MULTIPLE SCLEROSIS
Update

E. Torage Shivapour, M.D.

Clinical Professor
Department of Neurology
University of Iowa Hospitals & Clinics
Disclosures

• I do not have any disclosures.
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.
Jean Martin Charcot (1825-1893)
Who gets MS?


These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
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

Willer CJ (Br Med J 2005)
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 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 shows 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)
Natural History of MS

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
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 myelonecrosis. From Poser, 1993; reproduced with the permission of Elsevier Science BV.
MR Imaging in MS
Gd enhancement

T1 “black hole”

Brain atrophy (shrinkage)

T2 lesion

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 ( \leq 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), juxtaglomental, 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>

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
• Oligoclonal bands are more sensitive and specific (90-95%).
• IgG index or IgG synthesis are sensitive and specific (70-75%).
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
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
<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>
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)
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)
• 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)
Vitamin D

• Vitamin D is a protective factor in MS

• 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.

Otto, A (Clinical Neurology News, June 2012)
Additional CAM Therapies

- Ginkgo biloba
- Ginseng
- Omega-3 fatty acid (anti-inflammatory)
- Omega-6 fatty acid (pro-inflammatory)
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.
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.
Patients do not care about how much you know. What they want to know is how much you care!
Thank you!

Q & A