# Multiple Sclerosis for the Primary Care Provider

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## Disclosures

- Dr. Cameron has received research support from the VA RR&D Service, National MS Society, MS International Federation, Collins Medical Trust, Acorda Therapeutics
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## Outline

For Multiple Sclerosis (MS)

- Describe the following
  - Description and incidence
  - Typical presentation and progression
  - PCP work up
  - Referral – why, when, who
  - Management – medical, surgical, PCP, specialist, outcomes

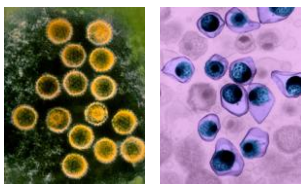
## What is MS

- CNS disorder (brain, spinal cord, optic nerves)
- Symptoms separated in time and space
- Complex immune-mediated disorder

## Demographics

- 400,000 patients in USA, 2.5 million worldwide, ~1/700 (total 5000) in Oregon
- Typical onset age 20-50 years, average 33-35
- Female:male 2-4:1
- Caucasians >> other ethnic groups
- Variable course of disease

# Pathogenesis





Infectious Agent

Genetic Predisposition

Environmental Factors

Abnormal immunologic response → MS

Gilden *Lancet Neurol* 2005;4:195-202; Noseworthy *NEJM* 2000;343:938-952.

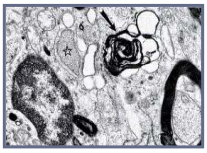
# Pathophysiology

MS DAMAGES…

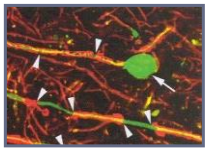
a) Myelin
b) Axons
c) Both

Inflammation

Demyelination



Axonal Loss

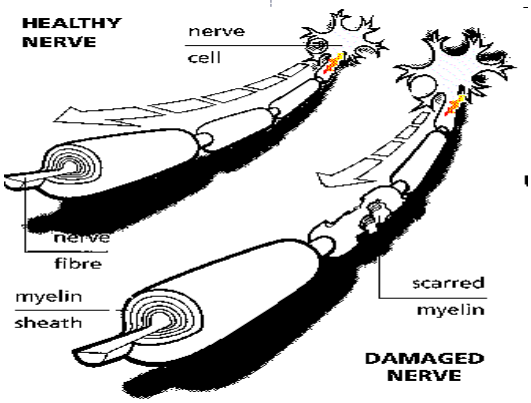


Trapp *Curr Opin Neurol* 1999;12:295-302; Trapp *J Neuroimmunol* 1999;98:49-56; Trapp *Neuroscientist* 1999;5:48-57.

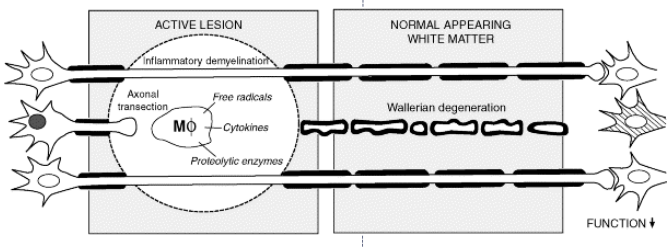
# Immunology/Inflammation

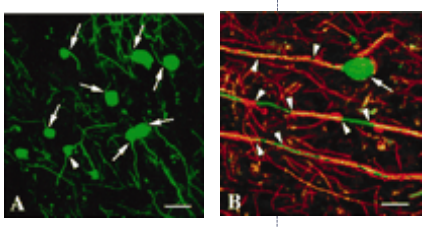
- Primarily T cell mediated
  - Activation in the periphery
  - Activated T cells enter the CNS
  - Reactivation of T cells in the CNS triggers cascade of reactions resulting in CNS damage
- B cells, specifics less clear
  - Antigen-presenting cells
  - Antibody production - ?pathogenetically relevant
  - Ectopic B-cell follicles in CNS adjoin to pial membrane
- Evidence for autoimmune hypothesis
  - Experimental autoimmune encephalomyelitis (EAE), mouse model
  - Genetics
  - Response to immunomodulating and –suppressive agents

# Demyelination




# Axonal damage




Bjartmar, J Neuro Sci 2003
Trapp, NJEM 1998

# Diagnosis

## 2010 Criteria

| Clinical Presentation | Additional data needed for MS diagnosis |
|---|---|
| ≥ 2 attacks; objective clinic evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack | None |
| ≥ 2 attacks; objective clinical evidence of 1 lesion | DIS by MRI; or await further clinical attack implicating a different CNS site |
| 1 attack; objective clinical evidence of ≥ 2 lesions | DIT by MRI; or await second clinical attack |
| 1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome) | DIS and DIT by MRI |
| Insidious neurological progression suggestive of MS (PPMS) | 1 year of disease progression (retrospectively or prospectively determined)<br>Plus 2 of the following 3:<br>1. Evidence for DIS in the brain based on ≥ 1 T2 lesion in characteristic area<br>2. Evidence for DIS in the spinal cord based on ≥ 2 lesions in the cord<br>3. Positive CSF (bands or elevated IgG index) |

## 2010 McDonald Criteria

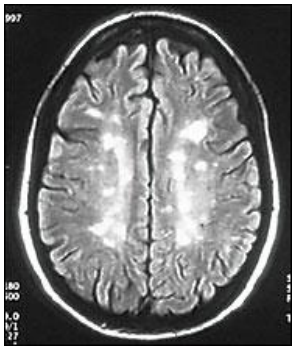
Dissemination in space (DIS)

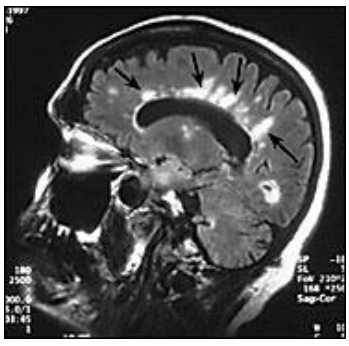
- ≥ 1 T2 lesions in at least 2 of the following 4 areas of the CNS
  - Periventricular
  - Juxtacortical
  - Infratentorial
  - Spinal cord

Dissemination in time (DIT)

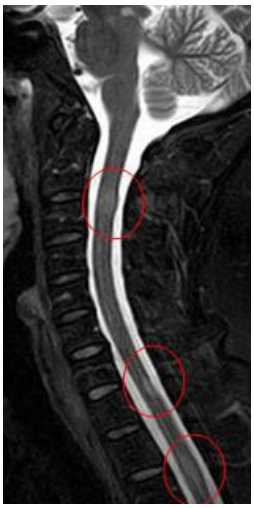
- A new T2 and/or Gd enhancing lesion on f/u MRI, with reference to baseline scan, irrespective of timing of baseline MRI
- Simultaneous presence of asymptomatic Gd enhancing and nonenhancing lesions at any time

## Brain MRI MS





## Spine MRI



Spine usually not involved in other diseases mimicking MS

## MS: PCP work up

- H & P (as always!) with a focus on prior neuro sx, time course, distribution, and the neuro exam
- MRI brain with and without contrast during relapse
- NOT generally spine MRI or CSF

## MS Referral – why, when, who

- To be sure of the diagnosis
- To help with treatment decisions
- Early but not emergent – weeks from onset is generally ok
- Neurologist, +/- subspecialist

# Clinical Course

# Clinical-isolated Syndrome (CIS)

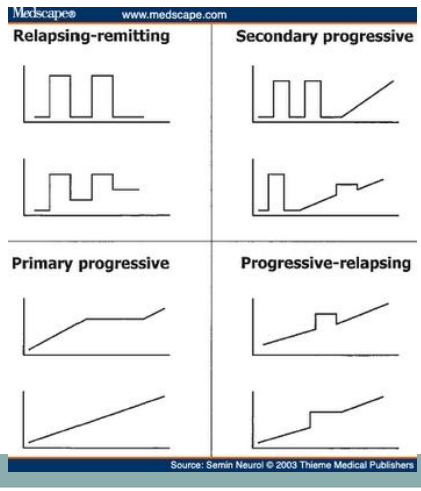
- First demyelinating event
- Future risk of definite MS defined by MRI

| Baseline Brain MRI | 1 yr | 5 yrs | 10 yrs | 14 yrs | 20 yrs |
|---|---|---|---|---|---|
| Abnormal *(=single lesion)* | 30% | 65% | 83% | 88% | 82% |
| Normal | 0% | 3% | 11% | 19% | 21% |

Fisniku Brain 2008:131;808-17

# Clinical Course

- **Which is the most common type of MS?**



## MS: Typical presentation and progression

- Usually starts with *relapsing remitting* course of focal neurological symptoms localizable to the CNS or optic nerves e.g. numbness, weakness, vision loss in 1 eye, double vision
- Relapses: come on over 1-3 days, last 4-8 weeks and then fully, or almost fully resolve
- Other common sx : cognitive, fatigue, heat intolerance, bladder, imbalance
- Usually later (10-15 years) in the course, relapses go away but sx gradually progress (*secondary progressive* MS)

## Natural History of MS

- 1/3 non-ambulatory 20 years after onset
- 50% unemployed 10-15 years after onset
- 15-30% have a "benign" course
  - Depends on definition and duration of follow-up
- Progressive forms of MS more disabling than RRMS

# MS Therapies

## Comprehensive MS Management

- Treatment acute relapse
- Disease-modifying therapies
- Symptom management
- Life-style counseling
  - Smoking cessation
  - Regular exercise
  - Albeit inconclusive data at this time, consider supplementation of Vitamin D (fish oil, antioxidants)

## MS Management – medical, surgical, specialist, outcome

- Medical – disease modifying therapies to reduce # of relapses and disease progression
- Steroids to shorten relapse duration
- Surgical – very rare (e.g. biopsy if diagnosis uncertain)
- Specialist – recommend DMT; sx management
- Outcome – variable, DMTs slow progression during relapsing phase, sx mgmt improves QOL

## Disease Modifying Therapy

- Favorable impact clinical course and MRI activity
  - Relapse rate, new/gd+ MRI lesions, brain atrophy, +/- disability
- Poor adherence
- Benefit of early treatment
  - ~70% vs 30% reduction annual relapse rate
  - Acute axonal loss greatest in early stages of disease
  - Impact on several predictive factors for long-term outcome
- CIS w/ abnl MRI: 45-50%/2y reduced conversion to MS

## FDA Approved MS disease modifying therapies - 2013

- Betaseron 1993
- Avonex 1996
- Copaxone 1997
- Mitoxantrone 2000
- Rebif 2002
- Natalizumab 2006
- Fingolimod 2010
- Teriflunomide 2012
- BG-12 ?2013

## Treatment of acute relapses

- IV methlyprednisolone, 1g IV x 3-5 days
- Shortens relapse duration
- No effect on time to next relapse, long term disability
- Weigh risks and benefits
- Consider if this is a “pseudo-relapse”

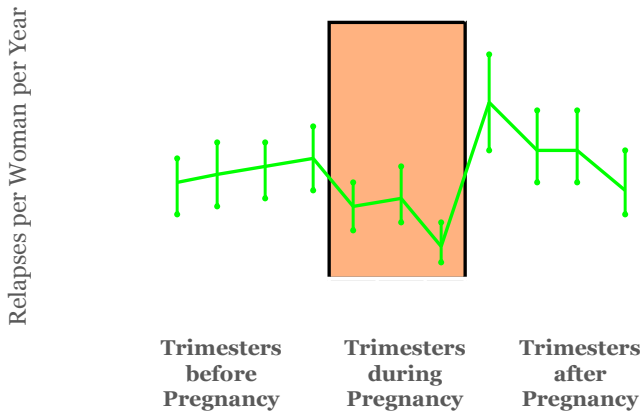
## PCP Role in MS Management

- Initiate diagnostic work up
- Monitor for drug AEs, e.g. CBC, LFTs;
- Sx management e.g. pain, bladder, bowel
- Steroids for relapses
  - Solumedrol 1g IV daily X 3-5 days
  - Shortens relapse but does not change outcome
  - Evaluate for psuedo relapse

## Symptom management

- Essential for QOL
- Cognition
- Vision
- Headaches
- Pain
- Weakness
- Fatigue
- Reduced mobility
- Bladder
- Bowel
- Sexual function
- Spasticity
- Social
  - Work
  - Home

# MS and pregnancy - Rate of Relapse




Confavreux. NEJM. 2003; 339(5): 285

## Summary

- MS is a CNS disease with variable progressive course
- Therapy includes relapse management, disease modifying interventions and symptom management
- There are a number of DMT available for RRMS
- Newer therapies appear to be more effective but carry increased risk

## Summary

- Diagnosis – 2 clinical events separated in time and space, supportive MRI, +/- ancillary tests, rule out other possible explanations
- Management – DMT, relapses, symptoms
- The future is bright – many new treatments on the horizon

## QUESTIONS