

Multiple Sclerosis

Diagnosing
Treating
Managing Symptoms

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Disclosures for Jennifer Chester

- ▶ Speakers' Bureau:
 - ▶ Biogen, EMD Serono, Abbvie, Biohaven

Disclosures for Jeffrey Kaplan

- ▶ Speaker Bureau:

- ▶ Biogen; Bristol Myers Squibb; Genentech; Genzyme; Horizon; Janssen; Mallinckrodt; Novartis; Teva; and EMD Serono.

Objectives

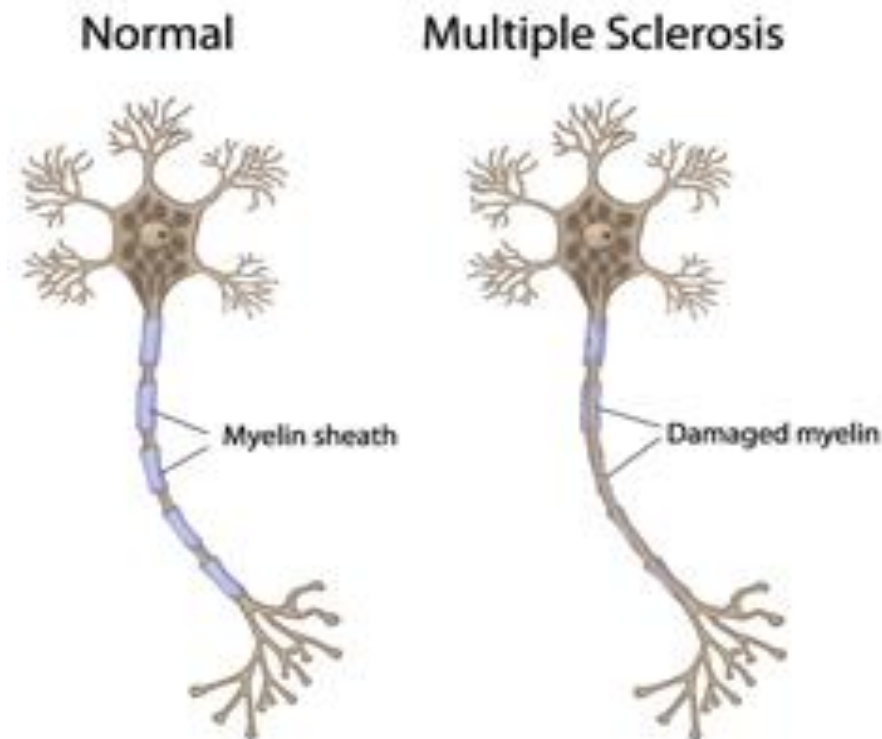
- ▶ 1. List the diagnostic criteria for Multiple Sclerosis (MS)
- ▶ 2. Discuss disease modifying therapies and their mechanism of actions
- ▶ 3. Describe common symptoms of MS and appropriate treatment strategies

Prevalence

- ▶ According to the National MS Society, nearly 1 million people in the United States are affected by MS
- ▶ Most often diagnosed between ages of 20 and 50
- ▶ Affects women more than men
- ▶ People are living longer; treating the geriatric population is challenging.
- ▶ Previously thought to be a disease mostly affecting Caucasian patients but it is now known that the disease is more common in African-American patients.

What is Multiple Sclerosis (MS)?

- ▶ Autoimmune Disorder - Attacks the myelin causing demyelination and axonal/neuronal damage
- ▶ Results in damage or scarring within the brain and spinal cord



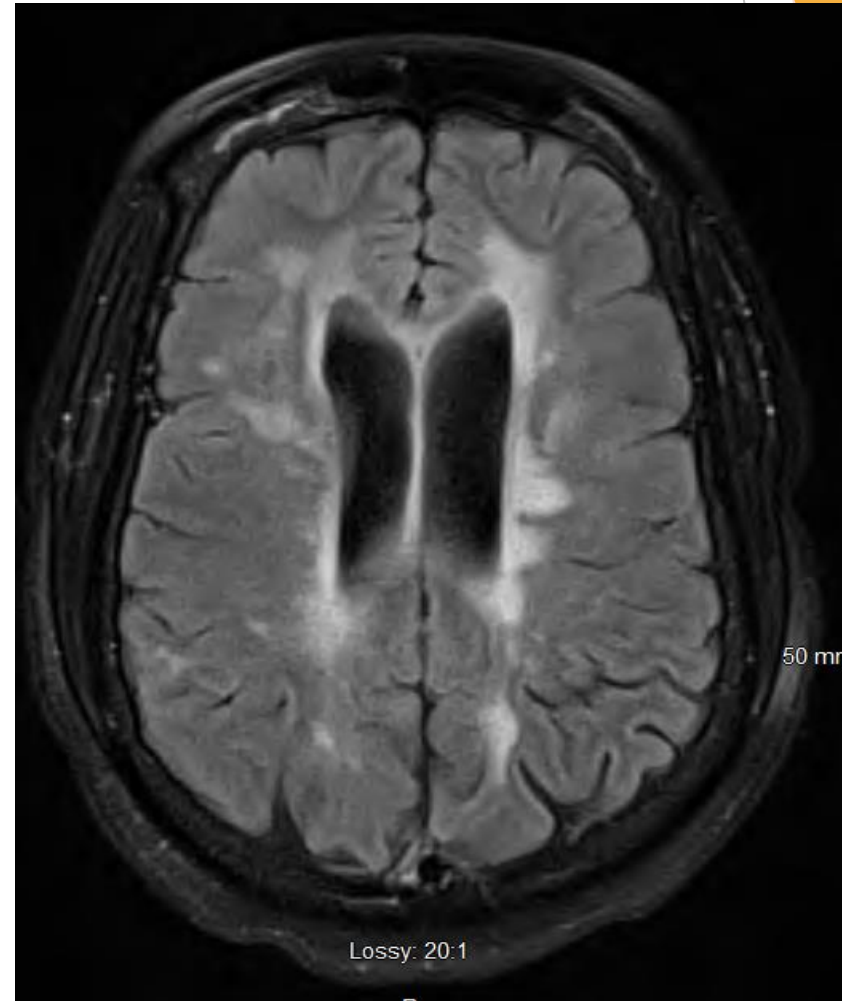
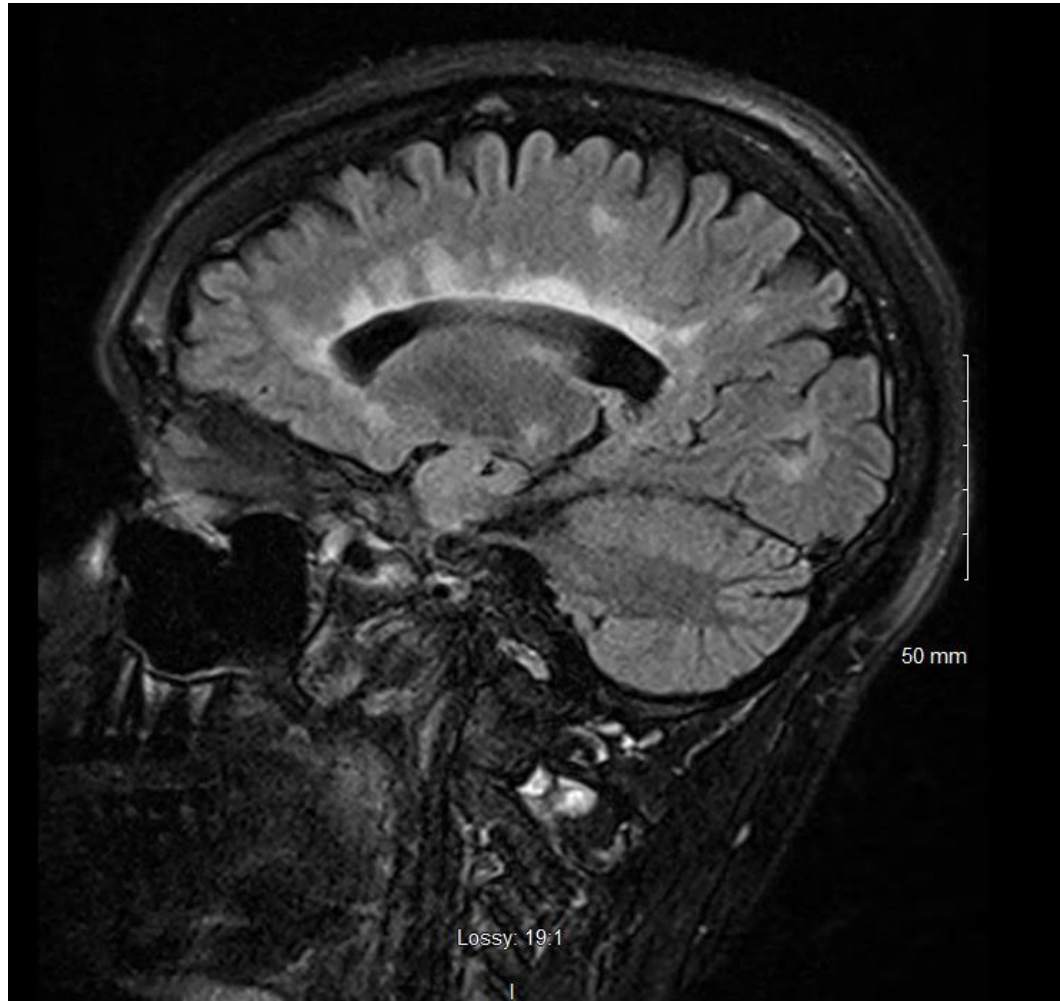
Cause(s)

- ▶ Theoretical causes of MS
 - ▶ Environmental
 - ▶ Genetics
 - ▶ Viral - Epstein Barr
 - ▶ Toxic exposure
 - ▶ Geography

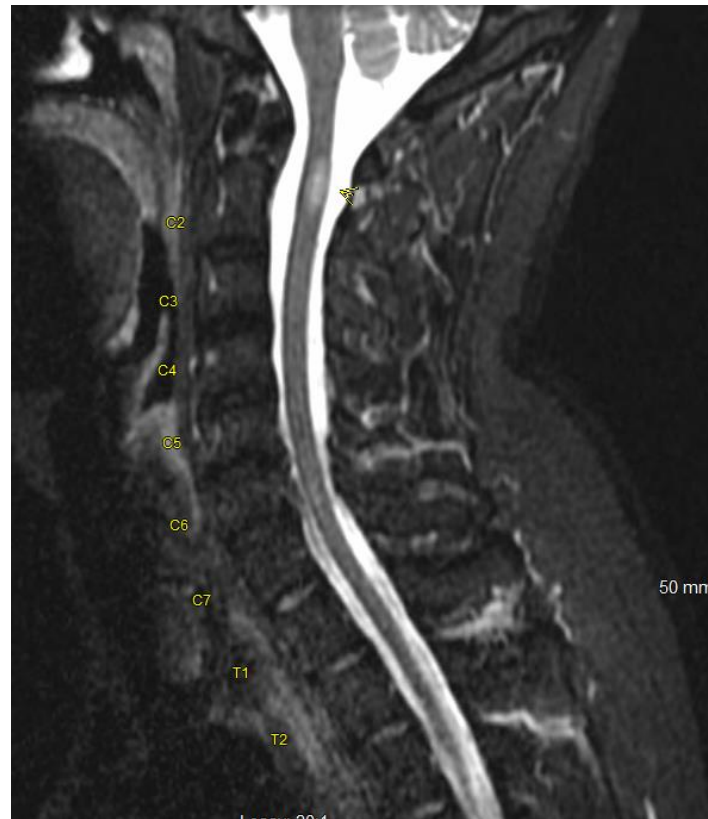
Diagnosis: McDonald Criteria 2017

- ▶ How many attacks or clinical events have they had?
- ▶ How many lesions do they have on their brain and spinal cord?
- ▶ Dissemination in space?
- ▶ Dissemination in time?

MRI Brain



MRI Cervical Spine



Cerebral Spinal Fluid Testing through Lumbar Puncture

- ▶ Presence of Oligoclonal bands (OCB) - indicates chronic immune-activation in the CNS, found in a variety of chronic inflammatory diseases
- ▶ Elevated IgG Index
- ▶ Elevated IgG synthesis

Blood work - other tests to rule out MS mimics

- ▶ Antinuclear Antibody Test (ANA)
- ▶ Angiotensin-converting Enzyme (ACE)
- ▶ Sjogren's Antibody testing (SS-A, SS-B)
- ▶ Rapid plasma regain (RPR) - Syphilis
- ▶ Epstein-Barr Virus (EBV)
- ▶ C-Reactive Protein (CRP)
- ▶ Human immunodeficiency virus (HIV)
- ▶ Sed Rate
- ▶ Copper

Other Demyelinating Illness

- ▶ Neuromyelitis Optica (NMO)
 - ▶ positive Aquaporin 4 antibody
- ▶ Myelin oligodendrocyte glycoprotein associated disease(MOGAD)
 - ▶ positive MOG antibody

Types of MS

- ▶ 1. Clinically Isolated Syndrome (CIS)
- ▶ 2. Relapsing Remitting MS (RRMS)
- ▶ 3. Secondary Progressive MS (SPMS)
- ▶ 4. Primary Progressive MS (PPMS)

Clinically Isolated Syndrome

- ▶ One clinical event corresponding to one lesion in the optic nerve, brain, or spinal cord (If MRI brain reveals even one T2 lesion, in an area of the brain commonly seen in MS, dramatically changes the incidence of developing MS)
- ▶ Do we treat? Or watch? Research favors treatment.
 - ▶ Test CSF
 - ▶ Bands or no bands?
 - ▶ Family history?

Relapsing Remitting MS (RRMS)

- ▶ About 80% of patients with MS
- ▶ Clearly defined attacks of new or recurrent neurologic symptoms (Relapses), may experience full or partial recover after attack
 - ▶ **Definition:** new or worsened symptom that lasts more than 24 hours, 30 days from last episode
 - ▶ **Treatment:** high dose steroids, plasma exchange

Secondary Progressive MS (SPMS)

- ▶ Initially present with RRMS, then after years of disease progression, continue to experience relapses but with worsened progression of symptoms between attacks. Eventually leads to worsened disability with no further attacks.
- ▶ “Approximately 90% of patients with RRMS convert to SPMS after 25 years”, Hunter (2016).

Primary Progressive MS (PPMS)

- ▶ Disease progression with disability from the onset, typically, no true relapses.
- ▶ 20% of patients with MS
- ▶ Does not respond well to treatment with disease modifying agents.

Disease Modifying Therapy (DMT)

- ▶ Over 20 FDA approved treatments for MS
- ▶ First drug was approved in 1993
- ▶ Medications target specific aspects of the immune system to slow or stop disease progression
- ▶ Will NOT improve symptoms of MS!

Progressive Multifocal Leukoencephalopathy (PML)

- ▶ Higher risk with natalizumab (Tysabri), also seen in other medications
- ▶ Caused by the John Cunningham virus (JCV) - more than half of all adults have been exposed, only a problem with weakened immune systems
 - ▶ Blood test for JCV status

Immunomodulators - Injectables

- ▶ **Interferon Beta 1a (Avonex, Rebif)** - binds to type 1 interferon receptors and activates tyrosine kinase, producing antiviral, antiproliferative, and immunomodulatory effects
- ▶ **Interferon Beta 1b (Betaseron)** - same as 1a
- ▶ **Glatiramir (Copaxone)** - induces and activates suppressor T-cells, modifying immune processes
- ▶ **Peginterferon beta-1a (Plegridy)** - long acting, less injections

Immunomodulators - Orals

- ▶ **Fumarates (Tecfidera, Vumerity, Bafiertam)** - activates nuclear factor-like 2 (Nrf2) pathway, resulting in cellular response to oxidative stress
 - ▶ 3 FDA approved medications in this class, 1 has gone generic
- ▶ **S1P Receptor (Gilenya, Mayzent, Zeposia, Ponvory)**- non-selectively binds to sphingosine 1-phosphate receptors; reduces lymphocyte egress from lymph nodes and migration in CNS
 - ▶ 4 FDA approved medications in this class, 1 just went generic

Immunomodulators - Oral, continued...

- ▶ **Teriflunomide (Aubagio)** - inhibits pyrimidine synthesis via dihydroorotate dehydrogenase (DHODH) inhibition, resulting in immunomodulatory and anti-inflammatory effects, may reduce the number of activated lymphocytes in CNS
 - ▶ Only 1 FDA approved medication in this class, going generic soon

Immunomodulator - intravenous

- ▶ **Natalizumab (Tysabri)** - binds integrins on leukocyte cell walls, preventing migration into inflamed parenchymal tissue (monoclonal antibody)
 - ▶ Risk for PML
 - ▶ Infuse every 4 - 6 weeks
 - ▶ Considered most effective drug to treat MS, no head to head trials

Immunosuppressants - intravenous

- ▶ Rituximab (Rituxan), Ocrelizumab (Ocrevus), and Ublituximab (Briumvi).
- ▶ Binds to B-cell (lymphocyte) CD20 surface antigens (monoclonal antibody) resulting in lysis.
- ▶ All are infused every 6 months

Immunosuppressant - injectable

- ▶ **Ofatumumab (Kesimpta)** - binds to B-lymphocyte CD20 surface antigens, resulting in lysis (monoclonal antibody)
 - ▶ Injected monthly

Immune Depletion and Reconstitution

- ▶ **Alemtuzumab (Lemtrada)** - binds to CD52 surface antigen of multiple cell types, resulting in lysis (monoclonal antibody), given intravenous
 - ▶ Given 5 days year 1, 3 days year 2; monthly lab work for 4 years
 - ▶ High efficacy, high risk
- ▶ **Cladribine (Mavenclad)** - impairs DNA synthesis with cytotoxic effects on B and T-lymphocytes, resulting in lymphocyte depletion, given orally
 - ▶ Given 8 - 10 days year 1 and 8 - 10 days year 2
 - ▶ weight based dosing

Monitoring while on DMT

- ▶ Depends on DMT
- ▶ Typically CBC and CMP
- ▶ Also consider GAME and Subsets, CD19, CD20, CD4, CD8
- ▶ Vitamin D
- ▶ MRIs of brain and spinal cord, at least annually, more often if JCV positive and on natalizumab

On the Horizon

▶ BTK inhibitors

- ▶ new class being studied, in Phase 2 and Phase 3 studies now
- ▶ Disrupts the signaling pathway in both normal and malignant B-cells

▶ Re-myelination

▶ Biomarkers

- ▶ Neurofilament light (NFL) protein

Symptoms of MS

- ▶ Anxiety and depression
- ▶ Bladder and bowel dysfunction
- ▶ Fatigue
- ▶ Gait difficulties
- ▶ Heat sensitivity
- ▶ MS Hug
- ▶ Numbness and tingling
- ▶ Vision changes
- ▶ Nerve Pain
- ▶ Spasticity
- ▶ Dizziness
- ▶ Weakness

Depression and Cognitive Changes

- ▶ 40 - 70% of patients with MS will show intellectual impairments and will increase with disease duration
- ▶ Affects employment and quality of life
- ▶ Dementia is not common
- ▶ MOCA, SLUMS, SDMT, Neuropsych testing
- ▶ Treatment: SSRIs, TCAs, SNRIs, NDRI, counseling

Bladder Dysfunction

- ▶ 80% of newly diagnosed MS patients, prevalence of 96% after 10 years
- ▶ Complicating factors: age, pregnancy
- ▶ Treatment: anti-muscarinic, anti-cholinergic or a mixed agent
- ▶ Refer to Urology

Bowel Dysfunction

- ▶ Incidence is less common
- ▶ May be side effect of medication, related to spinal cord lesion, or decreased mobility
- ▶ Treatment: Dietary changes, bulking agents, osmotic agents, enemas or suppository agents, stimulant agents, stool softeners, surgery
- ▶ Referral to GI

Fatigue

- ▶ More than 75% of MS patients
- ▶ “significant lack of physical and/or mental energy that is perceived by the individual or caretaker to interfere with usual or desired activity” (Clinician Reviews, June 2017)
- ▶ Primary fatigue - caused by disease itself
- ▶ Secondary fatigue - other cause, i.e. anemia, infection, insomnia
- ▶ Treatment: CBT, rest, exercise, medication (armodafinil, amantadine, stimulants), stress management, OT/PT

Gait Difficulties

- ▶ Ataxia
- ▶ Foot Drop
- ▶ Spasticity
- ▶ Weakness
- ▶ Assistive devices - cane, walker, electrical stimulation, bracing
- ▶ Physical Therapy
- ▶ Treatment: dalfampridine (Ampyra)

Heat Sensitivity

- ▶ **Uhthoff's Phenomenon** - exposure to heat, infection, or psychological stress, the perimenstrual period, or prolonged exercise may cause unmasking or worsening of neurologic symptoms
- ▶ Usually reversible
- ▶ Cooling methods: ingest cold liquids, cold shower, cooling vests, cold towel

MS Hug

- ▶ Tightness or pressure around chest and abdomen
- ▶ VERY PAINFUL
- ▶ Treatment: diazepam, other muscle relaxants

Numbness and tingling

- ▶ No treatment for numbness
- ▶ Paresthesias: can be very painful
- ▶ Determine cause once relapse is ruled out
- ▶ Treatment: gabapentin, nortriptyline, oxcarbazepine, topical creams, etc.

Vision Changes

- ▶ Optic Neuritis - loss of visual acuity, visual field defects, impaired color vision (especially green and red), and reduced intensity of light perception
 - ▶ Optic disc pallor on exam
- ▶ Symptoms can be exacerbated with Uhthoff's Phenomenon
- ▶ Internuclear ophthalmoparesis (INO), adduction slowing and abduction nystagmus during horizontal eye movements
- ▶ Treatment: steroids for acute case
- ▶ Refer to Neuro-ophthomology

Sexual Dysfunction

- ▶ Prevalence among patients with MS is twice that reported in individuals with other chronic disease and up to 5 times higher than the general population.
- ▶ Primary: caused by MS
- ▶ Secondary: consequence of MS or side effect of medication
- ▶ Tertiary: psychological, emotional and cultural influences
- ▶ Refer: Counseling, Urology, GYN, Psychiatry
- ▶ Be willing to discuss!

Spasticity

- ▶ Greater than 80% of patients with MS reports some spasticity, one-third reports significance that affects daily lives
- ▶ Daily stretching
- ▶ Oral medications: baclofen, tizanidine, diazepam
- ▶ Onabotulinum toxin
- ▶ Intra-thecal baclofen (ITB) pump
- ▶ Cannabis currently being studied

Sleep Disorders

- ▶ Difficulty falling asleep or difficulty staying asleep
- ▶ Excessive fatigue? Sleep study, possible obstructive sleep apnea
- ▶ Ask about restless legs or periodic limb movement disorder
- ▶ Nocturia

Swallowing and Speech Disorders

- ▶ Aspiration pneumonia is reported to be a leading cause of death in patients with MS.
- ▶ Screen for swallow problems - order swallow study, speech therapy
- ▶ Speech problems - spastic-ataxic dysarthria

Vestibular Dysfunction

- ▶ Benign paroxysmal positional vertigo (BPPV) is most common cause of vertigo
- ▶ Other cause: lesion location, migraines, virus
- ▶ Physical Therapy, Balance Institute
- ▶ Treatment - home exercises, meclizine, diazepam

Haematopoietic stem cell transplantation (HSCT)

- ▶ NOT FDA Approved
- ▶ Haematopoietic stem cells are taken from the bone marrow or blood, then a chemotherapy drug is used to wipe out the immune system. The stem cells are then reintroduced into the blood where a new immune system is formed that will no longer attack the myelin.
- ▶ High risk, highly effective

Questions?



Kansas City MS Center

References

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