Multiple Sclerosis

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MS Epidemiology

- Worldwide distribution varies
- Discontinuity in risk related to latitude
- Risk acquired in country of origin by 15 years
  - South African
  - Israel
- Highest prevalence in Orkney Islands (250/100,000)
- Higher prevalence in Caucasians in US
- Rare in Japan (2/100,000)
- Rarer still in Africa
Worldwide Prevalence of MS
MS Epidemiology

- Within USA, incidence and prevalence
  - N of $37^\circ = 5/100,000$ and $69/100,000$
  - S of $37^\circ = 3/100,000$ and $35/100,000$

- Annual prevalence (U.S.) 250,000 to 350,000

- MS kills > 3,000 Americans annually

- 2nd m.c. neurologic disability in early & middle adulthood

- Female to Male ratio of 1.4/1 to 2.0/1

- Age of onset
  - 0.3 to 04% in early childhood
  - peaks in early fourth decade
  - declines dramatically after age 60
MS Epidemiology - The Faroe Islands

- MS not present in Faroes prior to WWII
- Outbreak after with following point prevalences
  - 41 in 1950  64 in 1961
  - 38 in 1972  34 in 1977
- British troops garrisoned on island
- MS cases in close proximity to British troops
- MS cases resided more often in small communities
- Outbreak of canine distemper at same time
- Data suggests viral illness (Kurtzke)
<table>
<thead>
<tr>
<th>Viruses Associated with MS by Serological Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
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<tr>
<td>Mumps</td>
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<tr>
<td>Canine distemper virus</td>
</tr>
<tr>
<td>Parainfluenza 1 &amp; 3</td>
</tr>
<tr>
<td>Rubella</td>
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<tr>
<td>Influenza A,B,C</td>
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<tr>
<td>Herpes zoster virus</td>
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<tr>
<td>Adenovirus</td>
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<tr>
<td>Epstein-Barr virus</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Polyoma virus</td>
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<tr>
<td>Coronavirus</td>
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<tr>
<td>Vaccinia</td>
</tr>
<tr>
<td>HTLV-I</td>
</tr>
<tr>
<td>Paramyxovirus SV5</td>
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<tr>
<td>Retrovirus (HRES-1)</td>
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</tbody>
</table>
MS Epidemiology - Genetics

- Family history as a risk factor
- Higher rates if index case is female

**Relationship**
- General population: 0.1%
- Sibling: 2.0% (20 X)
- Fraternal twin: 2-12%
- Identical twin: 21-70%
- Child of MS patient: 1.0%
- Aunt/Uncle: 2.0%
- Niece/Nephew: 0.4%
- Conjugal: rare
MS Epidemiology - Genetics

- MHC Class and disease risk correlation
  - Varies with population studied
  - N. Europeans
    - Class I HLA A3 and B7
    - Class II HLA DR2 and DQw1

- V region genes for immunoglobulins

- T cell receptor at V\(\alpha\) and V\(\beta\) loci

- Other possibilities include
  - TNF\(\alpha\)
  - MBP
  - BcG locus
Schumacher Criteria for MS (1965)

- Designed for therapeutic trials
- Six criteria
  - Ages between 10 and 50 years
  - Objective abnormalities on neurological exam
  - Two or more separate lesions in the CNS
  - Predominantly involve the white matter
  - 2 episodes separated by >1 mos, lasting >24 hrs or progression over 6 months time
  - No better explanation for disorder
## McDonald Criteria 2002

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 attacks; obj. clinical evid of ≥2 lesions</td>
<td>None</td>
</tr>
<tr>
<td>≥2 attacks; obj. clinical evidence of 1 lesion</td>
<td>MRI evidence of dissemination in space <em>or</em> 2 lesions on MRI and +CSF</td>
</tr>
<tr>
<td>1 attack; obj. clinical evidence of ≥2 lesions</td>
<td>Dissemination in time by MRI or 2\textsuperscript{nd} clinical attack</td>
</tr>
<tr>
<td>1 attack; obj. clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space by MRI <em>or</em> ≥2 MRI lesions and +CSF <em>or</em> 2\textsuperscript{nd} attack</td>
</tr>
<tr>
<td>Insidious neurological progression suggesting MS</td>
<td>+CSF and dissemination in space by MRI <em>or</em> abnormal VEP with MRI having &lt;4 lesions and dissemination in time by MRI <em>or</em> continued progression over 1 yr</td>
</tr>
</tbody>
</table>
Table 1. Magnetic Resonance Imaging Criteria for Brain Abnormality

Three of four of the following
1. One gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium enhancing lesion
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least three periventricular lesions

Note: One spinal cord lesion can be substituted for one brain lesion. Data from Barkhof et al\textsuperscript{6} and Tintoré et al.\textsuperscript{7}

Table 2. Magnetic Resonance Imaging Criteria for Dissemination of Lesions in Time

1. If a first scan occurs 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T2- or gadolinium-enhancing lesion at this time then fulfills the criterion for dissemination in time.
2. If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice.
Triggers of MS Attacks

- Viral infections
- First 3 months of postpartum period
- $\gamma$-interferon and other lymphokines
  - $\gamma$-IFN study (K Johnson) 30-40% developed exacerbations within 4-6 weeks
  - $\gamma$-IFN down-regulated by $\beta$-IFN
- No epidemiologic support for these factors:
  - Stress
  - Trauma (physical injury rate 2-3X that of non-MS)
  - Vaccinations (hepatitis B and swine flu)
Model of MS Immunopathogenesis: Targets for Therapy of CNS Autoimmune Disease

1. Activation
2. Adhesion
3. Attraction
4. Invasion
5. Reactivation

Periphery

BBB

CNS

Bar-Or A, 2001
Cells Involved in MS Lesion Generation
MS Pathology

- Vary in size from < 1 mm to several cms
- Sharply delineated margins, “plaque”
- Confluence of small perivenous foci
- Preservation of axis cylinders
- Degeneration of oligodendroglia
- Astrocytic reaction
- Perivascular inflammation
- “Shadow plaques”

Locations
- periventricular, particularly, corpus callosum
- ON & chiasm, brainstem, sp cd, cerebellar peduncles
Multiple Sclerosis Pathology

Multiple periventricular and WM lesions

Small subcortical plaque
MS Pathology

Various brain stem lesions
Multiple Sclerosis Histopathology
MS Histopathology

Perivascular inflammation
Clinical and MRI Course in MS

- CIS
- RRMS
- SPMS

Clinical Threshold

Relapses and Disability

MRI

- T2 Burden
- Axonal loss
- △ MTR
- Brain Volume
- Gado +

Bar-Or A, 2002
Clinically Isolated Syndromes

- Isolated involvement of a region of the CNS
  - optic neuritis, brainstem, spinal cord

- Risk of development of MS related to baseline MR and CSF OCBs
  - CIS-MRI+ have 80% likelihood of progression in 10 years v. 20% with MRI–
  - MRI lesion load correlates crudely with disability at 5 years
  - in ON, +CSF OCBs increase likelihood of MS even with MRI–
MS Clinical Course

Categories

- **Relapsing remitting MS (RRMS) - 70%**
  - recovery between attacks; slow accretion of deficit
  - 0.4-1.1 relapses/year (1.5-2.3/year for first year)

- **Secondary progressive (SPMS)**
  - relapsing progressive
  - attacks at onset with increasing deficit

- **Primary chronic progressive (PCPMS) - 15%**
  - slow steady progression

- **Acute (malignant) MS**
  - polysymptomatic disease at onset that progresses

- **Benign MS**
  - no significant deficit after 10-15 years
Progression of Neurological Disability

Progression Rate of Neurological Disability in MS Patients
Lyon Cohort (1844 patients) Confavreux et al., NEJM (2000)

EDSS 4.0-7.0
Mean = 12.1 yrs
(Range 10-14)

EDSS 0.0-4.0
Mean = 11.4 yrs
(Range <1-31)

Years

EDSS
Disease progression

- **ONSET**
  - PPMS 15%
  - RRMS 85%

- **AFTER 10 YEARS**
  - PPMS 15%
  - SPMS 40-45%
  - RRMS 40-45%
MS – Prodromal Symptoms

- Limb pains
- Irritability
- Poor memory
- Weight loss
- Fatigue
  - unprovoked “lassitude”
  - may develop after minimal activity
  - worse in heat and high humidity
MS - Initial Manifestations

- Protean manifestations
- Monosymptomatic 45% vs. Polysymptomatic 55%

Initial symptoms (McAlpine 1972)
- weakness in one or more limbs 72%
- optic neuritis 22%
- paraesthesiae 21%
- diplopia 12%
- vertigo 5%
- disturbance of micturition 5%
Optic Neuritis

- pain behind eye common and may occur first
- typically begins as rapid visual loss
  - cecocentral scotoma
  - occasionally slowly progressive over weeks
- occasionally both optic nerves involved either simultaneously or within days to weeks
- improvement over 2 weeks
- 1 in 8 have repeated attacks of ON
- 1/2 will develop other signs of MS
  - 74% of women and 34% of men within 15 yrs
Optic Neuritis

Persistent Abnormalities
- optic disk pallor
- reduction in light intensity associated with Marcus Gunn pupil
- loss of color vision (Ishihara plates)
- bright lights cause a prolonged afterimage
- "movement phosphenes"
- depth perception impaired, particularly with movement (Pulfrich phenomenon)
The Marcus Gunn Pupil

Normal disk OD; Optic atrophy OS  
 Levatin’s swinging flashlight test
Acute Transverse Myelitis

- rapidly evolving over hours to days
- 1/3 report preceding viral illness
- initial sx: parasthesiae, back pain, leg weakness
- common signs: sensory level, sphincter dysfunction, leg weakness, Babinski’s sign
- maximal deficit within 1 d in 37%; 1-10 d in 45%; and >10 d in 18%
- <50% with asx lesion elsewhere in CNS
- outcome good 42%; fair 38%; poor 20%
- 7% to 50% develop MS
MS Cerebellar Symptoms and Signs

- part of Charcot’s triad
  - scanning speech, intention tremor, and nystagmus
- uncommon as an initial manifestation
- present in 37% at first exam (McAlpine)
- pure cerebellar disease unlikely to be MS
- early appearance bad prognostic sign
- cerebellar signs frequently persist
Paroxysmal symptoms in MS

- Trigeminal neuralgia
- Paroxysmal dysarthria
- Paroxysmal ataxia
- Tonic seizures
- Paresthesiae
- Visual loss
  - Uhthoff's phenomenon
- Diplophia
- Itching
- Pain
- Akinesia
- Epileptic seizures
Evolution of MS lesions over time
Brain Atrophy in Untreated MS
One should no more tell our patients they have multiple sclerosis than we should tell them they have inoperable cancer...When I have to make the diagnosis of multiple sclerosis, I make it to the relations, not to the patient; and I try to defend the patient from hearing the name because once the name is heard, it is vested with lamentable result.
And I certainly agree with him that the diagnosis should never be told to the patient unless it is absolutely essential to that patient for the arrangement of his life, and that the facts should be explained to the family.

H. Houston Merritt, M.D.
Optic Neuritis

- multicenter placebo controlled trial
  - IV MP 250 mg q6h X 3 d w/OP (1mg/kg) for 11 d
  - Vs. oral prednisone (1mg/kg) for 14 d
  - Vs. placebo for 14 d

- rate of definite MS development in 2 yrs
  - MP 7.5%
  - OP 14.7%
  - PL 16.7%

- signal abnormalities on MRI strong risk factor;
  MP most helpful in this group

- vision recovered quicker with MP, no difference in visual outcome at 6 mos

[Beck et al NEJM 1993]
Treatments for MS: An Advancing Landscape
From 5 to 15 Products for MS by 2012 ...

Dates refer to approval for U.S. market
Treatments for MS: An Advancing Landscape
From 5 to 15 Products for MS by 2012 ...

**Injectables**
- Rebif
- Betaseron
- Copaxone
- Avonex
- Novantrone (US)
- Tysabri®

**Orals**
- Oral Fumarate
- Cladribine
- Laquinimod
- Teriflunomide
- Oral Tau IFN

**Non Orals**
- Enhanced IFN Formulations
- Daclizumab
- Alemtuzumab
- Rituximab
- Biosimilars EU
- Biosimilars US
- Mitoxantrone

**Approved**

**Phase III**

**Phase II**
Yong, *Neurology*, 2002

**T<sub>H</sub>1 Cytokines**
- Pro-inflammatory
- IL-2
- IL-12
- IFN-γ
- TNF-α

**T<sub>H</sub>1 Cytokines**
- IL-12
- Naïve T cell

**T<sub>H</sub>2 Cytokines**
- Anti-inflammatory (regulatory)
- IL-4
- IL-10
- IL-13
- TGF-β

**Macrophage**

**B cell**

**T<sub>H</sub>1**

**T<sub>H</sub>2**

**Naïve T cell**
Yong, *Neurology*, 2002
Current Opinion of the Hypothetical Effect of Treatment

- Natural course of disease
- Later intervention
- Intervention at diagnosis
- Treatment at diagnosis
- Later treatment
Each Efficacy Measure Is Important in Evaluating Treatment Outcome in Clinical Trials

*The exact relationship between MRI findings and the clinical status of patients is unknown.
The Future of MS Therapy

- **Immune-directed therapies**
  - Immune ablation with reconstitution
  - Immunosuppression
  - Immunomodulation
  - Suppression of cell entry into CNS

- **Neuroprotective therapies**

- **Myelin repair strategies**
### Newer Immune Directed Therapies for MS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Proposed Mechanism</th>
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<tbody>
<tr>
<td>Rituximab (MAb to CD20)</td>
<td>Depletes B cells</td>
</tr>
<tr>
<td>Daclizumab (MAb to CD25)</td>
<td>Blocks IL-2 receptor and interferes with T cell activation</td>
</tr>
<tr>
<td>Alemtuzumab (MAb to CD52)</td>
<td>Long term T cell and transient B cell depletion</td>
</tr>
<tr>
<td>Cellcept (Mycophenolate)</td>
<td>Cytostatic for T and B lymphocytes</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Inhibits activated T cells</td>
</tr>
<tr>
<td>Fingolimod (FTY 720)</td>
<td>Sphingosin-1 phosphate receptor agonist alters immune cell homing</td>
</tr>
<tr>
<td>CDP 323</td>
<td>Blocks T cell migration into CNS (α4 integrin inhibition)</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>Inhibits CD4 and МΦ entry into CNS</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Purine nucleoside – specific lymphocyte toxicity</td>
</tr>
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Natalizumab Primary MOA

Natalizumab: VLA4 or α4β1 integrin antibody

Blocking the VLA4 receptor, prevents T cell entry into CNS
Recommendations for Surveillance of Newer MS Therapies

Maintain a high level of vigilance for the following

- Opportunistic infections
- Alteration in expression of other infections
  - Community-acquired infections
  - Emerging infections, e.g., West Nile virus
- Altered response to vaccination
- Solid malignancies
- Lymphoproliferative disorders
- Autoimmune disorders
- Other unusual adverse events