Multiple Sclerosis: Best Practices in Comprehensive Management

• Morning Session:
  – Examining the Complexity of MS: Implications for Diagnosis
  – The Clinical Course of MS: Presentation Through Progression
  – Treatment Optimization in MS

• Afternoon Session:
  – The Symptom Chain in Multiple Sclerosis
  – Quality of Life Considerations for Patients With MS and Their Families
  – Concerns for Special Patient Populations With MS
  – The Expanded Role of the MS Team
  – The Future of MS Diagnosis and Treatment: A Bright Outlook
Examining the Complexity of MS: Implications for Diagnosis

- Introduction to MS
- Environmental and Genetic Factors in MS
- Review of Pathophysiology
- Update on Immunopathology
- Diagnosing MS
- Neuroimaging in MS DVD
  - MRI Basics
Definition of Multiple Sclerosis

- The most common chronic disease affecting the central nervous system (CNS) in young adults
- The hallmark of MS is inflammatory, demyelinating plaques in the CNS
- Immune-mediated, chronic, inflammatory disease, precipitated by unknown environmental factors in genetically susceptible individuals
- Degenerative disease characterized by axonal loss

Epidemiology

- Approximately 400,000 cases in the United States\(^1\)
  - (estimates range from 250,000–500,000)
- The chances of developing MS are 1:1000 in the general population\(^2\)
- Estimated 2.5 million cases worldwide\(^3\)
- Higher prevalence in those with northern European ancestry\(^4\)
- Highest incidence in Caucasians
- Higher incidence in women (>2 to 3:1)\(^4,5\)
- 3/4 of cases present between ages of 15-45

Gender and Age in MS

- **Gender**
  - Women develop MS 2-3 times more than men
  - Women are more susceptible to developing MS in puberty. Do hormones play a role in MS?
  - MS relapses in women may be linked with hormonal changes (eg, during menstrual cycle, post-partum)

- **Age**
  - Studies show younger age at onset may be linked to better prognosis
  - Older age at onset to a worse prognosis

Ethnicity and MS

• African Americans with MS
  – Have more severe disease course; older age at onset; and are more likely to have optical and spinal symptoms, cerebellar dysfunction, and more rapid accumulation of disabilities than whites with MS\(^3, 4, 5\)

• 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 oligoclonal bands in CSF, different T cell responses in relapse and remission\(^7\)

• Non-white race/ethnicity with MS and younger age substantially increases risk for a second demyelinating event within one year of initial demyelinating event\(^1, 2\)

Smoking and MS

- Smoking increases risk of developing MS\(^4\)
- May increase disease progression\(^1\)
- Smoking associated with increased risk for early conversion to MS after a CIS\(^2\)
- Passive smoking associated with higher risk for MS\(^3\)
- Adults with disabilities tend to be heavier smokers. More nicotine dependent than the general population\(^5\)
- Studies indicate that smoking is a modifiable risk factor for MS\(^2\)
- Implications for MS team: importance of quit-smoking counseling

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Etiology Of MS

Genes ↔ Environment

Abnormal immune response

Multiple sclerosis

Immune stimulation (infections?) ↔ Secondary factors

Worsening MS

Etiology of MS

• Apparently, an interaction of genetics and environmental factors trigger MS:
  – Genetics: may determine individual susceptibility to MS
  – Environmental triggers may determine the onset and modulation of MS¹
    • Infectious agents (eg, virus, bacteria)
    • Metabolic
    • Lifestyle factors (eg, smoking status)
    • Seasonality of patient’s birth, disease onset, and exacerbations
    • Geographical factors (eg, latitude)
    • Vitamin D status
  – Studies in Australia:
    • Modifiable environmental factors may enable us to prevent up to 80% of MS cases²

Factors Studied

• Infectious agents:
  – Different agents have been studied, but Epstein-Barr virus (EBV) has attracted the most research. Findings include:
    • Persistence and reactivation of EBV in the CNS may be a key contributor to the development of MS
    • B cells have a receptor for EBV
    • Studies show risk of developing MS is 10x greater in individuals who have experienced undiagnosed EBV infection in childhood compared with those who did not
    • The risk increases to 20x greater in individuals who developed clinical infectious mononucleosis in childhood or adolescence
    • EBV may trigger increased risk of MS without attacking the CNS directly

Factors Studied, continued

• Environmental factors
  – Geography
    • Wide variability in prevalence of MS around the world
    • Incidence and prevalence increase farther from the equator
  – Vitamin D deficiency studies show:
    • Sunlight exposure may be connecting link between latitude and MS risk
    • High circulating levels of 25-hydroxyvitamin D associated with lower risk of MS in Caucasians
    • Study of nurses on supplements of ≥400 IU/day associated with 40% reduction in risk of MS
    • Vitamin D receptors are expressed on B cells infected by EBV

World Prevalence of MS

Genetics and MS

• Genetics play a role in individual’s MS susceptibility
• Risk increases from 1/1000 to 2-3/100 with MS in one first-degree relative
• All identified gene segments associated with the risk of getting MS appear to affect immune system functions
• Other genes may have a role in nerve survival and repair

Genetic Predisposition

- Genetic predisposition varies by race/ethnicity
  - First-degree relatives of those with MS have a 20-40fold increase in risk
  - Up to 2% of people with MS have at least one relative with MS
  - Concordance rates are higher in twins
    - Monozygotic (26%-30%)
    - Dizygotic (2.4%)
  - Risk of MS in one parent: 2%-4%
  - Risk of MS in both parents: 6%
  - Risk of MS in siblings: 3%-5%
  - Familial aggregations occur

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The pathophysiologic hallmarks of MS lesions include:

- Multifocal inflammation
- Damage to the blood-brain barrier (BBB)
- Demyelination of neuronal axons
- Oligodendrocyte loss
- Gliosis
- Axonal degeneration

Although the primary pathology is immune-mediated destruction of CNS myelin and oligodendrocyte loss, the major cause of neurologic disability is axonal loss.
Typical Magnetic Resonance Imaging (MRI) Lesions
Overview of Demyelination

A. Normal Myelinated Axon

B. Acutely Demyelinated Axon

C. Chronically Demyelinated Axon

Conduction restored by increase in density of sodium channels

D. Degenerated Axon

Axon

Demyelination

Myelin sheath

Sodium channels

Postsynaptic neuron

Introduction: Demyelination in MS

- MS plaques are:
  - Areas of demyelination followed by partial remyelination and gliotic scarring

MS Lesions in the Brain: Correlation Is With Cognitive Function

Photos Courtesy of Peter Ostrow, MD, PhD, State University of New York, Buffalo, NY.
Axonal Transection in Acute MS Lesions

No. of transected axons per cubic mm: 11,236 in active lesions; 3138 at edges of chronic active lesions; 875 in hypocellular centers of chronic lesions; <1 in normal-appearing white matter (NAWM) from control brains

Axonal injury is an early consistent pathological feature in MS lesions and closely associated with inflammation within the lesion

Underlying Pathology

Inflammatory

Degenerative

Axonal loss

Inflammation

Why Is Axonal Damage Important?

“Cumulative tissue loss in the grey and white matter, especially of axons, is important and probably the principal determinant of accumulation of irreversible neurological disability”

–W. Brück

Normal Nerve Conduction
Mild to Moderate Demyelination
Severe Demyelination
Brain Atrophy in MS

- Brain atrophy indicates loss of tissue
  - Gray matter atrophy may progress more rapidly than whole brain tissue loss
- Strong prognostic value and correlates with disability

EDSS=expanded disability status scale; PBVC=percent brain volume change

Cortical (Grey Matter) Lesions

“Our data confirm previous reports of cortical demyelination in MS brains and describe in these lesions axonal transection, dendritic transection, neuronal death by apoptosis, and reduced inflammatory cell content compared to white matter lesions.”

112 cortical lesions from 50 MS patients, identifying 3 patterns of cortical demyelination

Patterns of cortical demyelination: type I: both white and grey matter, type II: perivascular area, type III: extends from pial surface to cortical layer

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Overview of Immunopathology of MS

MS is an immune-mediated disease, precipitated by environmental factors in genetically susceptible individuals.

- MS is both inflammatory and neurodegenerative.
  - The dominant feature of MS is inflammatory, demyelinating plaques in the CNS.
  - Axonal injury and destruction is an integral and early pathological feature.
  - This causes altered and slowed nerve conduction.
  - Permanent neurological dysfunction is the outcome of these disease processes.

Overview of Immunopathology of MS, continued

- Predominantly a T-cell mediated inflammatory disorder
- T cells are activated against the CNS
- Involves overproduction of proinflammatory cytokines
- Disease is limited to the CNS
- Lesions result from a highly selective, destructive immune process

- In MS histology, new lesions are mixed with old lesions:
  - Old lesions: show few immune cells, may have scars
  - New lesions: show activated immune cells

Immunology Basics

• Immune system composed of:
  – Lymphoid organs (eg, spleen, lymph nodes)
  – Tissues
  – Cells (eg, T cells, B cells)
  – Biochemical mediators (eg, cytokines, chemokines)
  – Humoral factors

• Role of the immune system:
  – To recognize self from non-self
  – To recognize, neutralize, and eliminate potentially harmful invading non-self entities (eg, bacteria, viruses, foreign tissue, some malignancies)

Molecular Mimicry: An Inability to Distinguish Non-self From Self

Potential Non-self Antigens
- Viruses
  - Herpes
  - Adenovirus
  - Rubella
  - Retrovirus

Potential Self Antigens
- Bacteria/Toxins
  - *Borrelia*
  - Chlamydia
  - Superantigens

- Myelin basic protein
- Proteolipid protein
- Myelin oligodendrocyte glycoprotein
- Myelin associated glycoprotein
Immunology Basics: Immune System Key Cells

- **Antigen-presenting cells (APCs)**
  - Macrophages, microglia, etc.

- **T cells (T lymphocytes)**
  - Responsible for cell-mediated immune response
    - **T Helper cells (Th)**

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

Normal

Th1
Inflammatory
IFNγ
IL-12
TNF

Th2
Anti-inflammatory
IL-4
IL-10
TGFβ

MS

Th1
Inflammatory
IFNγ
IL-12
TNF

Th2
Anti-inflammatory
IL-4
IL-10
TGFβ

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

Immunoopathogenesis of MS

MMP=matrix metalloproteinase; APC=antigen presenting cell
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Diagnosing MS: Overview

• Clinical diagnosis
  – Medical history
  – Neurologic examination
• Laboratory studies
• Evoked potential testing
• Lumbar puncture
• Imaging: MRI of brain (+/- spine)
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
- Normal bladder/bowel function
- Progressive myelopathy
- Impaired level of consciousness
- Prominent uveitis
- Peripheral neuropathy
- Gray matter features (e.g., early dementia, seizures, aphasia, extrapyramidal features)
- Atypical presentation (e.g., fever, headache, abrupt hemiparesis, abrupt hearing loss, prominent pain, normal optic exam, normal sensory exam)

Prognostic Indicators: MRI Findings

- Presence of cerebral lesions at first attack of inflammatory demyelination (optic neuritis, acute myelopathy, acute brainstem syndrome) increases chance of developing MS over the successive 2-5 years.

Favorable Prognostic Indicators

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

Unfavorable Prognostic Indicators

- Later age of onset
- Multifocal onset
- Progressive course from onset
- Frequent exacerbations
- Poor recovery from exacerbations
- Involvement of cerebellar or motor functions
- Burden of disease: MRI at diagnosis
  - $\geq 2$ contrast lesions
  - $\geq 9$ T2 lesions

Assessment Tools

• Medical history
  – Age/gender/ethnicity
  – Identify any events that might be indicative of MS-related symptoms
  – Complete differential diagnosis
Assessment Tools, continued

- Neurological examination
  - Mental status
  - Cranial nerves (CNI–CNXII)
  - Motor assessment
  - Sensory exam
  - Coordination and gait
  - Reflexes
Cerebrospinal Fluid (CSF) and Lab Studies

- Lumbar puncture: CSF analysis findings of MS
  - Immunoglobulin (Ig) G elevation
  - Oligoclonal banding in IgG on electrophoresis
  - Mild leukocytosis
  - IgM specificity and prediction of adverse long-term outcomes

- Proteome profile
  - Potential biomarker to predict disease subtype

- Other laboratory studies
  - Test for oligoclonal banding in serum IgG
  - Assess patient’s health (eg, liver, kidney function)
  - Exclude concomitant illness (eg, meningitis)

**CSF Analysis**

- 90% of patients with MS have high levels of IgG (immunoglobulins, protein chains)
- Presence of oligoclonal bands (≥2)

Evoked Potentials

• Evoked potential testing
  – Visual evoked potentials (VEP): an alternating checkerboard pattern is displayed on a screen
  – Brainstem auditory evoked potentials (BAEP): a series of clicks in each ear
  – Sensory evoked potentials (SEP): Short electrical impulses are administered to an arm or leg

Note: a fourth type (motor evoked potentials) exists but is not commonly used to diagnose MS

Conventional MRI

- Conventional MRI
  - Useful for diagnosis when there have not been 2 clinically proven episodes, as required
  - Current preferred method of brain imaging
  - Can detect subclinical lesions
  - May identify active inflammation with gadolinium (Gd) contrast enhancement

Newer MRI Techniques

- Magnetization transfer (MT)
- Magnetization transfer ratio (MTR)
- Proton magnetic resonance spectroscopy (MRS)
  - Choline-containing compounds
  - Creatine/phosphocreatine
  - Lactate
  - N-acetylaspartate (NAA)
- Correlates with disability
- Diffusion-weighted MRI
- Functional MRI (fMRI)

Ford C, Wolinsky J. *Clinician’s Primer on MS: Basic Course on MRI.* 2009.
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

McDonald Criteria (2005)

- Objective evidence of dissemination in time and space of lesions is essential
- All other explanations for clinical features must be excluded prior to diagnosis of MS
- Clinical evidence must be based on objective clinical signs
- MRI, CSF, and visual evoked potentials (VEPs) are helpful for diagnosis when clinical presentation is not characteristic of a particular disease
- Following evaluation, diagnosis will be MS, not MS, or possible 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.

## McDonald Criteria (2005)

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
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<tbody>
<tr>
<td>2 or more attacks; objective clinical evidence of 2 or more lesions</td>
<td>None</td>
</tr>
<tr>
<td>2 or more attacks; objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by MRI OR 2 or more MRI-detected lesions consistent with MS + positive CSF OR Await further clinical attack implicating a different site</td>
</tr>
<tr>
<td>1 attack; objective clinical evidence of 2 or more lesions</td>
<td>Dissemination in space, demonstrated by MRI OR Second clinical attack</td>
</tr>
<tr>
<td>1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)</td>
<td>Dissemination in space, demonstrated by MRI OR 2 or more MRI-detected lesions consistent with MS + positive CSF AND Dissemination in time, demonstrated by MRI OR Second clinical attack</td>
</tr>
<tr>
<td>Insidious neurological progression suggestive of MS</td>
<td>One year of disease progression (retrospectively or prospectively determined) AND 2 out of 3 of the following: Positive brain MRI (9 T2 lesions or 4 or more T2 lesions) with positive visual evoked potentials; positive spinal cord MRI (2 or more focal T2 lesions); positive CSF</td>
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McDonald Criteria (2005): MRI Proof of Dissemination in Space

• Three of the following:
  1. One Gd-enhancing lesion or 9 T2-hyperintense lesions
  2. At least 1 infratentorial lesion
  3. At least 1 juxtacortical lesion
  4. At least 3 periventricular lesions

• Per 2005 revisions—substituting spinal cord lesion requirements for brain lesions
  1. A spinal cord lesion=a brain infratentorial lesion
  2. An enhancing spinal cord lesion=enhancing brain lesion
  3. Individual spinal cord lesions can contribute together to reach the required number of T2 lesions

McDonald Criteria (2005): MRI Proof of Dissemination in Time

1. Detection of Gd enhancement at least 3 months after initial event

OR

2. Detection of a new T2 lesion at any time compared with a reference scan done at least 30 days after the initial clinical event

<table>
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<tr>
<th>Patient Population</th>
<th>MRI Type and Indication</th>
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</table>
| For patients with a CIS and suspected MS: Recommendations for baseline evaluation | - Brain MRI with gadolinium  
- A spinal cord MRI if there is persisting uncertainty about the diagnosis and/or the findings on brain MRI are equivocal  
- A spinal cord MRI if presenting symptoms or signs are at the level of the spinal cord |
| For patients with a CIS and suspected MS: Recommendations for follow-up evaluation | - A brain MRI with gadolinium to demonstrate new disease activity |
| For patients with an established diagnosis of MS: Recommendations for baseline evaluation | - A brain MRI with gadolinium |
| For patients with an established diagnosis of MS: Recommendations for follow-up evaluation | - A brain MRI with gadolinium is recommended for the following MS patients:  
  - Unexpected clinical worsening for a secondary diagnosis  
  - Reassessment of the original diagnosis  
  - Reassessment before starting or modifying therapy  
  - To assess subclinical disease activity, MRI should be CONSIDERED every 1-2 years  
  - The exact frequency may vary depending on clinical course and other clinical features  
  - A spinal cord MRI with gadolinium is recommended for the follow-up of MS patients with clinical evidence of disease activity referable to the spinal cord and who do no have MRI evidence of disease activity in the brain |
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Subsequent slides in the handout are for your review. These slides will not be discussed in the presentation as you will be watching a DVD on Neuroimaging in MS.
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MRI Basics

- Uses magnetic fields and radiowaves to provide cross-sectional views of the body
- Shows structural details of soft tissue
- Intensity of the MRI signal will vary based on:
  - Water content of different tissue types
  - Magnitude and timing of radio frequency pulses
  - Use of paramagnetic MRI enhancement agents

Location of MS Lesions on MRI

- MS lesions vary in size, shape, and location; however, they occur most frequently
  - Periventricular, often perpendicular to the axis of the lateral ventricles (ie, “Dawson’s fingers”)
  - In the corpus callosum
  - Below the tentorium cerebelli

T1-Weighted vs T2-Weighted Images

• T1-weighted images
  – Lesions appear as hypointense (dark) areas in comparison with the surrounding normal brain tissue
  – Acute lesions are T1 hypointense due to local edema, which may be reversible

• T2-weighted images
  – More sensitive than T1-weighted MRI
  – T2 quantifies lesion load or disease burden
  – New or enlarging lesions suggest increasing inflammation and demyelination
  – In a T2-weighted scan, the gray matter appears lighter and brighter than the white matter
  – T2 lesions appear hyperintense

T1-Weighted Images: Enhancing vs Non-enhancing Lesions

- Enhancing lesions—These lesions are seen with gadolinium enhancement, reflecting leaks in the BBB (the site of immune attack)
- Gadolinium-enhanced lesions are considered new or active; enhancement of these lesions comes and goes
- Non-enhancing lesions—These lesions are detected without gadolinium. Hypointense lesions are believed to represent areas of axonal loss and therefore more permanent damage

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”

T1-Weighted, Gadolinium-Enhanced MR Image

- New and active lesions appear bright on Gd-enhanced images, reflecting:
  - Areas of BBB disruption
  - Local edema (e.g., T1 hypointensity)

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
T2 Fluid-Attenuated Inversion Recovery (FLAIR)

• Provides more specific information compared with unmodified T2 images
• Visualizes up to 3 times as many lesions as unmodified T2 images
• Increases lesion conspicuity in neurons adjacent to ventricles and CSF spaces

T2 FLAIR

- Provides greater contrast between CSF and lesion

Proton Density MR Image
(No weighting of T1 or T2 allows the periventricular lesions to be more visible)

T2-weighted image; high contrast

Proton density weighted image; low contrast

Brain Atrophy
(Represents the cumulative effect of demyelination, axonal loss, and diffuse, non-focal damage)

33-year-old man with RRMS for 2 years

47-year-old man with RRMS for 20 years

Courtesy of Dr. D. Mikol.
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

Courtesy of Dr. D. Mikol.
Spinal Cord Lesion
Spinal Cord Lesion
New imaging techniques are more sensitive to CNS changes, including white and grey matter:

- Magnetization transfer ratio
- Magnetic resonance spectroscopy (MRS)
- Diffusion-weighted MRI (DWI)
- Functional MRI (fMRI)
- Optical coherence tomography (OCT)

Magnetization Transfer Ratio: Overview

• Magnetization transfer is a sensitive MRI technique measuring the state of tissue integrity: myelin and axons

• The ratio of these signals when applied to the less-mobile protons and transferred to mobile ones defines the MTR

• Decreased MTR reflects tissue damage or destruction
  – The lower the MTR, the greater the damage to myelin and large macromolecular structures associated with myelin

• Highly sensitive

Magnetic Resonance Spectroscopy: Overview

- Measures metabolic changes in lesions and NAWM
- Quantity of NAA decreases at sites of neuronal-axonal dysfunction or loss
- Elevated choline peak represents heightened cell-membrane turnover in demyelination, inflammation, or gliosis
- May evaluate severity of disease, follow disease evolution, and assess efficacy of therapeutic interventions

NAA: N-acetyl aspartate (biochemical marker)

MRS

- N-acetyl aspartate (NAA) = a biomarker of axonal integrity
- Evaluates metabolic changes in lesions and NAWM
- Findings on MRS support the fact that axonal integrity declines in acute lesions
- Studies have demonstrated correlations between NAA reductions and clinical disability

MRS and NAA: A Biochemical Marker

**Diffusion-Weighted MRI**

- A quantitative measure of the effect of cellular environment of CNS tissue on diffusion properties of water molecules
- DWI indicates loss or increase in permeability of barriers, thus identifying loss of tissue integrity
  - Sensitive to fiber tract damage in MS, reflecting demyelination or inflammation
  - Reflects changes in tissue architecture (e.g., lesion orientation, size, geometry of tissue)
- Main parameter is mean diffusivity (MD)
  - MD increases if tissue integrity is compromised
  - Provides a relative measure of the degree of tissue impairment

Neuroimaging Techniques: Summary

• MRI techniques have improved the ability to determine disease status and follow treatment response in MS
• Conventional MRI methods have identified the CNS activity of disease-modifying therapies
  – Indicate effect on lesion activity
  – Reveal impact on lesion volume
• Advanced MRI technology may offer a role in assessing and predicting disease progression
  – Correlates with demyelination and axonal loss
  – May reflect future clinical status
Optical Coherence Tomography

- Widely used to assess retinal and optic nerve pathology
- Currently being studied for use in diagnosing MS and following MS progression
  - Noninvasive, noncontact technique
  - Evaluates qualitative and quantitative changes of the retinal nerve fiber layer (RNFL)
  - Measures axonal pathologic changes
  - Is useful as an outcome in both longitudinal and cross-sectional studies

Optical Coherence Tomography

- OCT is a noninvasive technology that can accurately and reproducibly quantitate the micron thickness of the retinal nerve fiber layer (RNFL).
- Originating from the retinal ganglion cells, unmyelinated central nervous system axons comprise the RNFL.
- RNFL thickness serves as an in vivo biomarker for axonal loss.
- Healthy RNFL thickness is 100-110 mcm; on average, loss of 10 mcm between 10-70 yrs; in MS rate of loss: 10-40 mcm in 1 year.

RNFL thickness declines with increasing neurologic impairment and correlates with disease duration.

“Eyes with a history of acute optic neuritis (MS ON Eyes) demonstrate the greatest reductions in RNFL thickness, MS non-ON eyes are also abnormal... supporting the occurrence of anterior visual pathway axonal loss in MS patients that occurs in the absence of obvious attacks of acute optic neuritis.”

ON=optic neuritis