Etiology, Pathophysiology & Diagnosis of MS

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Multiple Sclerosis

- The most common chronic disease affecting the central nervous system (CNS) in young adults
- MS is an Immune mediated disease
- The hallmark of MS is inflammatory, demyelinating plaques in the CNS
- The plaques are a sign of the underlying damage to the brain and spinal cord = demyelination & degeneration (axonal loss)

Epidemiology of MS

- 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 (>2:1)\(^4\)
- 3/4 of cases present between ages of 15-45

How does MS attack?

- Nerves act like messengers in the body.
- Most healthy nerve fibers (axons) have a shield (myelin) to protect them.
- With MS, the myelin is attacked by the immune system, causing lesions.
- This damage interferes with the messages that are sent by the nerves to the body, causing the major symptoms of MS.

Diagram: How MS attacks

- Normal nerve cell: A normal nerve cell with an intact myelin sheath.
- Nerve cell affected by MS: A nerve cell with damage to the myelin sheath.

Central nervous system (brain and spinal cord)
Genetic Factors & Others are Involved in MS?

- **Genes**
  - Certain genes are associated with MS, e.g. HLA-DR2 in Caucasians

- **Family**
  - Identical twins and siblings of MS patients have increased risk of developing MS

- **Environment**
  - Certain racial groups have a high incidence of MS, whereas others have a low incidence
**MS as Immune Mediated Disease**

- $T_\text{H1}$ cells are stimulated in the periphery by presentation with antigen
  - eg, a virus particle
- Once activated
  - They proliferate
  - They release cytokines and metalloproteinases that break down the extracellular matrix of the BBB
Once in the CNS, TH1 cells

- Are presented with a myelin protein
- The myelin protein is similar to the antigen presented in the periphery
- Become reactivated
- Release damaging cytokines
- Interferon-gamma, TNF-beta, IL-2
- B-cell activity stimulated, antibody production and complement activation
Immune Imbalance in MS

**Normal**
- **Inflammatory**
  - IFNγ, IL-12, TNF
- **Anti-inflammatory**
  - IL-4, IL-10, TGFβ

**MS**
- **Inflammatory**
  - IFNγ, IL-12, TNF
- **Anti-inflammatory**
  - IL-4, IL-10, TGFβ

*Dhib-Jalbut, S*
Pathophysiology of MS

- The pathologic hallmarks of MS lesions include breakdown of the blood brain barrier (BBB), multifocal inflammation, demyelination, oligodendrocyte loss, gliosis, and 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.
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

  J Neurol. 2005;252[Suppl 5]:V/10 – V/15
Demyelination and Axonal Transection

Courtesy of Bruce Trapp
Brain Atrophy in MS

Brain atrophy represents the cumulative effect of:
- Demyelination and axonal loss
- Diffuse, nonfocal tissue damage

Global brain atrophy: 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

Brain Atrophy

- Marker of irreversible tissue damage
- Occurs in the early stages of MS
- Changes over time are small
- Correlated to concurrent and future disability

Diagnosis of MS

Medical history

Neurologic examination

MRI (brain, possible spinal MRI)

Laboratory studies

Evoked potential testing

Lumbar puncture

Medical History

Age/gender/ethnicity

Identify any events that might be indicative of MS-related symptoms

Complete differential diagnosis
Symptoms of Multiple Sclerosis: Neurologic Origins

Symptom presentation depends on lesion location

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

Sensory symptoms: Lhermitte’s pain, proprioception

Diagnosis of MS

MRI

- Can be useful for diagnosis when there have not been 2 clinically proven episodes as required
- Current preferred method of brain imaging
- Detects subclinical lesions in some people
- May identify active inflammation with gadolinium (Gd) contrast enhancement
Diagnostic Criteria for MS

- **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

Disease Progression

- Secondary-progressive
- Relapsing-remitting
- Preclinical

Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity

Disability
Time

Adapted with permission from JS Wolinsky.
Natural History

- Average is 1 relapse per year, fewer over time\textsuperscript{1}
- 25\% of patients never lose ability to perform activities of daily living\textsuperscript{1}
- 15\% become severely disabled in short time\textsuperscript{1}
- Median time to reach EDSS of 6 is 15 years; to reach EDSS of 8 is 46 years\textsuperscript{2}
- Mortality from MS as primary cause is low\textsuperscript{1}

Pooled data of placebo patients from trials

Patients were evaluated prior to, at the time of, and after an acute relapse

42% of patients had residual deficit of at least 0.5 EDSS

28% of patients had residual deficit of $\geq 1.0$ EDSS

EDSS change at $\sim$ average of 64 days after a relapse

Patients that had a measurable change in EDSS during a relapse had more impairment on future follow-up visits

MS relapses produce a measurable and sustained effect on disability

Lublin et al. Neurology 61 pp.1528-1532
Monitoring patients & the disease: Outcomes to Consider

- **Clinical relapses**
  - Frequency/severity and extent of recovery

- **Disease progression**
  - Expanded Disability Status Scale progression

- **MRI activity**
  - Increased disease burden or activity

MRI – Burden of Disease

Axial View

Axial Fluid-Attenuated Inversion Recovery (FLAIR) MRI

Sagital View
How to Measure Progression of Disease

- Well-defined methods (although still evolving as technology and knowledge improves)
  - Disability Rating Scales
    - EDSS (Expanded Disability Status Scale)
    - MSFC (Multiple Sclerosis Functional Composite)
  - MRI changes
    - Gd-enhancing lesions (T1-weighted)
    - Measurement of brain atrophy (using visual analysis of MRI data to estimate brain atrophy)
Expanded Disability Status Scale (EDSS)

Increasing Disease Burden

EDSS Score

0 1 2 3 4 5 6 7 8 9 10

Normal neurologic exam

No disability

Minimal disability

Moderate disability

Fully ambulatory severe disability

Ambulatory without aid 200 m

Ambulatory with unilateral assistance 100 m

Wheelchair

Bedridden

Helpless

Death due to MS

m=meters

## Multiple Sclerosis Functional Composite

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<thead>
<tr>
<th>Clinical Dimension</th>
<th>Test Name</th>
<th>Measurement</th>
<th>Metric</th>
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<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</td>
<td>Number correct</td>
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