapses in MS**

- Relapse is a defining clinical feature of MS
- Synonyms:
  - Attack
  - Exacerbation
  - Flare
- Definition:
  - Sudden worsening of any MS symptom or the appearance of new symptom
  - Last at least 24 hours
  - Separated from a previous exacerbation by at least 1 month
  - Occur in absence of environmental, metabolic, or infectious processes

Treatment of Relapses

• High-dose steroids
  – IV methylprednisolone
  Various treatment regimens
  – Often 1 g/day for 3–5 days with /without oral prednisone taper
  – Canadian protocol: 1250 mg qod 5 doses

Burden of Disease

• Physical disability
  – Median time to requiring cane/crutch: 9 years
  – Median time to wheelchair confinement: 12 years
  – During relapsing-remitting stage, unresolved relapses are major contributor

• Cognitive dysfunction
  – Prevalence: 43% to 65%
  – Affects employment, activities of daily living, family, and social contacts

• Life shortening
  – 5- to 7-year decrease in life expectancy
  – 2- to 7-fold increase in suicide risk
  – ~50% of MS patients die of disease-related causes

**Prognostic Indicators for MS**

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Younger age at onset</td>
<td>• Older age at onset</td>
</tr>
<tr>
<td>• Female sex</td>
<td>• Male sex</td>
</tr>
<tr>
<td>• Normal MRI at presentation</td>
<td>• High lesion load on MRI at presentation</td>
</tr>
<tr>
<td>• Complete recovery from first relapse</td>
<td>• Lack of recovery from first relapse</td>
</tr>
<tr>
<td>• Low relapse rate</td>
<td>• High relapse rate</td>
</tr>
<tr>
<td>• Long interval to second relapse</td>
<td>• Early cerebellar involvement</td>
</tr>
<tr>
<td>• Low disability at 2 and 4 years</td>
<td>• Short interval to second relapse</td>
</tr>
<tr>
<td></td>
<td>• Early development of mild disability</td>
</tr>
</tbody>
</table>

**Diagnosis—Basic Principles**

- Ultimately a clinical diagnosis; no definitive laboratory test
- Clinical profile
- Laboratory evaluation
- Evidence of dissemination of lesions in space and time
- Exclusion of other diagnoses
Diagnosis—History

• Most important component of diagnostic process
  – Suggestive of previous symptoms to establish dissemination in time
  – Suggests differential diagnosis list

• Basics: Two episodes of neurological symptoms referable to the CNS separated in space and time and are not due to any other diagnosis

Assessments—Medical History

• Chief complaint, obtained in patient's own words

• Chronological narrative of present illness

• Childhood or adult illnesses, psychiatric illness, injuries, surgeries, and hospitalizations

• Medications, allergies, immunizations, abnormal test results, and exposure to environmental hazards

• Exercise/leisure activities, including sleep patterns, diet, tobacco, alcohol and other substance use

• Family health

• Psychosocial situation
Diagnosis—Neurological Examination

- Cranial nerves
- Sensory system
- Motor system and reflexes
- Cognition
  - Self awareness
  - Executive function
  - Verbal skills
  - Memory/learning
- Functional status
  - Ambulation
  - Upper extremity function

Diagnosis—Differential

Inflammatory conditions
- Systemic lupus erythematosus
- Neuromyelitis optica
- Sjogren syndrome
- Vasculitis
- Behcet’s disease
- Sarcoidosis
- Acute disseminated encephalomyelitis

Infections
- Lyme disease
- Syphilis
- Progresive Multifocal Leukoencephalopathy (PML)
  - HTLV-1
- Herpes zoster

Metabolic and genetic
- Vitamin-B deficiency
- Wilson Disease
- Lysosomal disorders
- Adrenoleukodystrophy
- Mitochondrial disorders
- CADASIL
- Inherited ataxias

Other
- CNS lymphoma
- Spinal diseases
- Radiation therapy

Diagnosis—Other tests

• Evoked potentials (measure response of brain and/or spinal cord to stimuli)
• CSF examination (to detect presence of cellular and chemical abnormalities)
• Blood count, Lyme Titer, HIV, tests for vasculitis, heavy metal testing in urine and hair, and tests for syphilis are used to rule out other potential diagnoses

Diagnosing MS: Diagnostic Criteria

• Poser criteria published in 1983
  – Required clinical evidence of 2 attacks occurring disseminated in time and space
• McDonald criteria published in 2001
  – reaffirms importance of diagnosis based on clinical findings
  – Expands role of MRI findings as an alternate method of meeting time or space criteria
• McDonald criteria revised in 2005
  – Diagnosis can still be made per clinical findings
  – Earlier diagnosis facilitated with expanded role of MRI findings (particularly spinal MRI findings) to meet dissemination in time or space criteria, when available

Diagnosing MS: McDonald Criteria (2005)

2005 revisions focused on 2 main areas:

- **Spinal cord lesions**
  
  *MRI evidence of spinal cord lesions are more liberally accepted as evidence of dissemination in space*

- **Dissemination of lesions in time**

  *New T2, as well as contrast-enhancing, lesions can qualify after only 1 month instead of 3 months*

These changes allow for diagnosis earlier in the course of disease with the intent of optimizing patient management and outcomes.

The ability to diagnose per clinical criteria remains unchanged.


Focus on Early Treatment

- Results of CHAMPS/ETOMS studies
  - autoimmune component of the disease may be more amenable to treatment during this early phase

- Secondary Progressive trials
  - the effect of immunomodulatory therapy is greater earlier in the disease
Risk for a Person with Clinically Isolated Syndrome Developing MS

- **High Risk:** When the CIS is accompanied by MRI-detected brain lesions that are similar to those seen in MS, the person has a high risk of a second neurologic event, and therefore a diagnosis of clinically definite MS, within several years.

- **Lower Risk:** When the CIS is not accompanied by MRI-detected lesions, the person has a lower risk of developing MS over the same time period.

Treatment for CIS

- Interferon Beta 1 a Avonex®
  - The **CHAMPS** (Controlled High-Risk Subjects Avonex® MS Prevention Study) study
- Interferon B 1 b Betaseron®
  - The **BENEFIT** (Betaseron® in Newly Emerging MS For Initial Treatment) study.
- Glatiramer acetate (Copaxone ®)
  - PreCISe study

- Interferon beta 1 a (Rebif ®)
  - The **ETOMS** (Early Treatment of MS )European study
  (not approved in US for CIS treatment)
Diagnosis—MRI

- MRI demonstrates approximately 90%–95% of white matter lesions in brain
- MRI demonstrates 50%–75% lesions in spinal cord
- Looks for new or recent lesions in CNS myelin
- Based upon the new criteria, MRI can be utilized to facilitate a definitive diagnosis of MS in the absence of clinical symptom, if the following criteria are met:
  - A Gd-enhancing lesion demonstrated in a scan done at least 3 months following onset of clinical attack at a site different from attack
  - In absence of Gd-enhancing lesions at 3 mo scan, follow-up scan after an additional 3 months showing Gd-lesion or new T-2 lesion

Diagnosis—Typical MRI lesions

Gd-Enhancing, T2, and T1-Hypointense Lesions

<table>
<thead>
<tr>
<th>Gd-enhancing lesions:</th>
<th>T2-hyperintense</th>
<th>T 1 Hypointense</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBB breakdown &amp; Inflammation</td>
<td>Global lesion load</td>
<td>Reversible (oedema and demyelination)</td>
</tr>
<tr>
<td>Transient</td>
<td>Pathologically non-specific</td>
<td>Irreversible (axonal loss)</td>
</tr>
</tbody>
</table>
Case Study: Katherine

– 21-year-old college senior (majoring in biology)
– New onset visual loss
  – Began yesterday upon awakening after a long night studying for a midterm examination
  – Describes right eye pain when moving eyes
  – Notes reduced field of vision superiorly and “diluted” color perception
  – No prior neurologic or medical history except for intermittent fatigue

Katherine: Clinical findings

– 20/70 vision OD, 20/20 OS
– Right relative afferent pupillary defect (RAPD)
– Reduced color vision on the right
– Fundus examination normal
– Exam is otherwise normal except for brisk reflexes
– Laboratory studies are all negative
Katherine: MRI

Coronal fat suppressed T1 MRI with Gad (A). Note enhancement (arrow). Also note periventricular plaques on axial FLAIR MRI (B).
Katherine: Discussion

What is your diagnosis?

Katherine: Diagnosis and Treatment

– Diagnosis
  – Treatment
    – Corticosteroids for the optic neuritis
    – Recommend a disease-modifying therapy
    – Adherence
    – Surveillance strategy (clinical, labs, MRI, ADLs)
Katherine: Outcome at 2 years

—After 2 years on injectable medication
—Katherine has been attack free
—Independent for all activities of daily living and feels well
—MRI assessed yearly has been stable except for 1 small new lesion in 2 years
—Neurologic exam is normal except for some right optic disc pallor

Goals of MS Disease Management

• Treat/manage relapses
• Modify the course of disease
  —Relapses, disability
• Manage symptoms
• Improve QoL
The Importance of Early Effective Treatment

- MS may be active in the brain and spinal cord in the absence of clinical symptoms
- Lesions may occur early and may be associated with irreversible damage
- Evidence suggests that degenerative changes can occur in normal-appearing white matter
- Damage can lead to permanent disability
- Starting effective treatment early may help slow the accumulation of damage


Currently Approved Therapies for MS

- Interferon (IFN)
  - IFNβ-1b (Betaseron, Extavia)
  - IFNβ-1a IM (Avonex)
  - IFNβ-1a SC (Rebif)
- Glatiramer acetate (GA) (Copaxone)
- Mitoxantrone (Novantrone)
- Natalizumab (Tysabri)
- Gilenya (Fingolimod)
### Disease Modification—Injectable Agents

<table>
<thead>
<tr>
<th></th>
<th>IFN β-1b (Betaseron®) (Extavia ®)</th>
<th>IFN β-1a (Avonex®)</th>
<th>Glatiramer acetate (Copaxone®)</th>
<th>IFN β-1a (Rebif®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relapsing-remitting MS</td>
<td>Relapsing-remitting MS</td>
<td>Relapsing-remitting MS</td>
<td>Relapsing-remitting MS</td>
</tr>
<tr>
<td></td>
<td>SC every other day</td>
<td>IM once weekly</td>
<td>SC every day</td>
<td>SC TIW</td>
</tr>
<tr>
<td></td>
<td>Reconstitution</td>
<td>Reconstitution</td>
<td>Reconstitution</td>
<td>Reconstitution</td>
</tr>
<tr>
<td></td>
<td>Prefilled syringe</td>
<td>Premixed syringe</td>
<td>Prefilled syringe</td>
<td>Premixed syringe</td>
</tr>
<tr>
<td></td>
<td>Autoinjector</td>
<td>Autoinjector</td>
<td>Autoinjector</td>
<td>Autoinjector</td>
</tr>
</tbody>
</table>

IFN=interferon  
SC=subcutaneous  
IM=intramuscular  
TIW=three times weekly

### Disease Modification—Side Effects

<table>
<thead>
<tr>
<th></th>
<th>IFN β-1b (Betaseron®)</th>
<th>IFN β-1a (Avonex®)</th>
<th>Glatiramer acetate (Copaxone®)</th>
<th>IFN β-1a (Rebif®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flu-like symptoms</td>
<td>Flu-like symptoms</td>
<td>Injection site reactions</td>
<td>Flu-like symptoms</td>
</tr>
<tr>
<td></td>
<td>Injection site reactions</td>
<td>Depression*</td>
<td>Post-injection reaction†</td>
<td>Injection site reactions</td>
</tr>
<tr>
<td></td>
<td>Allergic reactions*</td>
<td>Mild anemia*</td>
<td>Premixed syringe</td>
<td>Liver abnormalities*</td>
</tr>
<tr>
<td></td>
<td>Depression*</td>
<td>Liver enzymes*</td>
<td>➤ Liver enzymes*</td>
<td>Depression*</td>
</tr>
<tr>
<td></td>
<td>➤ Liver enzymes*</td>
<td>Allergic reactions*</td>
<td>➤ Allergic reactions*</td>
<td>Allergic reactions*</td>
</tr>
<tr>
<td></td>
<td>➤ WBC*</td>
<td>➤ WBC*</td>
<td>➤ WBC*</td>
<td>➤ WBC*</td>
</tr>
</tbody>
</table>

*Rare  †Includes anxiety, chest pain, palpitations, shortness of breath, and flushing  
WBC=white blood cell count; RBC=red blood cell count
Mechanism of Action of DMTs—Interferons

- Anti-proliferative effect
- Down-regulation of HLA-class II
- Apoptosis of autoreactive T-cells
- IFN-gamma antagonism
- Induction of cytokine shifts (Increased IL-10, Decreased IFN-gamma and IL-12)
- Decreased VLA-4 on T-cells and increase in sVCAM
- Inhibition of MMPs
- Possible anti-viral effect


Mechanism of Action of DMTs—Glatiramer acetate

- Binds to human leukocyte antigen (HLA) Class II molecules on an antigen-presenting cell and recognition by the T-cell receptor
- Systemic effects include:
  - Competition with myelin antigens binding to the HLA class II molecules
  - T-cell receptor modulation
  - Induction of anergy in myelin reactive T-cells
- Results in the expansion of the pool of anti-inflammatory Th2 cells.

Mitoxantrone: FDA-Approved for Worsening RRMS, SPMS, and PRMS

- Synthetic anthracycenedione derivative, originally used in the treatment of malignant diseases
- Approved for SPMS and worsening relapsing MS
- Reduces exacerbations, disability progression, and MRI activity
- Given IV 12 mg/m² every 3 months
- Lifetime dose: 140 mg/m²
- Cardiotoxicity limits lifetime dosing
- Other risks: infections, sterility, secondary leukemia
- Side effects: nausea, vomiting, alopecia


Natalizumab

Natalizumab (Tysabri®) -- monoclonal antibody that selectively inhibits an adhesion molecule, alpha4beta1 integrin

- Inhibits adhesion of activated lymphocytes to blood vessel endothelium
  - Restricts trafficking of lymphocytes into the CNS
  - Approved initially in 2004 for RRMS; however, two deaths in clinical trial participants due to PML led to the voluntary withdrawal from marketing and distribution
- Decreases exacerbations, disability progression, and MRI activity
- Given IV q4w

**PML**

- Rare, progressive, demyelinating disease of CNS (1:200,000 in the United States)
- Lytic infection of oligodendrocytes by JC virus, a human polyomavirus
- Often fatal within 6 months of diagnosis
- Reactivates in settings of profound immunosuppression
- Primarily affects immunocompromised (HIV, transplant, hematologic malignancy)

**MRI**

- PML
- MS

**Fingolimod (Gilenya™)**

- Sphingosine-1P (S-1P) receptor modulator
- Blocks lymphocyte egress and migration from nodes

- Approved for RRMS 9/10.
- Key Safety Issues
  - Hepatic enzyme elevation
  - Hypertension
  - Cardiac abnormalities (e.g., bradycardia, AV block)
  - Malignancies
  - Herpes viral infections
  - Macular edema

**Nursing tasks**

**Universal**
- Therapeutic relationship
- Comprehensive assessment
- Collaborative treatment plan

**MS-specific**
- Full knowledge of disease
- Empowerment
- Advocacy
Disease Modifying Therapy—Selection

• Factors that influence choice of therapy
  – Clinical subtype
  – Disease duration
  – Prognostic profile
  – Clinical disease severity (relapse rate, type of relapse, extent of recovery, disability)
  – MRI disease severity
  – Comorbidity
  – Lifestyle preferences
  – Ability to self-inject
  – Compliance
  – Lifestyle

Making Treatment Decisions
Considering the Benefits and Risks

Treatment decisions

- Evidence based approach
- Safety
- Tolerability
- MOA
- Convenience
- Response
- Monitoring
- Physician experience
- Patient preference
- Cost
- Pregnancy issues
How to Measure Progression of Disease in MS

Well-defined methods

- Relapses
- Disability Rating Scales
  - Expanded Disability Status Scale (EDSS)
  - Multiple Sclerosis Functional Composite (MSFC)
- MRI changes
  - Gadolinium-enhancing lesions (T1-weighted)
  - Measurement of brain atrophy (using visual analysis of MRI data to estimate brain atrophy)

Other methods under development

- Optical coherence tomography (a structural biomarker)
- Visual evoked potentials
- Biologic markers

Disease Modification—Assessing Outcomes: Relapses

<table>
<thead>
<tr>
<th>Relapses</th>
<th>Notable</th>
<th>Worrisome</th>
<th>Actionable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency/severity</td>
<td>1 mild</td>
<td>1 moderate/year &gt;6 mo after start of therapy</td>
<td>&gt;1 moderate or 1 severe/year &gt;6 mo after start of therapy</td>
</tr>
<tr>
<td>Recovery</td>
<td>Rapid following prompt steroid Rx</td>
<td>Slow following prompt steroid Rx</td>
<td>Incomplete recovery</td>
</tr>
</tbody>
</table>

Disease Modification—Assessing Outcomes: Progression

<table>
<thead>
<tr>
<th>Progression</th>
<th>Notable</th>
<th>Worrisome</th>
<th>Actionable</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS (\leq 3.5)</td>
<td>(&lt;2) point change</td>
<td>2 point change</td>
<td>(&gt;2) point change</td>
</tr>
<tr>
<td>EDSS (\geq 4)</td>
<td>(&lt;1) point change</td>
<td>1 point change</td>
<td>(&gt;1) point change</td>
</tr>
<tr>
<td>Clinically documented progression</td>
<td>No motor; minor sensory</td>
<td>Some motor, cognitive, or more pronounced sensory</td>
<td>Pronounced motor, cognitive, sensory</td>
</tr>
</tbody>
</table>


Expanded Disability Status Scale (EDSS)

**Increasing Disease Burden**

- Normal neurologic exam
- No disability
- Minimal disability
- Moderate disability
- Fully ambulatory, severe disability
- Ambulatory without aid 200 m
- Ambulatory with unilateral assistance 100 m
- Ambulatory wheelchair
- Bedridden
- Helpless
- Death due to MS

**EDSS Score**

Multiple Sclerosis Functional Composite

<table>
<thead>
<tr>
<th>Clinical Dimension</th>
<th>Test Name</th>
<th>Measurement</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm</td>
<td>9-hole peg test</td>
<td>Mean of right and left arm scores</td>
<td>Time to insert and remove 9 pegs</td>
</tr>
<tr>
<td>Leg</td>
<td>Timed walk</td>
<td>A walk of 25 ft</td>
<td>Time taken in seconds</td>
</tr>
<tr>
<td>Cognitive</td>
<td>PASAT</td>
<td>Paced auditory serial addition test, 3 min version</td>
<td>Number correct</td>
</tr>
</tbody>
</table>


MS Functional Composite

- Developed for use in clinical trials
- Individual components used in clinical practice:
  - Timed 25-Foot Walk
    - Quantitative mobility and leg function performance test
  - 9 Hole Peg Test
    - Quantitative test of upper extremity function
  - Paced auditory serial addition test (PASAT)
    - Measure of cognitive function

Disease Modification—Assessing Outcomes: MRI

<table>
<thead>
<tr>
<th>MRI</th>
<th>Notable</th>
<th>Worrisome</th>
<th>Actionable</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Gd-enhancing lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New T2 lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarging T2 (burden of disease)</td>
<td>Change in 2 categories</td>
<td>Change in 3 categories</td>
<td>Change in ≥3 categories</td>
</tr>
<tr>
<td>New T1 hypointense lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarging T1 hypointense lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Suboptimal Response to DMTs

- Response to DMTs is highly variable
- DMTs may become ineffective as the disease progresses; why?
- MS is a heterogeneous disease with great variability in clinical presentation and underlying pathology
- 1 DMT might work while others may not

**Signs of Worsening MS**

- Increasing disability without relapses
- Increasing relapses without return to baseline
- Decreased cognitive function
- Increasing MRI activity
- Increased use of MS-related medicines to control symptoms
- Decline in activities of daily living and Quality of Life


---

**Addressing QoL**

- Individualized care is critical to treating the inter-relatedness of:
  - Neurological symptoms
  - Side effects of therapies
  - Adherence to therapies
- DMTs must be part of the treatment plan as they can alter the course of MS
- Symptoms need to be aggressively managed as they negatively impact QoL
- Care must be comprehensive and culturally sensitive

On the Horizon

New Imaging Techniques
New Treatments

New Imaging Techniques

- MR spectroscopy
- DTI
- High-field strength MRI
- fMRI

DTI = diffusion tensor imaging; fMRI = functional MRI.
**MR Spectroscopy**

- Looks at various CNS metabolites
- NAA is a marker of neuronal and axonal integrity
- NAA is decreased in MS, especially in progressive MS
- Potential use in MS treatment trials to measure neuroprotection

NAA = \(N\)-acetylaspartate.

---

**DTI - Diffusion Tensor Imaging**

- Measures the diffusion of water molecules in tissues
- Enables diffusion to be measured in multiple directions and the fractional anisotropy in each direction to be calculated
- With this technique, areas of neural degeneration and demyelination can be visualized and quantified
- Allows for visualization of very early changes caused by MS

Slide courtesy of Peter Calabresi, MD.
High-Field-Strength MRI

- High strength magnet 3-8 Tesla
- Ability to visualize more MS pathology
- Ability to visualize gray matter pathology


fMRI

- fMRI provides information about brain plasticity, which follows MS inflammation and damage
- Demonstrates areas of brain activation
- fMRI demonstrates the recruitment of regions, which are not typically activated in healthy controls for a given task

New Treatments for MS

Symptomatic Therapy

- 4-aminopyridine
  - FDA-approved January 2010
  - Symptomatic treatment
  - Oral treatment to improve walking in patients with MS

Disease Modification

- Fingolimod (oral) approved 9/10
- Cladribine (oral)
- Laquinimod (oral)
- BG-12 (oral)
- Alemtuzumab (IV)
- Rituximab (IV)
- Daclizumab (IV)


Therapeutic Agents Under Investigation

<table>
<thead>
<tr>
<th>AGENT</th>
<th>MECHANISM</th>
<th>ROUTE</th>
<th>PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan</td>
<td>Anti CD20</td>
<td>IV (2 x year)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Campath</td>
<td>Anti CD52</td>
<td>IV (1 x year)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Anti CD25</td>
<td>IV or SC (q month)</td>
<td>Phase II</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>Stavastatin</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>Cladribine</td>
<td>immunosuppressant</td>
<td>oral</td>
<td>Phase III competed</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>Estrilol</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>Fumarate</td>
<td>immunomodulator</td>
<td>oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>MBP 8392</td>
<td>immunomodulator</td>
<td>IV (q month)</td>
<td>Phase III</td>
</tr>
</tbody>
</table>
**MS Pipeline**

**Different therapeutic approaches**

**Protein-based therapeutics**
- Anti-Cholinergic peptides
- Anti-IL12
- Ante-IL12/23
- Anti-CCR2
- Anti-CD52
- Anti-CD52
- Anti-CCR1

**Stem cell therapies**
- T cell vaccine
- Alemtuzumab
- Rituximab
- IFN tau
- Anti-IL-12/23
- Anti-CCR2
- Anti-CD52

**Other**
- IFNb-1a IM
- IFNb-1a SC
- IFNb-1b (Extavia®)

**Oral treatments**
- IFNb-1b
- GA
- Mitoxantrone
- Natalizumab
- Fampridine
- Cladribine
- Fingolimod
- Laquinimod
- BG-12
- Alemtuzumab

After Dr. G. Comi

89 DOS CNE Course 2011

**MS Treatment Pipeline**
Summary

• MS is a complex disease of the CNS
• Early treatment is important for long-term outcomes
• Many DMTs are currently available, with several promising treatments in late-stage development
• Nurses play a unique role in comprehensive management
  – Assessment, education, counseling, symptom management
  – Improvement in QoL

Thank you for your attention……
Cleveland Clinic

Every life deserves world class care.