MULTIPLE SCLEROSIS
Diagnosis and Novel Therapies

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Disclosures

• I do not have any disclosures.
Objectives

• To improve the understanding of the etiology, pathology, and radiographic findings of MS

• To improve confidence in diagnosis and management of patients with MS

• To develop individualized MS therapies that optimize adherence and improve patient outcomes.
Multiple Sclerosis

- Most common demyelinating disease of the CNS
  - > 90% affected prior to age 55
  - < 5% diagnosed before the age of 14

- Multifocal with lesions of different ages, time and site

- Relapsing and remitting (80%) vs progressive course (15%), focal single lesion (<5%)

- Classification:
  - Classic (Charcot type)
  - Acute (Marburg type)
  - Concentric sclerosis (Balo’s type). Very rare
  - Schilder’s disease – occurs in children, extensive demyelination, acute, can be remitting, responds to steroids.
MS: History

• 1860s - Jean Martin Charcot first studied MS where he referred to it as “disseminated (cerebrospinal) sclerosis”

• 1890 – Wilhelm Uthoff described a temporary worsening of vision with exercise and heat production in patients with optic neuritis (Uthoff’s phenomenon)

• 1916 – James Dawson detailed microscopic description of MS lesion

• 1920 – Jean Lhermitte described an electrical sensation that runs down the back, and into the limbs. Produced by bending neck forward/backward. (Lhermitte’s Sign, also known as Barber Chair phenomenon)
MS: History (con’t)

- 1946 – Sylvia Lawry founded National Multiple Sclerosis Society

- 1955 - disorder was universally named Multiple Sclerosis

- 1981 – use of MRI revolutionized diagnosing and provided evidence that MS is a constantly active disease, even when symptoms abate

- 1993 – Betaseron approved as first drug to alter the course of MS
Jean Martin Charcot (1825-1893)
Who gets MS?

Each week, about 200 Americans are diagnosed with MS\textsuperscript{1}

Most people are diagnosed between the ages of 20 and 50 (average age, 31-33)\textsuperscript{1,2}

More than twice as many women have MS as men\textsuperscript{1}

MS is more common in Caucasians, especially those of northern European descent\textsuperscript{1}

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MS: Magnitude of the Problem

Global prevalence of multiple sclerosis (MS) in 2013

People per 100,000 with MS

- >100
- 60.01-100
- 20.01-60
- 5.01-20
- 0-5
- Data not provided

Epidemiology of MS

- Individuals who migrate to high risk area before age 10 have a high risk for disease
- Individuals who migrate to low risk area before age 10 assume a low risk for disease
- Individuals who migrate after the age of 10 assume the risk of the area in which they spent their first 10 years
Birth Month and Risk of MS

• N = 17,874 Canadian patients with MS

• Significantly fewer patients with MS were born in November ($p = .009$) and more were born in May ($p < 0.0001$) compared with other months

• Vitamin D influences the expression of HLA-DRB1*15

Ramagopalan, S.V. (*AAN*, December 10, 2009)
Potential Triggers for Multiple Sclerosis

- Infectious agent
- Genetic predisposition
- Environmental factors

Abnormal immunologic response → MS

MS = multiple sclerosis
Genetic predisposition
Twins studies
HLA
TCR

Environmental factors
Demographics/Epidemics
Vitamin D
Microbial
Viral

Immune Dysregulation
CD4, Th1, Th17 mediated
CD8, CD20 + T Cells

MS

Dhib-Jalbut, S.
Genetic Prevalence of MS

• In a recent genome wide transcription analysis for MS, 48 new genetic variants were identified

• Of interest most genes reverted back during pregnancy.

(Nature Genetics, September 2013)
Genetic Prevalence of MS

• 10 X increase for MS if direct relative affected

• Siblings of an affected person have a 2-5% risk of developing MS.

• Higher prevalence in identical twins

• Variability in severity of disease in twins and affected relatives
EBV and Children

- Children with MS demonstrate abnormally increased rates of EBV viral reactivation and a broader range of genetic variants, suggesting a selective impairment in their immunologic control of EBV.

Yea, C (AAN, Oct 15, 2013)
Update on IM and MS

• Research on EBV has continued to evolve.

• Latest findings show that it is unlikely any of the studied polymorphisms contribute to explaining association between anti-EBNA1 Ab titer or history of IM and MS.

Simon, KC (Multiple Sclerosis and Related Disorders, 2015)
Neuropathology of MS
Components of Multiple Sclerosis Pathogenesis

Inflammation

Demyelination

Axonal Loss

Natural History of MS

Natural History of Relapsing-Remitting MS

Silent Phase

Relapse

Relapsing-Remitting

Visible

Invisible

MRI Activity

Disability progression

Axonal loss

Figure 52 Safety factor in the progression of multiple sclerosis: As long as the required minimum number of nerve fibers remains intact, the patient is asymptomatic. When symptomatic myelin edema occurs during an exacerbation, remission may result in either complete or partial recovery, depending upon functional restoration of the required minimum number of fibers, or in a permanent deficit, as a result of myelino-clasia. From Poser, 1993; reproduced with the permission of Elsevier Science BV.
Multiple Sclerosis is defined by:

- DIS: Disseminated in Space
- DIT: Disseminated in Time
- NBE: No Better explanation
MR Imaging in MS
Gd enhancement

T2 lesion

Brain atrophy (shrinkage)

T1 “black hole”

Spinal cord lesion
47 year old female; RN
## MRI Findings in the Diagnosis of MS

<table>
<thead>
<tr>
<th>MRI Findings Supporting the Diagnosis of MS</th>
<th>MRI Findings cautioning against the Diagnosis of MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lesion size &gt; 5 mm in diameter</td>
<td>• Lesion size smaller, many or all ≤ 5 mm in diameter</td>
</tr>
<tr>
<td>• Lesion shape – ovoid or oval</td>
<td>• Lesion shape – linear, punctate, comma, subtle</td>
</tr>
<tr>
<td>• Lesion location</td>
<td>• Lesion location – lack of periventricular involvement</td>
</tr>
<tr>
<td>– Periventricular, perivenular (Dawson’s fingers), juxtacortical, corpus callosum, intratentorial, spinal cord</td>
<td>• Meningeal/basilar enhancement</td>
</tr>
<tr>
<td>• Homogeneous or open ring-enhancing</td>
<td>• Normal scan of brain and spinal cord</td>
</tr>
<tr>
<td>• Presence of T1 black holes</td>
<td></td>
</tr>
</tbody>
</table>
• Oligoclonal bands are more sensitive and specific (90-95%).
• IgG index or IgG synthesis are sensitive and specific (70-75%).
Diagnosing MS

• Still a clinical diagnosis
  – No single diagnostic laboratory test
  – No standardized laboratory work-up for MS or CIS

• Requires a combination of the following:
  – At least one relapse of neurologic dysfunction localizing to white matter
  – MRI showing white matter lesions, with or without enhancing pattern
  – Dissemination of these white matter lesions in time either clinically or radiologically
  – Oligoclonal banding in CSF
  – All of which may be mimicked by other disease
Early diagnosis vs. misdiagnosis

- Destructive changes from multiple sclerosis occur very early and causes permanent disability.

- Guidelines now advocate treatment after the first relapse.

- But this trend can tempt us to rush through the diagnostic process, sometimes diagnosing and treating...
  - Before an atypical course has been fully revealed
  - Despite red flags or other causes of uncertainty.

- Rate of misdiagnosis: 5-10% (usually over-diagnosis)
  - 1 in 20 patients diagnosed with MS actually have another, potentially treatable, condition
  - 2.4-7.1% of patients misdiagnosed with MS actually have migraines.
Red Flags

• Age of onset < 15 or > 50
• History of progressive dysfunction rather than a relapse
• Unusually sudden onset of symptoms
• Unusual neurologic symptoms
  – Seizures, aphasia, headaches, confusion, parkinsonism, deafness, peripheral nerve involvement
• Strong family history
• Atypical MRI
  – Normal MRI
  – Mass lesions
  – Atypical white matter lesions
    • Tiny
    • Subcortical
    • Symmetric, confluent
    • Basal ganglia involvement
    • Extensive spinal lesions
  – Prolonged enhancement
• CSF
  – negative for banding
  – WBC’s > 50
MS: Clinical Subtypes

Progressive-relapsing multiple sclerosis
Steady decline in function since onset, with superimposed attacks

Secondary progressive multiple sclerosis
Initial relapsing-remitting multiple sclerosis followed by a sudden decline in function, with periods of remission

Primary progressive multiple sclerosis
Steady increase in disability without attacks

Relapsing-remitting multiple sclerosis
Unpredictable attacks, which may or may not leave permanent deficits, followed by periods of remission

**FIGURE 3** Types of multiple sclerosis. Adapted, with permission, from a slide presented by Anne Gocke, PhD, at the 2014 joint CMSC/ACTRIMS annual meeting.
Differential Diagnosis of MS

- **Inflammatory diseases**
  - SLE
  - Sjogren’s disease
  - Behcet’s disease
  - Polyarteritis nodosa
  - Granulomatous angitis
  - Sarcoidosis
  - Paraneoplastic encephalomyetopathies

- **Infectious diseases**
  - Lyme disease
  - HTLV-1
  - PML
  - HIV myelopathy/encephalopathy
  - Neurosyphilis

- **Disease of myelin**
  - ALD
  - ADEM
  - Central pontine myelinolysis

- **Vascular**
  - Lacunes
  - Embolic
  - CADASIL
  - Stroke due to APLA

- **Miscellaneous**
  - Spinocerebellar disorders
  - Cervical spondylosis
  - Arnold-Chiari malformation
  - Syrinx
  - Vitamin B12 deficiency
  - Hashimoto Thyroiditis
  - Leber’s Optic Atrophy
Clinically Isolated Syndromes (CIS)

- For 85% of patients, the clinical onset of MS is characterized by a CIS of the
  - Optic nerve (acute optic neuritis)
  - Spinal cord (partial transverse myelitis); or
  - Brainstem/cerebellum (acute brainstem syndrome)

- 50-88% of untreated CIS patients who have abnormal MRI results with no alternate explanation will eventually develop MS in 5 years.

Robinson, R (Neurology Today, 2013)
Radiologically Isolated Syndrome RIS

- Subclinical demyelinating lesions may occur in the brains of asymptomatic individuals.
- 70 patients followed for a mean of 5.2 years. First MRI was for non MS concerns.
- 34% had clinical conversion during their follow-up period.
- ? treatment

Robinson, R (Neurology Today, May 2013)
Clinical Presentations of MS
## Multiple Sclerosis: Common Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder symptoms</td>
<td>90</td>
</tr>
<tr>
<td>Fatigue</td>
<td>80</td>
</tr>
<tr>
<td>Spasticity</td>
<td>70</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>64</td>
</tr>
<tr>
<td>Pain</td>
<td>62</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>50 in 15 yrs, 90 in 25 yrs</td>
</tr>
<tr>
<td>Depression</td>
<td>50</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>40</td>
</tr>
</tbody>
</table>

Fatigue in MS

• Probably the single most common symptom shared by patients with MS
  – Reported > 75% of patients
  – In 30% of patients, it occurs before other symptoms of the disease

• In many patients, fatigue is the most disabling symptom and one of the most common reasons for retirement due to disability
Depression and Multiple Sclerosis

• Does MS cause depression?

• Does the therapy for MS (specifically IFN) cause depression?

• How is depression best managed?
Cognitive Impairment in Untreated MS

- Occurs in approximately half of all people with MS
- Often under recognized or misdiagnosed as depression, stress, or personality disorder
- Impairs daily functioning of people with MS
- Leading cause of unemployment in persons with MS
MS Therapeutic Timeline

• Adrenal Steroids (1954)
• ACTH (1961-1968)
• Prednisone (1965)
• Imuran (1975)
• IVMP (1980)
• Plasmaphoresis (1985)
• Cytoxan (1983)
• HIGG (1983)
• Methotrexate (1991)
ACTHar

• No evidence that ACTHar gel is superior to methylprednisolone for MS relapses.

• Current average wholesale price of $40,840.80 for a 5 ml/40 unit bottle makes routine use of this product for MS relapses difficult to justify.

Kister and Corboy (Neurology Today, September 2016)
## Currently Approved Disease-Modifying Therapies for Patients with Relapsing-Remitting Multiple Sclerosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic name (trade name)</th>
<th>Route and frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Interferon β-1b (Betaseron)</td>
<td>Subcutaneous injection every other day</td>
</tr>
<tr>
<td>1996</td>
<td>Interferon β-1a (Avonex)</td>
<td>Intramuscular injection once a week</td>
</tr>
<tr>
<td>1996</td>
<td>Glatiramer acetate (Copaxone)</td>
<td>Subcutaneous injection once a day</td>
</tr>
<tr>
<td>2000</td>
<td>Mitoxantrone (Novantrone)</td>
<td>Intravenous infusion every 3 months</td>
</tr>
<tr>
<td>2002</td>
<td>Interferon β-1a (Rebif)</td>
<td>Subcutaneous injection 3 times a week</td>
</tr>
<tr>
<td>2004</td>
<td>Natalizumab (Tysabri)</td>
<td>Intravenous infusion once a month</td>
</tr>
<tr>
<td>2009</td>
<td>Interferon β-1b (Extavia)</td>
<td>Subcutaneous injection every other day</td>
</tr>
<tr>
<td>2010</td>
<td>Fingolimod (Gilenya)</td>
<td>Orally once a day</td>
</tr>
<tr>
<td>2012</td>
<td>Teriflunomide (Aubagio)</td>
<td>Orally once a day</td>
</tr>
<tr>
<td>2013</td>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>Orally twice a day</td>
</tr>
<tr>
<td>2014</td>
<td>Glatiramer acetate (Copaxone)</td>
<td>Subcutaneous injection 3 times a week</td>
</tr>
<tr>
<td>2014</td>
<td>Peginterferon β-1a (Plegridy)</td>
<td>Subcutaneous injection every 14 days</td>
</tr>
</tbody>
</table>

(ACTRIMS, Summer 2014)
Currently Approved DMTs (Con’t)

• 2014 Lemtrada (alemtuzumab)
  – 12 mg/day by IV for 2 treatment courses
    • 1\textsuperscript{st} Treatment Course: 12 mg/day on 5 consecutive days
    • 2\textsuperscript{nd} Treatment Course: 12 mg/day on 3 consecutive days administered 12 months after 1\textsuperscript{st} treatment course

• 2016 Zinbryta (daclizumab)
  – 150 mg SQ once/month

Due to safety profile, use of Lemtrada or Zinbryta is only for pts who have failed 2 or more DMTs.
Stem Cell Treatment for MS
Mesenchymal Stem Cells as a Treatment for MS

- Mesenchymal stem cells (MSCs) could reduce inflammatory lesions in patients with MS.

- MSCs can be derived from bone marrow or placenta.

(Neurology Reviews, July 2013)
Chronic Cerebrospinal Venous Insufficiency (CCSVI)

• Is an abnormality of how venous blood drains from brain and spinal cord.

• Increased deposition of iron triggers inflammation and lesions in brain; leading to degeneration of myelin sheath.

• There is no rationale for a trial exploring the efficacy of the liberation therapy; a randomized trial in MS patients would be unethical.

Presented at ECTRIMS 2012
• Functional brain abnormalities linked to cognitive impairments in MS patients who use Marijuana

• Medical Marijuana does not appear to have curative effects on any neurologic condition, but it may ameliorate unwanted symptoms and ease suffering.

  Hurley (Neurology Today, 2014)
  Fife (AAN, 2015)
Complementary & Alternative Medicine in MS

• The guidelines demonstrate that even though there are multiple CAM therapies, there is little evidence that most of them are effectively treating MS.

(Neurology Today, 2014)
Vitamin D

• Vitamin D is a protective factor in MS.

• Vitamin D supplementation is a modest MS disease modifier.

• For every 10 ng/mL increase in Vitamin D levels in patients with MS, their EDSS scores were 0.05 points lower.

• Recommended Vitamin D levels of 50-80 ng/mL.

(NEJM, December 2015)
Immunologic Effects of Vitamin D Relevant to MS

• Increases expression of anti-inflammatory cytokines IL-4, IL-10, TFGβ-1
• Inhibits expression of proinflammatory cytokines IL-12, IL-17, INFγ, and TNFa
• Modulates T helper (Th cells)
• Shift APC and CD4+ cells to anti-inflammatory state
• Induces anti-inflammatory state in CD8+ cells

(International Journal of MS Care, September 2015)
Medical Management During Pregnancy, Delivery, and Postpartum

• None of the disease-modifying medications are approved for use during pregnancy.

• The disease-modifying drugs are also not recommended for use during breastfeeding.

• Women with MS usually do not need special gynecologic care during pregnancy, labor and delivery.
Figure 1. Effect of Pregnancy on Relapse Rate in PRIMS Trial

Conclusion

• MS is the most common demyelinating disease of the CNS.

• Relapsing remitting (80%), Progressive (15%), Focal Single Lesion (< 5%)

• 200 Americans (primary between ages 20-50) diagnosed weekly with MS.

• More than twice as many women have MS than men.

• Less than 10% of all MS patients are younger than age 18.

• 10% increase for MS if direct relative affected.
Conclusion (con’t)

• Correlation between EBNA-1 IgG and gadolinium enhancing lesions in MS disease activity.

• Patients need to undergo an MRI and CSF for oligoclonal bands and IgG index/synthesis.

• Diagnosing MS is still a clinical diagnosis (no single diagnostic laboratory test).
Conclusion (con’t)

• Common symptoms include neurogenic bladder, fatigue, spasticity, sexual dysfunction, pain, cognitive dysfunction, and depression.

• There are several different types of injectable and oral medications for treatment.
Take Home Message

Patients do not care about how much you know. What they want to know is how much you care!
Thank you!

Q & A