

Early Recognition and Intervention in MS: A Continuum of Care Model

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Learning Goals

- Recognize the neurological symptoms that should raise clinical suspicion of a diagnosis of multiple sclerosis.
- Initiate prompt referral to a neurologist in patients presenting with symptoms that may be indicative of a diagnosis of multiple sclerosis.
- Establish a communication strategy with the treating neurologist to discuss treatment, side effects, and barriers to adherence in patients with multiple sclerosis.

Aaron Boster, MD

Disclosures

- *Research/Grants:* Actelion Pharmaceuticals Ltd; Biogen Idec; EMD Serono, Inc.; Jazz Pharmaceuticals, Inc.; National Institutes of Health (NIH); National Multiple Sclerosis Society; Questcor Pharmaceuticals, Inc.; Roche
- *Consultant:* Biogen Idec, Inc.; Genzyme Corporation; Medtronic, Inc.; Novartis Pharmaceuticals Corporation; Questcor Pharmaceuticals, Inc.; Teva Pharmaceuticals

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Disclosures

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What Is Multiple Sclerosis?

- **A chronic, inflammatory, demyelinating disorder of the central nervous system of uncertain etiology, likely autoimmune, associated with destruction of myelin sheaths and axons**

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.

Ideal Management of Multiple Sclerosis

- **As a dynamic disease, multiple sclerosis (MS) requires a multitude of healthcare providers with various expertise to help patients throughout their lives.**
- **“In an ideal [patient-centered medical home], a patient with MS would receive both primary care and specialty care at the appropriate time, moving seamlessly between providers who communicate with each other and the patient.”**

Wallin MT. *J Rehabil Res Dev* 2010;47:ix-xiv.

Sources of MS Care^a

| Provider | Number (%) |
|--------------------------------|--------------|
| Neurologist ^a | 1,510 (72.2) |
| Primary care physician | 362 (19.6) |
| Another physician | 76 (3.7) |
| Nurse | 15 (.07) |
| Unknown or nonmedical provider | 71 (3.4) |
| No MS care | 22 (1) |

^aData from 2056 participants in the Sonya Slifka Longitudinal Multiple Sclerosis Study
^bIncludes MS specialist, neurology clinic, MS clinic

Minden SL, et al. *Neurology* 2008;70:1141-9.

Initial Presentation to the Primary Care Provider

Susan F.

- 29-year-old woman from Iowa
- Right eye
 - Blurred vision
 - Pain with extraocular movement
- Denies history of similar symptoms
- Recalls 1-week episode of left-arm paresthesias 10 years ago that resolved spontaneously



Photo: CDC/ Amanda Mills

MS Presentation



Common Initial Presentation of MS

| | |
|--|---------------------------------------|
| Optic neuritis | Lhermitte sign |
| Subacute onset of unilateral vision loss | Pathologic fatigue |
| Pain with extraocular movements | Heat intolerance (Uhthoff phenomenon) |
| Transverse myelitis | |
| Bilateral leg numbness, weakness, and tingling (could be asymmetric) | |
| Bowel and bladder dysfunction | |

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.



Presentation of MS on Neurologic Examination

| |
|---|
| Upper motor neuron syndrome |
| Weakness |
| Hyperreflexia |
| Spasticity |
| Clonus |
| Babinski sign |
| Brainstem syndromes |
| Dysfunction of cranial nerves or cerebellar connections |
| Diplopia |
| Internuclear ophthalmoplegia |
| Vertigo |
| Dysarthria |
| Dysphagia |
| Incoordination |
| Poor balance |

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.



Presentation of MS on Ophthalmologic Examination

| |
|------------------------------------|
| Pale optic disk |
| Poor visual acuity |
| Pain with extraocular movement |
| Relative afferent pupillary defect |
| Red color desaturation |
| Internuclear ophthalmoplegia |

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.



Red Flags That the Diagnosis Is Likely not MS

| |
|---|
| Acute onset of symptoms |
| Age, years |
| < 10 |
| > 50 |
| Altered level of consciousness |
| Aphasia |
| Apraxia |
| Fasciculations |
| Parkinsonism |
| Peripheral neuropathy |
| Prominent early encephalopathy/dementia |

Calabresi PA. *Am Fam Physician* 2004;70:1935-44.



What Are the Next Steps for the Primary Care Provider?

- Recognize that this is likely a demyelinating CNS disorder

Refer?



Photographer: Ernie Branson

Continue work-up?



Referral to the Neurologist

- Susan comes to the neurologist (in this case, an MS specialist) for further workup of her symptoms.



Photo: CDC/ Amanda Mills

The Diagnosis of MS

Key Factors

Exclude alternative etiologies



MS Differential Diagnosis

- **Metabolic:** SCD (B₁₂ deficiency),
- **Connective tissue diseases:** Sjögren syndrome, SLE
- **Infectious:** HIV, HTLV1, Lyme disease, syphilis
- **Structural:** Chiari malformation, spinal cord compression

Genetic: ataxias, paraplegias, mitochondrial disorders, adrenomyeloneuropathy

Neoplastic: CNS lymphoma, paraneoplastic disease

"MS variants": ON, TM, ADEM, NMO

Other: neurosarcoidosis, CNS vasculitis

Psychiatric

SCD = subacute combined degeneration of the spinal cord; SLE = systemic lupus erythematosus; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus; CNS = central nervous system; ON = optic neuritis; TM = transverse myelitis; ADEM = acute disseminated encephalomyelitis; NMO = neuromyelitis optica
Trojano M, et al. *Neuro Sci.* 2001;22 Suppl 2:S98-102.



Laboratory Studies to Rule Out Other Disorders in the Differential

- B₁₂ levels
- Rapid plasma regain or fluorescent treponemal antibody
- Antibody confirmation
 - HIV
 - HTLV-1
- Extractable nuclear antigens panel

Maloni HW. *Nurse Pract* 2013;38:24-35..



Laboratory Studies to Rule Out Other Disorders in the Differential

- Antinuclear antibody panel
- Antiphospholipid antibodies
- Erythrocyte sedimentation rate
- C-reactive protein
- Thyroid function
- Long-chain fatty acids
- Lyme titer

Maloni HW. *Nurse Pract* 2013;38:24-35..

The Diagnosis of MS

Key Factors

MRI Findings

MS Diagnostic Criteria

- Dawson criteria: 1916
- Schumacher criteria: 1965
- Poser criteria: 1983
- McDonald criteria: 2001
- **Revised McDonald criteria: 2010**
- All criteria require:
 - Dissemination in space and time
 - No better explanation

Polman CH, et al. *Ann Neurol* 2011;69:292-302.

Dissemination in Space and Time

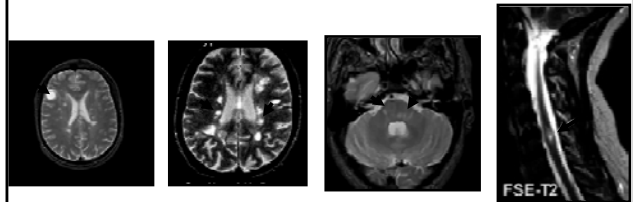
1. Dissemination in space: Objective evidence of neurologic deficits localized to 2 separate parts of the CNS
2. Dissemination in Time: Onset of neurologic deficits separated by at least 1 month
3. Rule out other explanations!



Polman CH, et al. *Ann Neurol* 2011;69:292-302.

Dissemination in Space

- At least 1 asymptomatic T2 lesion in at least 2 of 4 locations

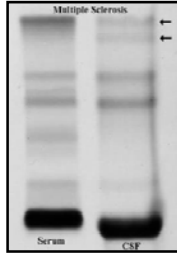


Swanton JK, et al. *Lancet Neurol* 2007;6:677-86.

CSF Analysis

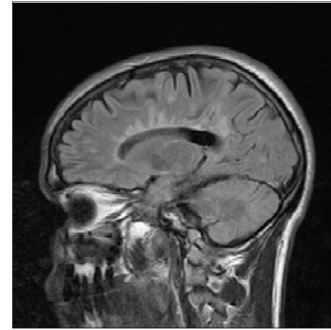
Most helpful for suggesting an alternative diagnosis

- High protein, marked pleocytosis, PMNs
- Elevated IgG Index ≥ 0.7
 - Increased CNS IgG synthesis with normal serum IgG *is consistent with MS*
- Oligoclonal bands
 - Presence of ≥ 2 distinct bands in CSF and none in serum *is consistent with MS*



CSF = cerebrospinal fluid; PMN = polymorphonuclearcytes; IgG = immunoglobulin G
Petzold A. *J Neuroimmunol* 2013;262:1-10.

Susan's MRI Findings




MS Treatment



FDA-Approved Treatments for MS Disease-modifying Therapy: Injectable


| Generic name | Trade Name | Laboratory Assessments | Side Effects |
|------------------------|------------|--|--|
| Interferon β -1a | Avonex | Check LFTs and CBC quarterly or every 6 months | Flu-like symptoms Liver dysfunction Bone marrow suppression Other |
| | Rebif | Check LFTs and CBC quarterly or every 6 months | Endocrine abnormalities Depression Spasticity Headaches |

LFT = liver function tests; CBC = complete blood count

 **FDA-Approved Treatments for MS**
Disease-modifying Therapy: Injectable


| Generic name | Trade Name | Laboratory Assessments | Side Effects |
|------------------------|------------|--|--|
| Interferon β -1b | Betaseron | Check LFTs and CBC quarterly or every 6 months | Flu-like symptoms Liver dysfunction Bone marrow suppression Other |
| | Extavia | Check LFTs and CBC quarterly or every 6 months | Endocrine abnormalities Depression Spasticity Headaches |
| Glatimer acetate | Copaxone | | Injection site reactions Idiopathic injection reactions Lipoatrophy |

LFT = liver function tests; CBC = complete blood count

 **FDA-Approved Treatments for MS**
Disease-modifying Therapy: Infusion


| Generic name | Trade Name | Laboratory Assessments | Side Effects |
|--------------|------------|---|--|
| Mitoxantrone | Novantrone | This drug is rarely used because of adverse effects | Treatment-related acute leukemia (1/100) Cardiotoxicity |
| Natalizumab | Tysabri | Check JC virus antibody status every 3-4 months | Infusion reactions PML Other infections |

PML = Progressive multifocal leukoencephalopathy

 **FDA-Approved Treatments for MS**
Disease-modifying Therapy: Oral

| Generic name | Trade Name | Laboratory Assessments | Side Effects |
|---------------------------|------------|---|---|
| Fingolimod | Gilenya | ECG, VZV titer, LFTs, and ophthalmologic exam ^a before beginning treatment. Biannual LFTs and ophthalmologic exam. | Macular edema Transient bradycardia Liver dysfunction |
| Teriflunomide | Aubagio | Pregnancy test and TB skin test before beginning treatment. Monthly LFTs for 6 months and then every 3 to 6 months | Teratogenicity Transient alopecia |
| Dimethyl fumarate (BG-12) | Tecfidera | Annual CBC | Facial flushing Gastrointestinal side effects |

^aTo check for macular edema. ECG = electrocardiogram; VZV = varicella zoster virus; LFTs = liver function tests; TBC = tuberculosis; CBC = complete blood count

 **FDA-Approved Treatments for MS**
Symptomatic Therapy

| Generic name | Trade name | Indication |
|--------------------|------------|---|
| Dalfampridine | Ampyra | To improve walking in patients with MS |
| OnabotulinumtoxinA | Botox | Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition in adults who have an inadequate response to or are intolerant of an anticholinergic medication |

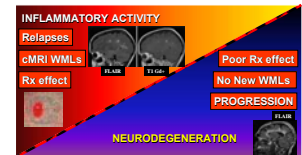
Disease Modifying Therapies: 1993-2002

| | Glatiramer acetate 1997 | IFN β -1b 1993 | IFN β -1a 2002 | IFN β -1a 1996 |
|----------------|----------------------------------|--|---|--|
| Type | Polypeptide mixture | Recombinant protein | Recombinant protein | Recombinant protein |
| Indication | Reduce freq. of relapses in RRMS | Reduce freq. of relapses. Slow disability in relapsing forms | Reduce freq. of relapses. Delay disability in relapsing forms | Slow progression in relapsing forms. Prevent 2 nd attack in CIS |
| Injection | SC | SC | SC | IM |
| Administration | Daily | Every other day | 3x/week | Weekly |
| Dosage | 20 mg | 250 μ g (8 MIU) | 44 μ g | 30 μ g |

Freq = frequency; RRMS = relapsing remitting multiple sclerosis; SC, subcutaneous; IM = intramuscular; CIS = clinically isolated syndrome

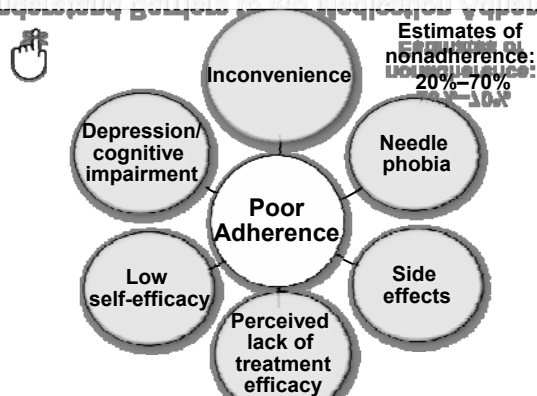
Rationale for Early MS Treatment

- Permanent tissue damage occurs from recurrent bouts of inflammation, even during the silent periods of so-called remission.
- Accumulated disability is at least in part secondary to early active inflammatory disease.
- We can treat inflammation!
- During later disease stages our treatments are less effective



WMLs = white matter lesions; RX = treatment

Understand Barriers to MS Medication Adherence

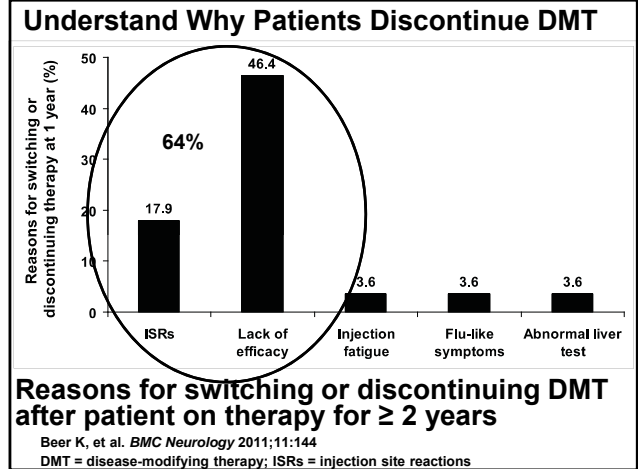
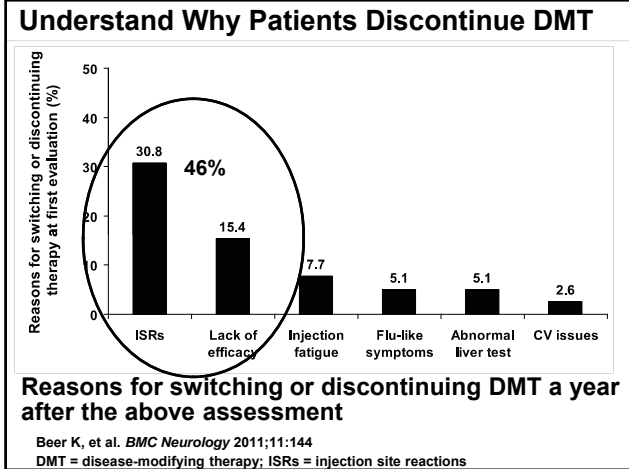


Patti F. *Patient Prefer Adherence*. 2010;4:1-9.


Understand the Challenges to Adherence

- Up to 50% patients discontinue because of side effects or lack of efficacy
- Adherence tends to decrease over time (eg, "treatment fatigue")
- Cognitive and physical limitations negatively impact adherence
- Comorbid depression carries a 3-fold risk of nonadherence
- Reimbursement challenges (eg, formulary changes; copay)

Rio J, et al. *Mult Scler*. 2005;11:306-9; Twork et al. *Curr Med Res Opin*. 2007;23(6):1209-15; O'Rourke KE, et al. *Mult Scler*. 2005;11(1):46-50; Ross AP. *Neurology*. 2008;71(Suppl 3):S1-2; DiMatteo MR, et al. *Arch Intern Med*. 2000;160:2101-7.




Ongoing Communication



Referrals and Communication

- Referrals
- Team members
- Communication with PCP
 - Summarize my findings
 - Provide feedback
 - Identify laboratory tests that the PCP could monitor



Photographer: Ernie Branson

Key Points Regarding Treatment

- Biggest point is adherence
 - “Are you taking your drug?”
- Safety monitoring
 - “Are you being safe about taking your drug?”
 - “Are you having your labs checked?”
 - “Are you having your eye exams?”



PCP Role in the Treatment of MS

- Keep the patient safe
 - Monitor results of recommended laboratory studies
- Identify local resources
 - Social support
 - Community resources
 - Neurologic-specific physical therapy
- Facilitate ADHERENCE

Improving Adherence

General Counseling

- Stress adherence
- Patients must immediately report significant changes
- Foster realistic expectations
 - Expected attack rate: 1 every 3-5 years
 - Treatments are not curative
 - Cannot stop disability
 - Cannot repair existing damage

International Working Group for Treatment Optimization in MS. *Eur J Neurol*. 2004;11:43-7.



PCP Role in the Treatment of MS

- Encourage smoking cessation^a
- Discuss increased risk for osteopenia^a
 - Monitor bone density
 - Provide osteopenia prophylaxis
- Screen for depression, cognitive status, and fatigue on a routine basis
 - Beck Depression Inventory
 - Multiple Sclerosis Neuropsychological Questionnaire
 - Modified Fatigue Impact Scale



^aSmoking and vitamin D levels are the only currently identified modifiable risk factors to decrease the risk of developing MS and to decrease the severity of MS symptoms. Ascherio A, Munger KL. *Ann Neurol* 2007;61:504-13.

Follow-up Primary Care Visit

- Nine months after initial diagnosis
- Prescribed DMT, which she administers via subcutaneous injection
- Being seen for annual exam
- Reports tingling sensation in her left hand
- You determine that “*something ain’t right*” (SAR)
- Is this a relapse of her MS?



PCP Role in Identification of MS Relapse

- **CRITICAL**, compare with previous examinations (history and examination), whenever possible
- Be aware that relapse may be precipitated by heat, infection, and stress
 - Check urinalysis for occult urinary tract infection
- Evaluate adherence with MS treatment
 - Reinforce importance of adherence



CDC/ Doug Jordan, M.A.

CC By 2.0 aloha_pineapple - Flickr

Follow-up Visit: When SAR

Susan reports

- Adherence with injections
- No recent
 - Infection
 - Obvious physiologic or psychological stress
 - Heat exposure
- You refer her back to Dr. Boster



Photo: CDC/ Amanda Mills



Key Points

1. MS is the most common cause of neurologic disability among young adults in the US.
2. MS today is a completely different animal than it was 10 years ago.
3. Early diagnosis leads to early treatment, which has shown better outcome.



Key Points

4. Help keep your patients with MS on their prescribed medicine and keep them safe.
5. Smoking is particularly bad for people with MS.
6. It takes a team to treat MS – the neurologist and PCP working together can provide the best care possible.

Appendix



FDA-Approved Treatments for MS *Disease-modifying Therapy: Injectable*

| Generic name | Trade Name | Link to PDR.net |
|------------------------|------------|---|
| Interferon β -1a | Avonex | http://www.pdr.net/drug-summary/avonex?druglabelid=1623&id=255 |
| | Rebif | http://www.pdr.net/drug-summary/rebif?druglabelid=146 |
| Interferon β -1b | Betaseron | http://www.pdr.net/drug-summary/betaseron?druglabelid=1316 |
| | Extavia | http://www.pdr.net/full-prescribing-information/extavia?druglabelid=428 |
| Glatimer acetate | Copaxone | http://www.pdr.net/full-prescribing-information/copaxone?druglabelid=568 |



FDA-Approved Treatments for MS *Disease-modifying Therapy: Infusion*

| Generic name | Trade Name | Link to PDR.net |
|--------------|------------|---|
| Mitoxantrone | Novantrone | http://www.pdr.net/drug-summary/mitoxantrone?druglabelid=2630 |
| Natalizumab | Tysabri | http://www.pdr.net/drug-summary/tysabri?druglabelid=2802 |



FDA-Approved Treatments for MS
Disease-modifying Therapy: Oral

| Generic name | Trade Name | Link to PDR.net |
|---------------------------|------------|---|
| Fingolimod | Gilenya | http://www.pdr.net/full-prescribing-information/gilenya?druglabelid=432 |
| Teriflunomide | Aubagio | http://www.pdr.net/drug-summary/aubagio?druglabelid=2614 |
| Dimethyl fumarate (BG-12) | Tecfidera | http://www.pdr.net/drug-summary/tecfidera?druglabelid=3095 |



FDA-Approved Treatments for MS
Symptomatic Therapy

| Generic name | Trade name | Link to PDR.net |
|--------------------|------------|---|
| Dalfampridine | Ampyra | http://www.pdr.net/drug-summary/ampyra?druglabelid=1227 |
| OnabotulinumtoxinA | Botox | http://www.pdr.net/drug-summary/botox?druglabelid=52 |