Disclosures

- Biogen Idec
- Novartis
- Acorda
- Genzyme
- Roche
- Pfizer
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LIVING WITH MULTIPLE SCLEROSIS
Objectives

- Understanding of the clinical spectrum and diagnosis of multiple sclerosis in adults.
- Understanding of the epidemiology and progression of multiple sclerosis in adults.
- Knowledge of the common complications of multiple sclerosis in adults.
History

St. Lidwina of Schiedam 14th Century
Robert Carswell (1793-1857)
Jean-Martin Charcot (1825-1893)
Louis Ranvier 1878
Uhthoff’s Phenomenon 1901

**FIG. 1.** Wilhelm Uhthoff (seated, center) with his assistants in Breslau. On his left is his nephew, Karl August Uhthoff.
What is Multiple Sclerosis?

Chronic, debilitating, inflammatory, neurodegenerative and eventually progressive disease of the Central Nervous System (CNS)

**Pathophysiology**
- Inflammation
- Myelin destruction
- Axonal transection
- Atrophy

**Clinically**
- Relapses
- Sustained physical disability
- Cognitive dysfunction
MS Subtypes

Relapses With Disability

- Relapsing Remitting: 85%
- Secondary Progressive: 45%
- Primary Progressive: 10-15%

Increasing Disability

(10 years after disease onset)

Disability Progression No Distinct Relapses

*Progressive relapsing, Balo’s concentric sclerosis, Schilder’s disease, and Tumefactive/Marburg
Clinically Isolated Syndrome (CIS)

- 50-80% already fulfill established diagnostic criteria for multiple sclerosis
- Certain syndromes are more common and characteristic for MS including optic neuritis and partial myelitis
- Other noteworthy presentations: Lhermitte’s, MS hug, trigeminal neuralgia, INO, other sensory disturbance, bladder/bowel/sexual dysfunction
Immunopathogenesis of MS

- Inflammation
  - Demyelination
    - Loss of axons
      & gliosis
Pathophysiology: Two Sides of Inflammation

Proinflammatory and neurotoxic factors

- TH1 cytokines
- TNF
- IL-1
- osteopontin
- leukotrienes
- MMP
- plasminogen activators
- nitric oxide
- reactive oxygen species
- glutamate
- antibody + complement
- cell-mediated cytotoxicity
- neurotrophins via p75

Antiinflammatory and neuroprotective factors

- TH2 cytokines
- TGF
- TNF ?
- soluble TNF receptor
- soluble IL-1 receptor
- IL-1 receptor antagonist
- some prostaglandins
- lipoxins
- TIMP
- antithrombin
- BDNF
- NGF
- NT3
- NT4/5
- GDNF
- LIF

Destruction

Protection

Kerschensteiner M et al, Annals of Neurology 2003
Pathophysiology: B Cells

- Antigen presentation resulting in $\text{CD}_4^+ \text{T-cell}$ expansion and cytokine production
- Cytokine production (IL-6, TNF-alpha, and IL-10) that activate macrophages and stimulate further B-cell proliferation
- Differentiation into plasma-blasts and plasma cells
- Evidence for involvement in MS: oligoclonal bands, IgG index and synthetic rate, antibodies to myelin basic protein and other myelin components, and suppression of B cells with rituximab and ocrelizumab appears as effective as natalizumab
Demographics

- US prevalence – 400,000
- 1:1000 – general population
- World prevalence
  - 1.1 – 2.5 million cases
- Female : Male ratio
  - RR – 3:1
  - PP – 1:1
Risk factors for development of MS

- Genetic predisposition
- Environmental factors
- Infectious agent

Abnormal immunologic response → MS
Genetics/Risk

- 30% concordance rate in monozygotic twins
- 5% in dizygotic twins
- 3-4% risk with 1st degree relative
- In addition...
Genetics/Risk

- **HLA association**
  - DRB1*1501: increased risk, female predominance, and earlier disease onset
  - DR15 and DR3: increased risk for relapsing forms
  - DR4 and DR3: increased risk for progression

- **Non-HLA associations**
  - IL7R and IL2R
  - APOE
  - Osteopontin polymorphisms
Environment

Vitamin D
Higher levels of serum 25-hydroxyvitamin D levels associated with lower incidence of developing MS
(Munger et al. JAMA. Dec 2005)

HLA DR and DQ sit in close approximation to the vitamin D receptor (HLA DRB1*1501 is strongest genetic risk factor for MS)

Toxin exposure
No relation with mercury, zinc or organic solvents

Tobacco
Smokers have a two fold increased risk of developing MS compared to non smokers.
(Riise et al. Neurology 2003)

MS smokers convert to secondary progressive MS three times more rapidly than non smokers. (Hernán et al. Brain 2005)
Infectious Etiology

Epstein Barr Virus
- Strongest infectious associations
- Significantly elevated titers in people up to 5 years prior to diagnosis of MS (Ascherio, et al. JAMA 2001)

HSV 1, 2

HHV-6

C. pneumoniae
Clinical characteristics and Diagnosis of MS

Dissemination in Space & Time
# Common clinical presentations

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features</th>
</tr>
</thead>
</table>
| **Optic Neuritis**        | 1. Typically unilateral  
                            2. Typically painful  
                            3. VA recovery expected  
                            4. Retrobulbar  
                            5. No retinal exudates  
                            6. No macular star  
                            7. No disc hemorrhages |
| **Myelitis**              | 1. Partial sensory or motor  
                            2. Sensory common  
                            3. Lhermitte's sign  
                            4. Bowel and bladder dysfunction may be present  
                            5. 'Band-like' abdominal or chest pressure  
                            6. Acute dystonias (rare) |
| **Brainstem/Cerebrum**   | 1. Ocular motor syndromes (e.g. Internuclear ophthalmoparesis/nystagmus)  
                            2. Hemisensory, crossed sensory syndromes  
                            3. Hemiparesis  
                            4. Trigeminal neuralgia  
                            5. Hemifacial spasm |
| **Cerebellum**           | 1. Cerebellar outflow tremor  
                            2. Acute ataxic syndrome |
| **Paroxysmal Symptoms**  | 1. Tonic Seizures  
                            2. Paroxysmal dysarthria/ataxia |
What is the single most important ancillary test in MS?

- Cerebrospinal fluid
- Serology and other
- MRI
- Visual evoked potentials
- Other
**MRI and MS**

- Single most important diagnostic test for evaluation of multiple sclerosis
- Helps form basis of the McDonald criteria

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 attacks(^a); objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack(^b)</td>
<td>None(^c)</td>
</tr>
<tr>
<td>≥2 attacks(^a); objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)(^d); or Await a further clinical attack(^a) implicating a different CNS site</td>
</tr>
<tr>
<td>1 attack(^a); objective clinical evidence of ≥2 lesions</td>
<td>Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack(^a)</td>
</tr>
<tr>
<td>1 attack(^a); objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)(^d); or Await a second clinical attack(^a) implicating a different CNS site; and For D1: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack(^a)</td>
</tr>
<tr>
<td>Insidious neurological progression suggestive of MS (PPMS)</td>
<td>1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria(^e): 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligodendral bands and/or elevated IgG index)</td>
</tr>
</tbody>
</table>
MRI

Commissural Plaques

Juxtacortical Plaques

Open-ring Plaques

Closed-ring Plaques
Radiographic Signatures of MS
Cervical Skip Lesions
MRI

Brain Atrophy

Gray matter lesions


Courtesy of K Rammohan, MD.
Atypical MRI
Number and Volume of Asymptomatic Lesions on T2-Weighted MRI of the Brain at Presentation in Patients with Isolated Syndromes, and their Clinical Outcome After 14 Years

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>No. and Median Volume of Asymptomatic Lesions at Base Line*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (0 cm³) (N = 21)</td>
</tr>
<tr>
<td></td>
<td>1-3 (0.6 cm³) (N = 18)</td>
</tr>
<tr>
<td></td>
<td>4-10 (0.9 cm³) (N = 15)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 (5.6 cm³) (N = 17)</td>
</tr>
<tr>
<td>Isolated syndrome - no. (%)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Clinically probable multiple sclerosis - no. (%)</td>
<td>1 (6)</td>
</tr>
<tr>
<td></td>
<td>2 (13)</td>
</tr>
<tr>
<td>Clinically definite multiple sclerosis - no. (%)</td>
<td>4 (19)</td>
</tr>
<tr>
<td></td>
<td>16 (89)</td>
</tr>
<tr>
<td></td>
<td>13 (87)</td>
</tr>
<tr>
<td></td>
<td>15 (88)</td>
</tr>
<tr>
<td>EDSS score - no.</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>0</td>
</tr>
<tr>
<td>&gt;6</td>
<td>5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Median EDSS score</td>
<td>1.75</td>
</tr>
<tr>
<td>Range if EDSS scores</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

*The median volume was included when available  Brex et al, N Engl J Med, Vol. 346:158-164
What about CSF and oligoclonal bands?
# Oligoclonal bands in Neurologic Disease

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Approximate incidence of oligoclonal bands (%)</th>
<th>Suggested supplementary investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>98</td>
<td>MRI</td>
</tr>
<tr>
<td>SSPE</td>
<td>100</td>
<td>Anti-measles antibody</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>95</td>
<td>Anti-treponemal antibody</td>
</tr>
<tr>
<td>Neuro-AIDS</td>
<td>80</td>
<td>Anti-HIV antibody</td>
</tr>
<tr>
<td>Neuro-Lyme disease</td>
<td>80</td>
<td>Anti-borrelia antibody</td>
</tr>
<tr>
<td>Neuro-SLE</td>
<td>50</td>
<td>Anti-nuclear factor</td>
</tr>
<tr>
<td>Neuro-Behçet's disease</td>
<td>20</td>
<td>C3 and CSF polymorphs</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>60</td>
<td>Serum IgA</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>100</td>
<td>Long-chain fatty acids</td>
</tr>
<tr>
<td>Harada's meningitis-uveitis</td>
<td>60</td>
<td>Serum CRP</td>
</tr>
<tr>
<td>Neuro-sarcoid</td>
<td>&lt;5</td>
<td>Kveim test</td>
</tr>
<tr>
<td>Acute encephalitis (&lt; 7 days)</td>
<td>&lt; 5</td>
<td>Viral antibody</td>
</tr>
<tr>
<td>Acute meningitis (&lt; 7 days)</td>
<td>&lt; 5</td>
<td>CSF lactate, serum CRP</td>
</tr>
<tr>
<td>Tumour</td>
<td>&lt; 5</td>
<td>Brain scan</td>
</tr>
</tbody>
</table>
Other studies as indicated

- RPR, ESR, CRP, ANA, dsDNA, SSA/SSB, ACE, Lyme, etc.
- CXR, Ocreotid/PET scan
- VEP, SSEP, BAEP
- And others
Diagnosis

Clinical
Supported by MRI* and laboratory findings

Diagnosis of exclusion
Must rule out mimickers

“Normal” MRI ≠ no MS
Diagnosis of Multiple Sclerosis
- red flags in history and examination -

- Normal neurological examination
- Clinical signs attributable to a single CNS location
- Progression from onset
- Onset in early childhood or over age 50
- Systemic disease present
- Prominent family history of MS
- Prominent grey matter symptoms: Dementia, seizures, aphasia
- Peripheral symptoms
- Lack of typical symptoms (eye, bladder, sensory, Lhermitte)
Diagnosis of Multiple Sclerosis
- red flags in laboratory and imaging tests -

• Normal or MS-atypical CSF (e.g. pleocytosis >50 cells)
• Normal or MS-atypical MRI
• Abnormal blood tests (CRP, ESR very high)
• Normal evoked potentials (VEPs)
Natural History

- Benign MS – 10% will have minimal disability for 20+ years
- Malignant MS – 5% at 5 years with significant disability
- About 50% will be dependent on a walking aid within 15 years of disease onset
- 90% of patients with RR-MS will eventually (over 25 years) develop SP-MS
- 45-65% of patients will develop cognitive difficulties over 10 years
- 50-80% of CIS patients have occult lesions
- Atrophy, number, and volume of lesions early in the disease course is associated with a greater risk of disability.

Weinshenker et al. *Brain.* 1989;112:133
Characteristics of ‘Milder’ Disease Course

Female
Younger age of onset (<40 yrs old)
Caucasian (vs African-American)
Sensory symptoms
Absent or low lesion burden on MRI at presentation
Complete recovery from 1\textsuperscript{st} relapse
Longer interval to 2\textsuperscript{nd} relapse
Fewer relapses in earliest phase of disease
Low level of disability at 5 to 7 yr milestone
More ‘Aggressive’ Risk Factors

- Male
- Older age at onset (>40 yrs old)
- Motor, cerebellar, or sphincter symptoms at onset.
- Multifocal disease at onset
- Higher lesion burden on MRI at presentation
- Progressive course
- Frequent attacks within 1st five years
- Shorter interval to reach EDSS 4
MS complications

- Fatigue
- Neurogenic bladder: Neurogenic overactivity, DSD, urinary retention
- Falls
- Cognitive impairment
- Heat sensitivity
- Wounds
- Depression
- Spasticity
- Weakness
- Tremor and ataxia

- Pain
- Social isolation
- Loss of employment
- Drug complications
  - PML (natalizumab, BG12)
  - Skin changes (injectables)
  - Liver injury
  - Macular edema and bradyarrhythmias (fingolimod)
  - Heart failure and malignancy (mitoxantrone)
Effect of MS Therapies on Relapse Rate: Phase III Results

Note: These trials were not designed for comparison of data across studies.

*Patients who completed 2 years in the study; †Intent to treat; ‡FDA reported results using 3-year phase III data.

Thank you.