MS: Diagnosis and Treatment Update

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What is MS?
Multiple Sclerosis

- Multiple Sclerosis is a chronic inflammatory disease of the central nervous system, the brain and the spinal cord.
- It is a dysfunction of the immune system which leads to attacks against, and causes destruction of the myelin sheath.
### Demographics of MS

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>15 to 45 years</td>
</tr>
<tr>
<td>Gender</td>
<td>70% women</td>
</tr>
<tr>
<td>US incidence cases</td>
<td>8,500 to 10,000 new cases per year</td>
</tr>
<tr>
<td>US prevalence</td>
<td>400,000</td>
</tr>
<tr>
<td>Life time risk</td>
<td>0.5% for women and 0.3% for men</td>
</tr>
<tr>
<td>Familial MS</td>
<td>5-10% in first degree relative, twins 20-30%</td>
</tr>
</tbody>
</table>

What causes MS?
Potential Triggers for Multiple Sclerosis

Infectious agent → Genetic predisposition → Abnormal immunologic response → MS

Environmental factors
Causative factors in Multiple Sclerosis

• Numerous environmental factors studied
  — Infection- EBV, HHV-6, Chlamydia pneumoniae
  — Immunization
  — Physical and emotional stress
  — Climate-sunlight exposure inversely linked to the risk
  — Diet
  — Occupational exposure

No single factor identified as causal factor
Genetic factors in MS

- In 1970s, human leukocyte antigens (HLA) linked to genetic susceptibility
- Alleles of IL2RA and IL7RA may be heritable risk factors for multiple sclerosis

Vitamin D and MS

- Vitamin D has role in regulating the immune system
- Activation of vitamin D receptors
  - down-regulates Th1 mediated production of IL-2 and IFN-γ
  - up-regulates Th2-mediated anti-inflammatory cytokine production, IL-4
- Protective against EAE
Vitamin D and MS

- 2004 study: women taking vitamin D supplement have a 40% reduced risk of developing multiple sclerosis
- 2006 study: higher vitamin D levels in Caucasians were associated with lower rates of multiple sclerosis

Vitamin D and MS gene

- Interaction between vitamin D and a common genetic variant DRB1*1501 may affect risk of MS
- The risk increases from 1 in 1,000 in general population to
  - 1 in 300 among people with single copy of the DRB1*1501
  - 1 in 100 with two copies
  - Proteins activated by vitamin D bind to a particular DNA sequence next to the DRB1*1501 variant, causes the gene to switch on
- In people with the DRB1 variant associated with MS, the gene may not function properly due to less vitamin D

Ramagopalan et al, PLoS Genetics, Feb 2009
Vitamin D and MS

- Vitamin D deficiency in mothers or in a previous generation may lead to altered expression of DRB1*1501 in offspring
- Vitamin D supplements during pregnancy and the early years may reduce the risk of child developing MS in later life
- The risk of MS lower among women born to mothers with high milk or vitamin D intake during pregnancy

Ramagopalan et al, PLoS Genetics, Feb 2009
Mirzaei et al, AAN 2010, IN2-2.003
What are the symptoms of MS?
Main symptoms of Multiple sclerosis

**Central:**
- Fatigue
- Cognitive impairment
- Depression
- Unstable mood

**Visual:**
- Nystagmus
- Optic neuritis
- Diplopia

**Speech:**
- Dysarthria

**Throat:**
- Dysphagia

**Musculoskeletal:**
- Weakness
- Spasms
- Ataxia

**Sensation:**
- Pain
- Hypoesthesias
- Paraesthesias

**Bowel:**
- Incontinence
- Diarrhea or constipation

**Urinary:**
- Incontinence
- Frequency or retention
MS Symptoms Vs Relapses... How Are They Different?

- **MS symptoms** are chronic or ongoing indicators of MS lesion damage to certain areas of the brain and/or spinal cord.
  - Infection, fever, and heat can increase symptoms and may mimic a relapse.

- **MS relapses** are sudden flare-ups or attacks during which the symptoms get worse or new symptoms appear that typically last several days to several weeks.
What are the types of MS?
Classification of disease subtypes

1. Benign Multiple Sclerosis
2. Relapsing Remitting Multiple Sclerosis
3. Secondary Chronic Progressive
4. Primary Progressive (10 - 20% of patients)
Benign Multiple Sclerosis

- Relapsing subtype
- Female sex
- Younger age at onset (before age 40)
- Prolonged remission after first attack
- Infrequent relapses
- Mild relapses, optic neuritis or sensory symptoms
- Good recovery
- Little disability over 25 years
- Low lesion load on MRI
Prognostic factors

- Progressive disease
- Higher relapse rate
- Development of disability in the first 5 years
- Shorter time before second relapse
- Multisystem involvement
- In secondary progressive MS: shorter time to progression

How do you diagnose MS?
Diagnosis of MS: Basic Principles

- Clinical diagnosis: evidence of dissemination of lesions in space and time: clinical or radiological
- No definitive laboratory test
  - Clinical profile
  - Laboratory evaluation to rule out other diagnoses
  - CSF analysis: IgG index, synthesis rate, OCB

Diagnosis of Multiple Sclerosis

<table>
<thead>
<tr>
<th>One or more episodes?</th>
<th>First clinical episode</th>
<th>Subsequent clinical episode</th>
<th>Paraclinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two</td>
<td>1 site affected</td>
<td>Different sites affected</td>
<td>Not required</td>
</tr>
<tr>
<td></td>
<td>1 site affected</td>
<td>Same site affected</td>
<td>Lesions disseminated in space on MRI</td>
</tr>
<tr>
<td></td>
<td>&gt;=2 sites affected</td>
<td>None</td>
<td>(if CSF positive, MRI criteria less rigorous) AND</td>
</tr>
<tr>
<td></td>
<td>1 site affected</td>
<td>None</td>
<td>Lesions disseminated in space on MRI</td>
</tr>
<tr>
<td></td>
<td>Insidious progression</td>
<td>None</td>
<td>(if CSF positive, MRI criteria less rigorous) AND</td>
</tr>
<tr>
<td></td>
<td>suggestive of multiple sclerosis</td>
<td></td>
<td>Lesions disseminated in time on MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>Positive CSF AND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lesions disseminated in space on MRI (if VEP abnormal, MRI criteria less rigorous) AND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lesions disseminated in time on MRI OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>continued progression for 1 year</td>
</tr>
</tbody>
</table>

**Investigations**

- **MRI scan**
- **CSF**
  - Normal
  - Abnormal
  - Oligoclonal bands absent
    - CSF
    - Plasma
  - Oligoclonal bands present
    - CSF
    - Plasma

- **VEP**
  - Normal
  - Abnormal
  - P100 wave latency:
    - 50 msec
    - 107 msec
    - 194 msec
The 2005 Revised McDonald Diagnostic Criteria for MS

<table>
<thead>
<tr>
<th>Attacks</th>
<th>Clinical lesions</th>
<th>Requirements for diagnosis MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>2 or more</td>
<td>None</td>
</tr>
<tr>
<td>2 or more</td>
<td>1 lesion</td>
<td>Dissemination in space demonstrated by MRI (or CSF or await further attack)</td>
</tr>
<tr>
<td>1 attack</td>
<td>2 lesion</td>
<td>Dissemination in time demonstrated by MRI (or second clinical attack)</td>
</tr>
<tr>
<td>1 attack</td>
<td>1 lesion</td>
<td>Dissem in space and time demonstrated by MRI (or CSF and second attack)</td>
</tr>
<tr>
<td>0 attack</td>
<td>Insidious neurological progression suggestive of MS</td>
<td>2 out of 3 of following: Positive brain MRI Positive spinal cord MRI Positive CSF</td>
</tr>
</tbody>
</table>

Diagnoses That Mimic MS

- **Infection**
  - Lyme disease
  - Neurosyphilis
  - PML, HIV, HTLV-1
- **Inflammatory**
  - SLE
  - Sjögren’s
  - Other CNS vasculitis
  - Sarcoidosis
- **Metabolic**
  - Vitamin B<sub>12</sub> and E deficiencies
- **CADASIL, other rare familial diseases**
- **CNS lymphoma**
- **Cervical spondylosis**
- **Motor neuron disease**
- **Myasthenia gravis**

Use of MRI in Diagnosis

- MRI is used to improve confidence in a clinical diagnosis of MS or to make a diagnosis of MS in clinically isolated syndromes\(^1\)
- May show dissemination of lesions in space
- Demonstrate dissemination in time (eg, new or enhancing lesions on follow-up MRI)\(^1\)
- Total lesion load at diagnosis tends to be predictive of future disability\(^2\)

MRI: Optic Neuritis
MRI in MS
Conventional MRI in MS Clinical Practices

T1 Gadolinium Contrast Image

- **Focal disruption of BBB**
- Leakage of Blood Brain Barrier (BBB)
- Acute inflammation
- **Contrast Enhancing Lesion (CEL) frequency:**
- Weak correlation with disability
- CEL tend to decline with age; duration of disease

*Lancet* 1999; 353 (1957): 964-969
Conventional MRI in MS Clinical Practice: T2 Weighted Image

**Burden of Disease**
- Highly sensitive
- Nonspecific
- Gliosis, axonal loss
- Edema, inflammation
- Demyelination, remyelination

**Lacks Pathological Specificity**
- Weak correlation with disability (SRCC 0.15-0.2)

T2 Weighted Image: Demyelination versus Ischemic brain lesions

http://www.uninet.edu/cin2003/conf/csierra/csierra.html
1. Most severe tissue damage (axonal loss)

2. Strongest correlation with progression of disability (SRCC: 0.7 RRMS; 0.81 SPMS)

3. Acute Hypointensities (less than 6 months, reversible tissue damage)

4. Chronic Black Holes (6 months or more, irreversible tissue damage)

Van Walderveen, et al. Neurol 1998; 50:1282-
Brain Atrophy

Treatment of MS
Treatment of Multiple Sclerosis

- Early treatment is key

Graph showing the progression of disease over time with different treatment scenarios:
- Treatment at diagnosis: lowest progression
- Later treatment: moderate progression
- Untreated natural course of MS: highest progression
- Delayed treatment: lower progression compared to untreated but higher than later treatment
Multiple Sclerosis: treatment

Disease modifying therapy
- can be considered as preventive therapy

Symptomatic treatment
- to help ongoing symptoms
Disease Modifying Therapies

- Aim to alter the natural course of the disease
  - Decrease relapses and MRI lesions
  - Delay disability
- Two classes of disease-modifying medications:
  - Immunomodulators
  - Immunosuppressants

MS Immunotherapy

- Immunomodulation
  - Interferon beta-1b (Betaseron®), Interferon beta-1a (Avonex®, Rebif®)
  - Glatiramer acetate (Copaxone®)
  - Natalizumab (Tysabri®)

- Nonspecific immunosuppression
  - Corticosteroids
  - Mitoxantrone (Novantrone®)
  - Cyclophosphamide (Cytoxan®)

- Experimental therapies* 

*These drugs do not have FDA approval for use in MS.
MS Therapy: Immunomodulators

- Six FDA approved therapies
  - Four platform therapies: ABCR drugs
  - Three of them are called interferons: **Avonex®, Betaseron®, and Rebif®**
  - **Copaxone**: protein similar to myelin
  - Natalizumab (Tysabri®): approved for relapsing MS but reserved for worsening MS
  - Mitoxantrone (Novantrone®): indicated for worsening relapsing and secondary progressive MS

Other Treatment Options for MS

- Other potential MS therapies
  - Intravenous immunoglobulin G (IVIG)
  - Plasmapheresis
  - Cyclophosphamide (Cytoxan®)
  - Azathioprine (Imuran®)
  - Methotrexate
  - Mycophenolate mofetil (Cellcept®)
  - Monoclonal antibodies
  - Cladribine
Mechanism of Action
Immunopathogenesis of MS
Cytokine Imbalance in MS

Normal

- Th1
  - Inflammatory
    - IFN-γ
    - IL-12
    - TNF
  - Anti-inflammatory
    - IL-4
    - IL-10
    - TGF-β
- Th2

MS

- Th1
  - Inflammatory
    - IFN-γ
    - IL-12
    - TNF
  - Anti-inflammatory
    - IL-4
    - IL-10
    - TGF-β
- Th2
Effects of IFN-β at Blood-Brain Barrier

Adapted from Yong VW. Neurology. 2002;59:802-808.
Effects of Copaxone at Blood-Brain Barrier

Adapted from Yong VW. Neurology. 2002;59:802-808.
IF natalizumab blocks the VLA4 receptor, then the T cell does not cross the BBB.
## Treatment Schedules for MS Therapies

<table>
<thead>
<tr>
<th>Product</th>
<th>Treatment schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVONEX® (Interferon beta 1-a)</td>
<td>1 injection IM weekly</td>
</tr>
<tr>
<td>Betaseron® (Interferon beta 1-b)</td>
<td>3-4 injections SC weekly</td>
</tr>
<tr>
<td>Rebif® (Interferon beta 1-a)</td>
<td>3 injections SC weekly</td>
</tr>
<tr>
<td>Copaxone® (Glatiramer acetate)</td>
<td>7 injections SC weekly</td>
</tr>
<tr>
<td>Tysabri® (Natalizumab)</td>
<td>IV infusion every 4 weeks</td>
</tr>
</tbody>
</table>
# Medication Guide for Patients

## Adverse Complications

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Avonex</th>
<th>Betaseron</th>
<th>Rebif</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like Symptoms</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Depression</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Blood Problems</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Liver Abnormalities</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Thyroid Dysfunction</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Seizures</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Heart Problems</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Injection Site Problems</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
<tr>
<td>Risk to Pregnancy</td>
<td>📐</td>
<td>📐</td>
<td>📐</td>
</tr>
</tbody>
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Long-term Safety and Tolerability Issues: IFN’s

- Flulike syndrome (fever, chills, fatigue)
  - Experienced by up to 75% of patients taking an IFN-β
- Injection-site reaction and necrosis
- Depression
- Liver function and bone marrow abnormalities
- Neutralizing antibodies

Freedman M. Presented at: The American Academy of Neurology 52nd Annual Meeting; April 29-May 6, 2000; San Diego, Calif.
Long-term Safety and Tolerability Issues: Copaxone®

- Injection-site reactions
- Immediate post-injection reaction

Important Safety Information

Copaxone® (Glatiramer Acetate)

The most common side effects of Copaxone are redness, pain, swelling, itching, or a lump at the site of injection, flushing, chest pain, weakness, infection, pain, nausea, joint pain, anxiety, and muscle stiffness. These reactions are usually mild and seldom require professional treatment. Be sure to tell your doctor about any side effects.

Some patients report a short-term reaction right after injecting Copaxone. This reaction may involve a flushing (feeling of warmth
Long-term Safety and Tolerability Issues: Tysabri®:
Progressive Multifocal Leukoencephalopathy (PML)

- Rare demyelinating disease commonly caused by reactivation of a latent polyomavirus known as JC virus (JCV)
- Initially reported in 2 patients who received Tysabri® in clinical trials, among 1869 patients with MS
- Third case occurred among 1043 patients with Crohn’s disease
- All three patients exposed to concomitant
Natalizumab (Tysabri®) and PML

- Post-marketing: 46 new cases of progressive multifocal leukoencephalopathy (PML) in patients receiving natalizumab monotherapy in Europe and US since its reintroduction (July 2006)

- Most patients had received natalizumab for more than 1 year

- Natalizumab monotherapy may confer a lower risk of PML than when natalizumab is used together with other immunomodulatory medications
Should all MS patients be treated?
MS treatment

● Disease modifying therapy currently indicated for
  ● Relapsing-remitting MS (RRMS)
    ● Phase III trials of Interferon and GA (Copaxone®)
  ● Clinically isolated syndrome (CIS)
    ● CHAMPS, ETOMS, BENEFIT, PreCiSe trials
  ● Secondary Progressive
    ● Conflicting study results
  ● Primary progressive
    ● No effective therapies
  ● Radiologically isolated syndrome??
Radiologically Isolated Syndrome (RIS)

- The natural history of patients with incidental imaging findings highly suggestive of MS was investigated in 44 patients.
  - Radiologic progression in 59% of cases.
  - Only 10 patients converted to either clinically isolated syndrome or definite MS.

- In another study: rate of clinical conversion (mostly CIS) 33% during a mean follow-up of 5.2 years.
- Another recent study: of 68 RIS cases with cervical spinal cord abnormalities, 88% converted to CIS over a median time of 5.2 years.

Some other points
Multiple Sclerosis and Vitamin D

- Average person could maintain high level by taking 2,000 IU of vitamin D (D3, not D2, which is less easily absorbed) daily and spending 10 to 15 minutes in the sun.

- Daily maximum tolerable amount: 2,000 IU

- Vitamin D Level:
  - <20: high dose supplement, 50,000 units weekly for 8 weeks
  - Should be maintained around 50 or 60 ng/ml
MS and Pregnancy

- Relapses decrease during pregnancy especially in second and third trimester, increase in post-partum period, no net increase over pregnancy year
- No increase in long term disability or relapse rate
- Minimal impact on pregnancy and birth outcomes
  - Marginal increase in rate of cesarean section in MS patients
- No increased risk of malformation or infant death

Dahl et al, J Neurol 2008;255:623
MS and Pregnancy

- **During pregnancy**
  - Not advisable
  - Should be discontinued 1-2 months prior to anticipated pregnancy
  - Most of symptomatic medications should also be discontinued or used in consultation with Ob/Gyn
  - Intravenous steroids and IVIG relatively safe after first trimester

- **Lactation**
  - Most DMA are excreted in breast milk and should not be used in nursing mother
  - Breastfeeding not associated with increased relapse rate
  - Recent study: breastfeeding associated with reduce postpartum relapse rate, woman not breastfeeding or using formula within 2 months of delivery had higher risk of relapse, 87% vs. 36% (exclusively breastfed)
  - Another recent study: no effect of breastfeeding on relapse rate

MS and Vaccination

- Common immunizations do not increase risk of relapse and may be helpful in preventing infections that may increase the risk of relapse.
- Influenza, hepatitis B, varicella, tetanus, other vaccines should be used per Centers for Disease Control indications/guidelines.
- Flu vaccine:
  - Generally recommended for patients with multiple sclerosis as the flu virus (like any other virus) can precipitate MS exacerbations.
  - People with limited mobility are more likely to develop complications of the flu, including pneumonia should specially be offered flu vaccine.
- Pneumococcal vaccine is indicated for patients with compromised pulmonary function, such as wheelchair-dependant or bed-bound patients.

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm
MS and Vaccination

- Live-virus vaccines are more likely than de-activated-virus vaccines to cause an increase in disease activity in people with MS.
- MS patients on immunosuppressive medications such as mitoxantrone (Novantrone®), cyclophosphamide (Cytoxan®), azathioprine (Imuran®), or methotrexate are more susceptible to developing an infection with the vaccine strain of the virus—an infection that may be particularly severe because the person’s immune system is suppressed.
- FluMist Intranasal® (a live attenuated vaccine) and attenuated nasal spray version of the H1N1 (Swine Flu) are not recommended for people with MS and should specifically be avoided by any person with MS who is on an immunosuppressive medication.
- Other Live vaccines that should not be given to MS patients include: MMR vaccine, varicella, yellow fever, poliomyelitis, oral typhoid, BCG, and rotavirus vaccine.

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm
Future therapies in MS

- Oral
  - Oral Cladribine (Mylinax®)
  - Fingolimod
  - BG-00012
  - Laquinimod
  - Teriflunomide
  - Atorvastatin (Lipitor®)
  - Minocycline
  - PPAR-γ agonist

- IV
  - Alemtuzumab (Campath®)
  - Rituximab (Rituxan®)
  - MBP-8298
  - Ofatumumab (HuMax CD-20)

- Injectable
  - Daclizumab (Zenapax®)
  - BHT-3009
THANK YOU