An Update on Multiple Sclerosis

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Multiple Sclerosis: Basic Facts

- An inflammatory demyelinating disease of the CNS. In its most common form (relapsing remitting MS; 85%), lesions/ clinical attacks are disseminated in time and space. Primary progressive MS (PPMS; 15%) is characterized by the gradual accumulation of disability from the time of initial clinical presentation.
- MS is the most common cause of non-traumatic neurological disability among young adults in the Western Hemisphere
- RRMS typically presents in young adulthood (20's-30's) with a female: male ratio of approximately 2-3:1
  PPMS typically presents in early middle age (40's-50's) with a female: male ratio of approximately 1:1

Epidemiology

- There are more than 2.3 million individuals with MS worldwide. However this number is likely an underestimate. Several studies indicate that the incidence of MS has been increasing at a significant rate, particularly among women and that MS is more common among African and Hispanic Americans than previously appreciated

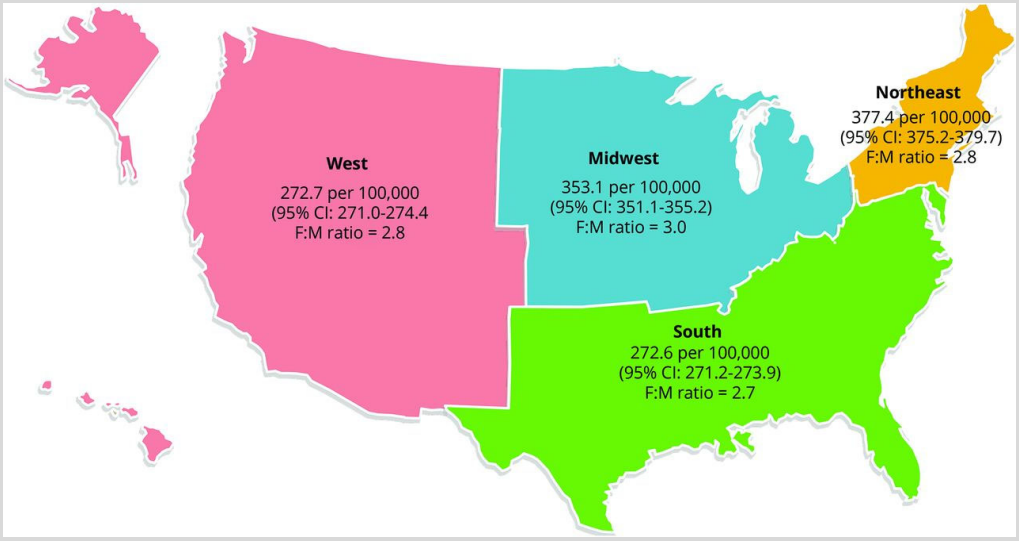
  Front Neurol. 2018;9:871; PLoS One. 2012;7(10):e48078; Neurol Clin. 2018;36(1):151

- The prevalence of MS has been rising in North America over the past 5 decades. In the most recent large scale study in the United States, the authors estimated the prevalence of MS to range from 851,749 - 913,925 persons.

  Neurology 2019;92(10):e1029

- MS tends to be more prevalent with increasing distance from the Equator. High incidence areas include Scandanavia, the northern UK, Canada and the northern United States.

2010 prevalence of MS in the United States per 100,000 population



Neurology 2019;92(10): e1029-e1040

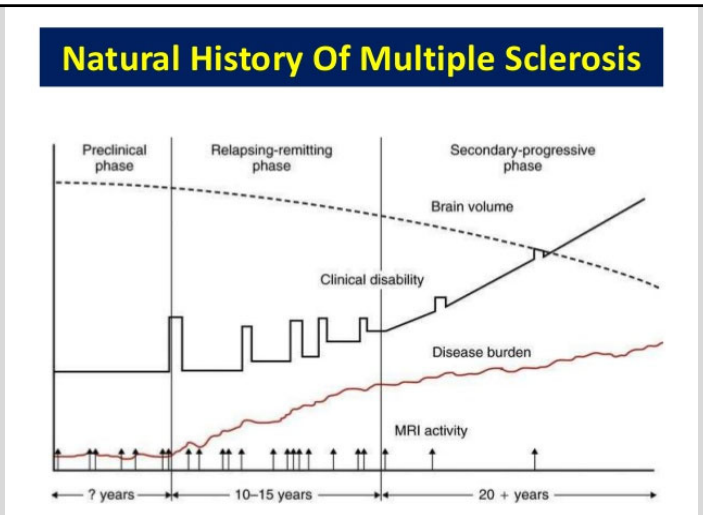
Risk Factors

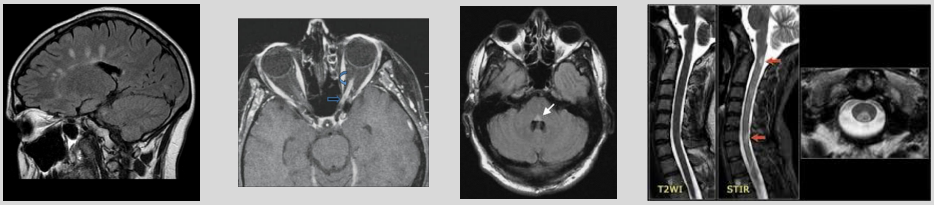
Genetic

- 1st degree relatives are at increased risk (2-4% versus 0.1-0.3% in general population)
- Approximately 20-30% of monozygotic twins of individuals with MS will eventually be diagnosed with the disease
- Over 200 MS genetic susceptibility loci have been identified, each of which contributes a small amount to overall risk. Strongest association is with genes in the MHC Class II region.

Environmental

- Geographic (Northern to Southern gradient in US and Europe). Migration studies demonstrate that risk is dependent on residence prior to adolescence.
- Low serum Vitamin D levels; low cumulative sun light exposure
- Exposure to Epstein Barr Virus as an adult
- Smoking is associated with a worse clinical course and, possibly to increased susceptibility

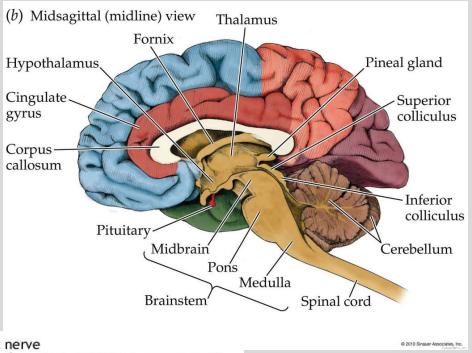


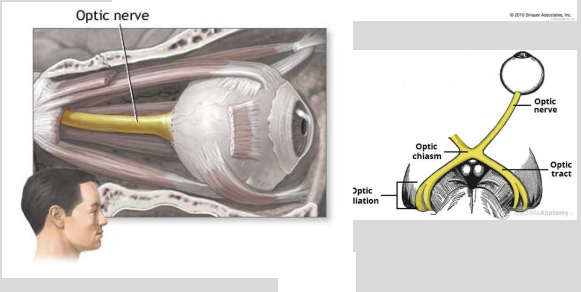


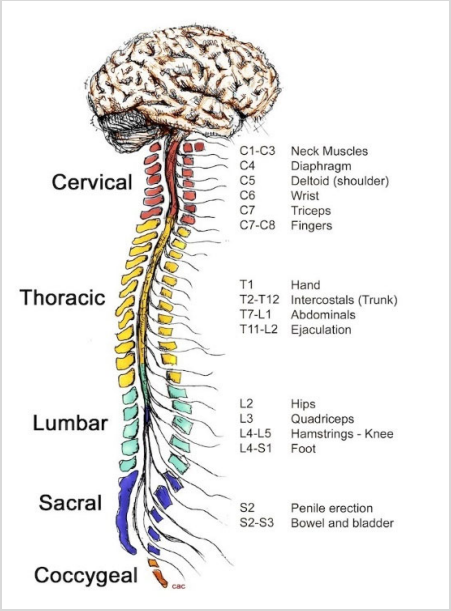
The MS "Prodrome"

- In the years leading up to MS diagnosis, patients have increased symptoms leading to increased health care visits. These symptoms are variable and do not suggest focal neurological deficits.
- The year before the first clinical episode of inflammatory demyelination there is a 78% increase in the rate of hospitalizations, an 88% increase in the rate of physician service use, and a 49% increase in the number of prescriptions filled.
- The symptoms/ diagnoses associated with increased health care visits include headache, fibromyalgia, urological complaints, irritable bowel syndrome, anxiety, depression and fatigue. There is an approximately 50% increase in psychiatrist or general physician visits for mental health issues in the 5 years prior to MS onset.
- Cognitive decline is measurable 2 years before MS symptom onset.
- A similar prodromal period has been described in other autoimmune disease such as rheumatoid arthritis and inflammatory bowel disease.

Multiple Sclerosis lesions can form at any site within the Central Nervous System







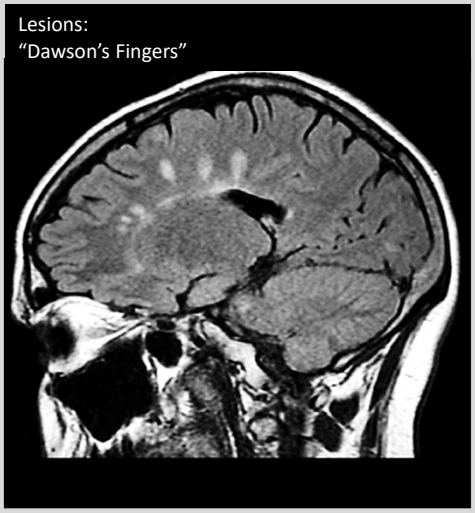
Common Ways that MS Presents: Multiple Sclerosis: Depend on lesion location	
Optic Neuritis (Optic Nerves)	Vision loss in one eye; pain on eye movement; red desaturation
Transverse Myelitis (Spinal cord)	Leg weakness; numbness and/ or tingling from the feet to the chest or abdomen); L'hermitte's sign (sudden buzzing or electric shock sensation that travels down the neck or spine, triggered by neck flexion); MS "hug"; urinary and/ or fecal sphincter dysfunction (over- or under-active bladder); sexual dysfunction
Posterior Fossa Syndrome (Brainstem /cerebellum)	Double vision; oscillopsia (bouncing vision); facial droop; facial numbness; vertigo; gait imbalance; slurred speech; difficulty swallowing; discoordinated/ imprecise movement of the limbs, intention tremor (tremor gets worse as you get closer to the target)
Other clinical manifestations	Fatigue Paroxysmal symptoms (including trigeminal neuralgia) Spasms/ spasticity Spastic gait (stiff legged with circumduction and foot drop) Cognitive impairment

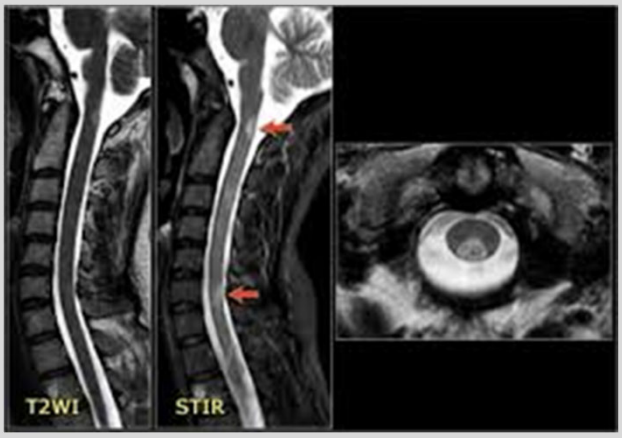
Eponymous Syndromes of MS

Uhthoff's Phenomenon:
Symptoms tend to resurface or get worse when body temperature rises

Magnetic Resonance Imaging (MRI) findings in MS

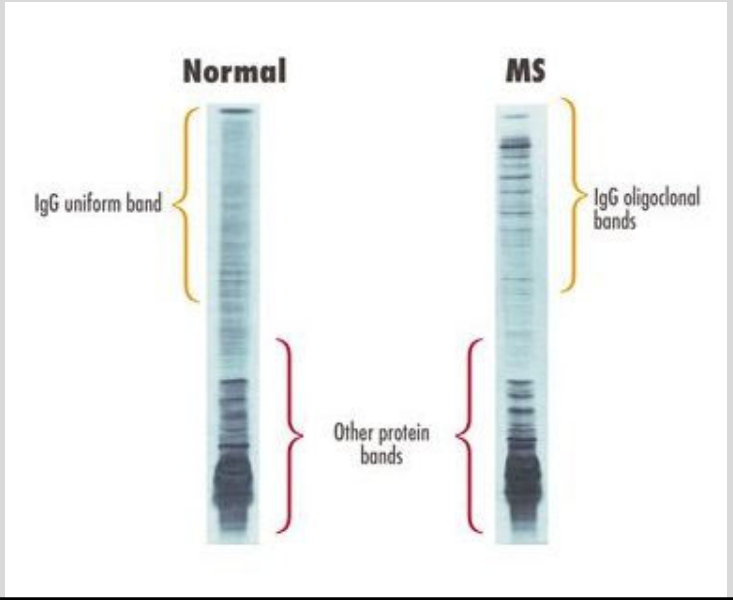
The majority of lesions are asymptomatic



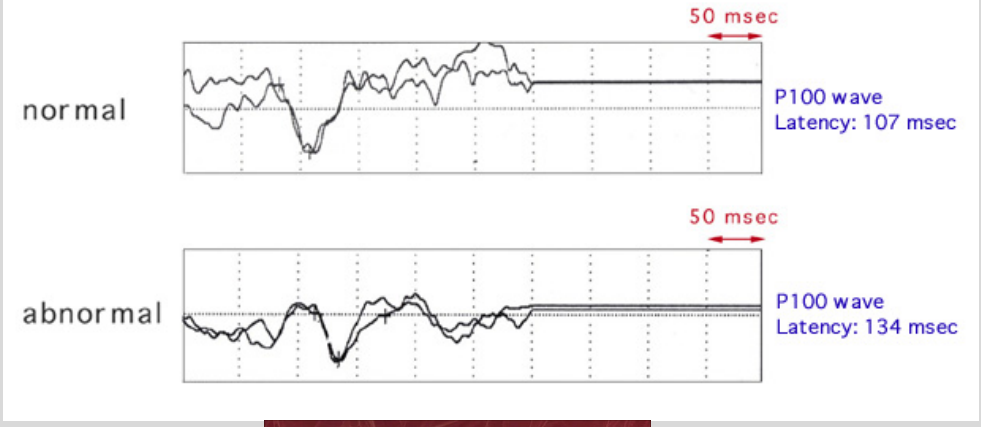


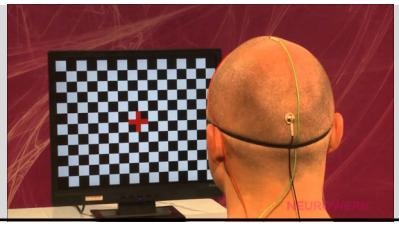
CSF Oligoclonal Bands

(must be absent in serum)



Visual Evoked Potentials





Accuracy of Referrals

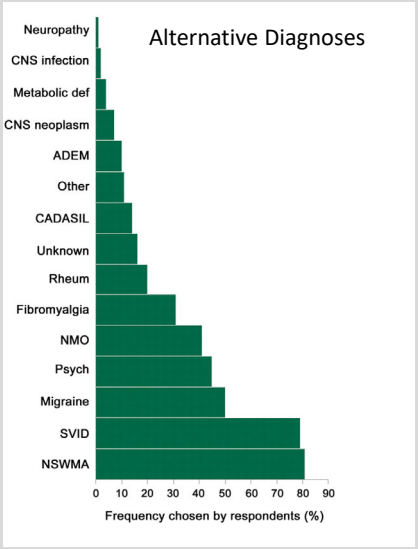
Institution	% with final dx of MS/ CIS	Alternative Diagnoses	Referral Source	Citation
St. Vincent's Hospital, Dublin, Ireland	49% (119/244)	neuropathy, migraine with aura, myelopathy, focal seizure disorders. Also CADASIL, neuro-bechet's	"Majority of referrals were from general practitioners"	Mult Scler. 2011 Aug;17(8):1017-21
American University of Beirut Medical Center, Lebanon and Amiri Hospitals Kuwait	70% (300/431)	Psychogenic, non-specific MRI white matter lesions, NMO, systemic autoimmune disorders	Approximately 50% of referrals from neurologists	Mult Scler Relat Disord. 2017 Nov;18:85-89
University of Colorado, USA	33% (93/281)	Migraine, stroke, neuropathy, transverse myelitis,, cervical stenosis, ADEM, possible psychiatric disease, unclear dx	64% primary care physicians, 25% neurologists, 11% other physicians	Arch Neurol. 2005 Apr;62(4):585-90

Rates of misdiagnosis of MS: a cross-sectional survey of 122 MS specialists in the USA and Canada

Table 2 Patients misdiagnosed with multiple sclerosis

Characteristics	No. (%)
Evaluated a misdiagnosed patient within last year	
Yes	116 (95.1)
No	6 (4.9)
No. seen within last year	
1-2	30 (25.9)
3-5	46 (39.7)
6-10	20 (17.2)
≥10	20 (17.2)
Estimated on DMT	
0%	6 (5.2)
1-25%	35 (30.2)
26-50%	28 (24.1)
51-75%	17 (14.7)
≥75%	30 (25.9)

Abbreviation: DMT = disease-modifying therapy.



Neurology. 2012 Jun 12;78(24):1986-91

Clinical Features of Relapsing Remitting Multiple Sclerosis

Dissemination in Time and Space; Discrete and diverse episodes of neurological function

Kinetics and Duration of Exacerbations

- Symptoms reach peak intensity over days to weeks. Exacerbations tend to be followed by full (particularly early in the course) or partial recovery.
- Episodes typically last 3 months or less (meaning the full extent of recovery is realized within that time frame). Though patients can continue to improve over a 9 month time frame.

Heterogeneity of Exacerbations

- Symptoms often vary from 1 exacerbation to the next, though the same symptom can recur multiple times during the clinical course

Chronic Sx

- The most common symptoms of MS is fatigue which, unlike the symptoms that occur during relapses, is chronic. Fatigue does not correlate with lesion burden or location. Subtle cognitive changes can arise even early in the course (difficulty with attention, muti-tasking, processing speed)

Clinical Features of Progressive Multiple Sclerosis

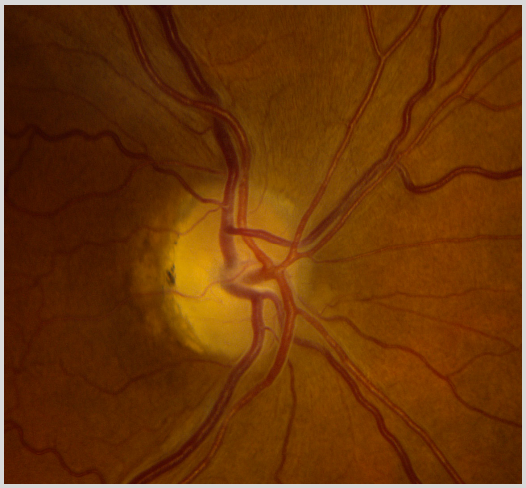
- Gradual accumulation of disability (not stable residual deficits following an exacerbation)
- Commons symptoms in progressive MS are increasing weakness and spasticity of a limb or multiple limbs (ex. both legs), worsening numbness or paresthesias of the extremities, and/ or gait imbalance. Dementia can also occur.
- These slow worsening symptoms can plateau during different time periods, but they do not remit
- Acute declines can occur in the setting of infection (manifestation of Uhthoff's). However, on occasion progressive patients can experience bonafide exacerbations superimposed on the gradual decline

Elements of the History

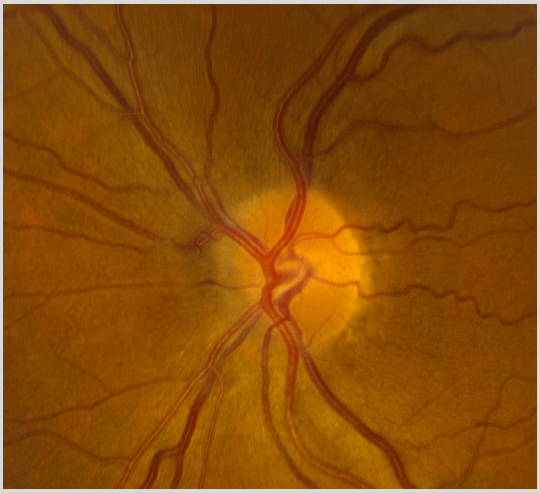
- **Demographics** *age, sex, ethnicity*
- **Presenting episode** *symptoms and signs, kinetics, duration, extent of recovery*
- **Subsequent relapses** *symptoms and signs, kinetics, duration, extent of recovery*
- **Chronic Sx** fatigue, cognitive impairment, bladder/ bowel/ sexual dysfunction/ neuropathic pain, spasms/ spasticity, gait disorders, Uhthoff's phenomenon, L'hermitte's, MS "hug"
- **Progressive Sx** gradual accumulation of disability
- **Paroxysmal symptoms** sudden onset, transient, repetitive (ex. dystonia/ trigeminal neuralgia)
- **Family hx** *2-5% of 1st degree relatives also have MS; increased incidence of psoriasis, thyroiditis, IBD*
- **Environmental Risk Factors** viral infections in relation to exacerbation/ infectious mononucleosis; sun exposure / vitamin D supplementation; cigarette smoking
- **Co-morbidities** diabetes, cardiovascular disease, rheumatological disease, depression
- **Screening for entitites in Differential dx** sarcoidosis (chronic cough, uveitis, rashes/ bumps), lupus/ connective tissue disease (joint pains/ swelling, malar rash; kidney failure); Lyme's disease (tick exposure, target rash, joint aches)

Classical Physical Exam Findings in MS

Optic disc pallor temporally, right eye.

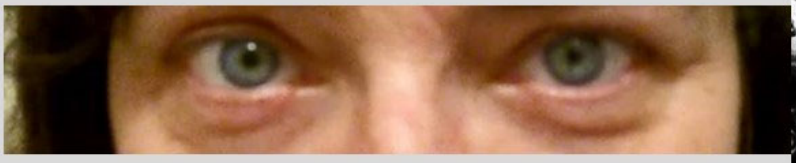


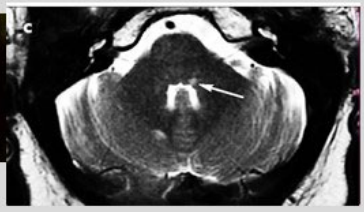
Left eye normal



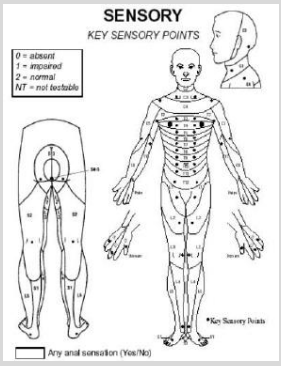
Right afferent pupillary defect

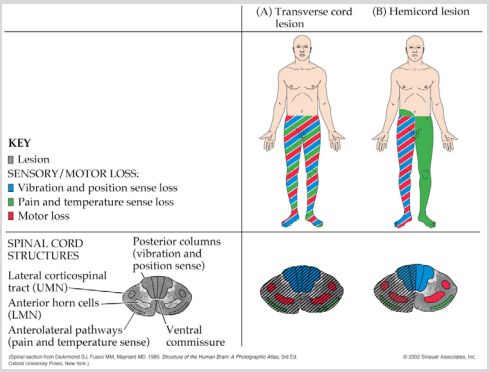
Internuclear Ophthamoplegia





Sensory Level Secondary Spinal Cord Lesion





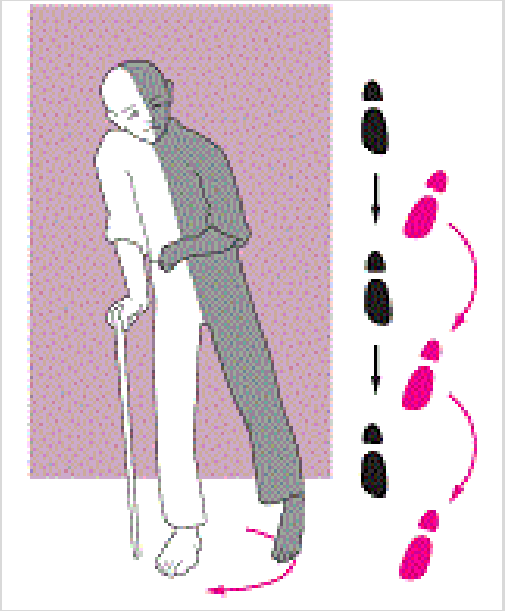
Proprioception

- If patient cannot detect small amplitude movements, or makes errors, increase the amplitude of movement
- If patient cannot detect larger amplitude movements, test proprioception at a more proximal joint (see next slide)

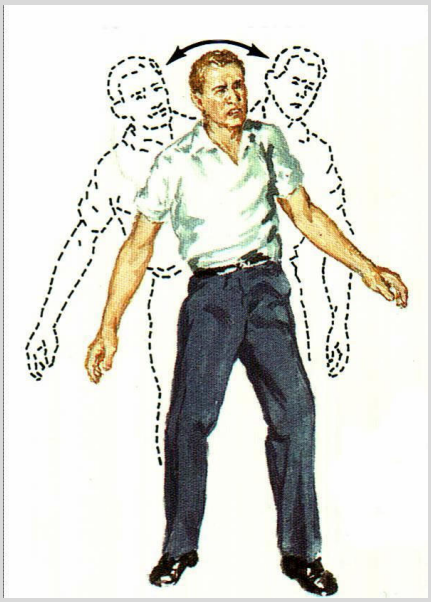
Vibratory Sense

- 128 or 256 Hz Tuning fork
- If impaired, proceed proximally

Spastic Gait

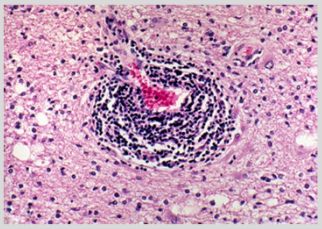


Ataxia

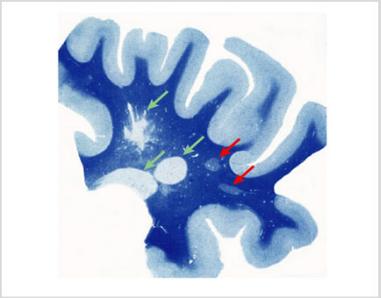


Neuropathological Features of MS

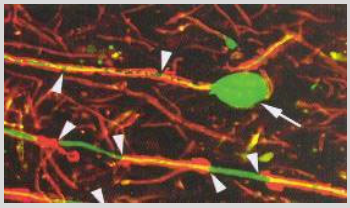
Perivascular infiltrates

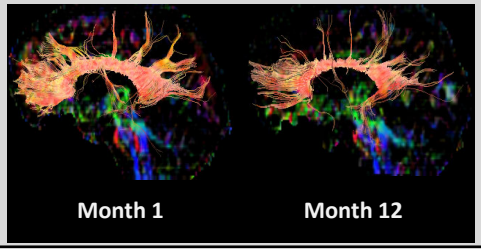


Demyelination

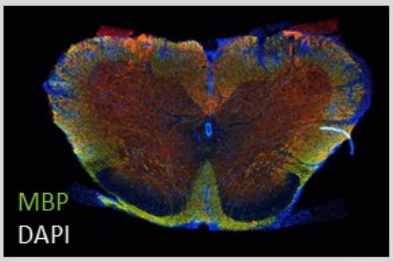


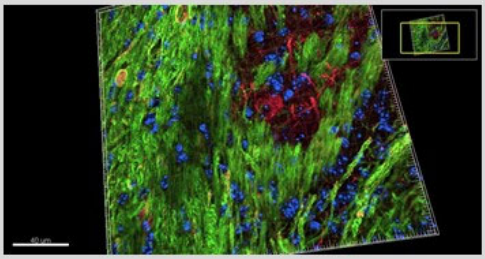
Axonopathy

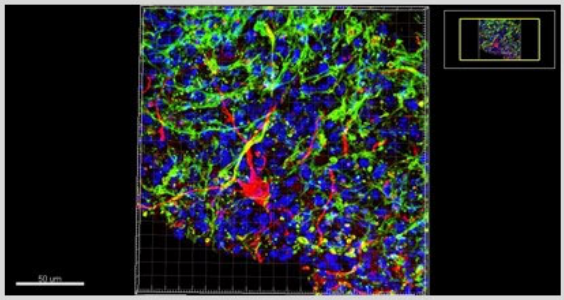


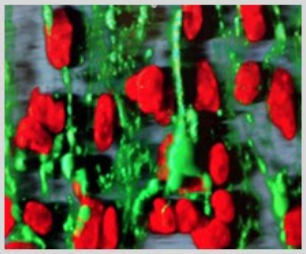


Demyelination and Inflammation in the Spinal Cord







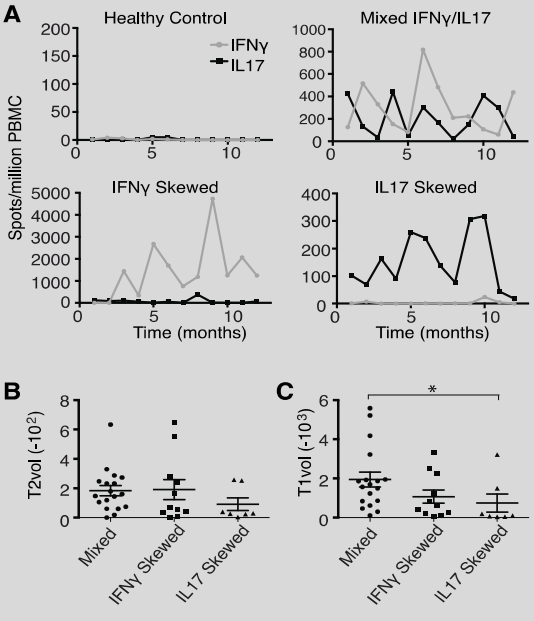


DAPI CTB-Tracer

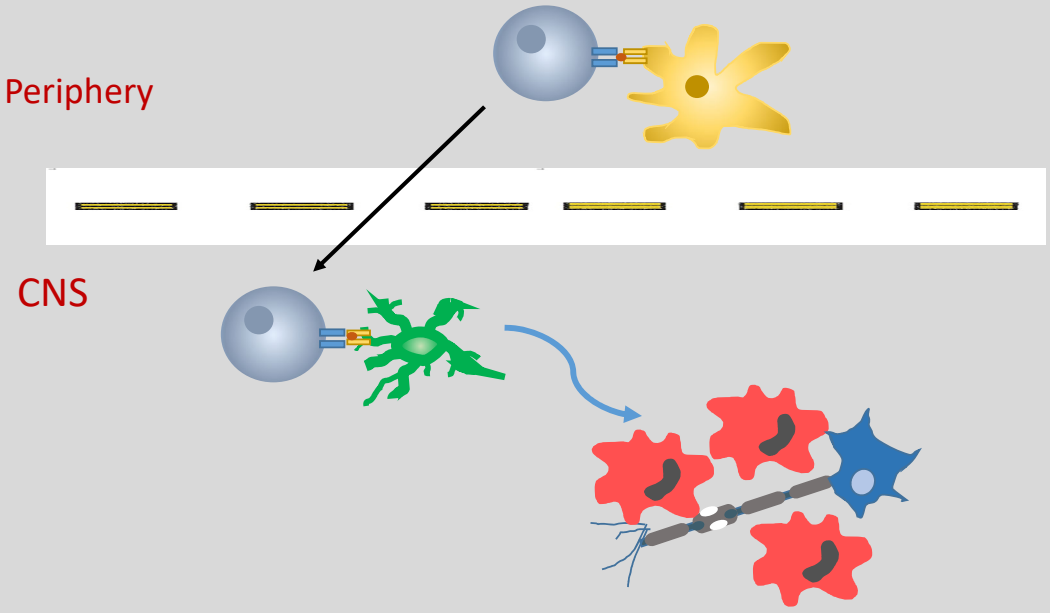
Evidence supporting an autoimmune etiology of MS

- There is abnormal neuroinflammation in the absence of overt infection or tumor
- $CD4^+$ and $CD8^+$ T cells and activated macrophages, dendritic cells and microglia are prominent constituents of perivascular infiltrates
- MHC Class II genes are associated with susceptibility, implicating a functional role of CD4+ T cells. GWAS studies demonstrate that MS clusters with other autoimmune diseases.
- Oligoclonal bands (monoclonal antibodies) are present in the CSF of most MS patients
- An inflammatory demyelinating disease of the CNS can be induced in laboratory animals via active immunization with myelin proteins/ peptides or by the adoptive transfer of myelin-reactive $CD4^+$ T cells. This animal model, referred to as experimental autoimmune encephalomyelitis (EAE), has clinical and histopathological similarities with MS.
- Lymphocyte targeting agents (alemtuzamab, rituximab/ocrelizumab, fingolimod/ siponimod) suppress relapses and new lesion formation

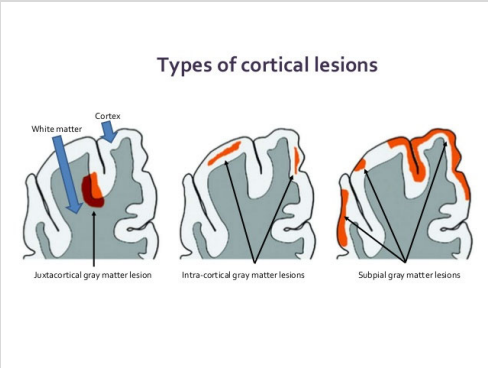
Sustained myelin-reactive IFNg- or IL-17- skewed immune responses in MS



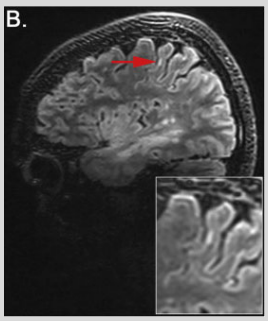
"T CELL- CENTRIC" MODEL OF MS PATHOGENESIS



Neurodegenerative Aspects of MS:
Cortical Lesions occur in MS but are not visible on conventional MRI



7 Tesla MRI

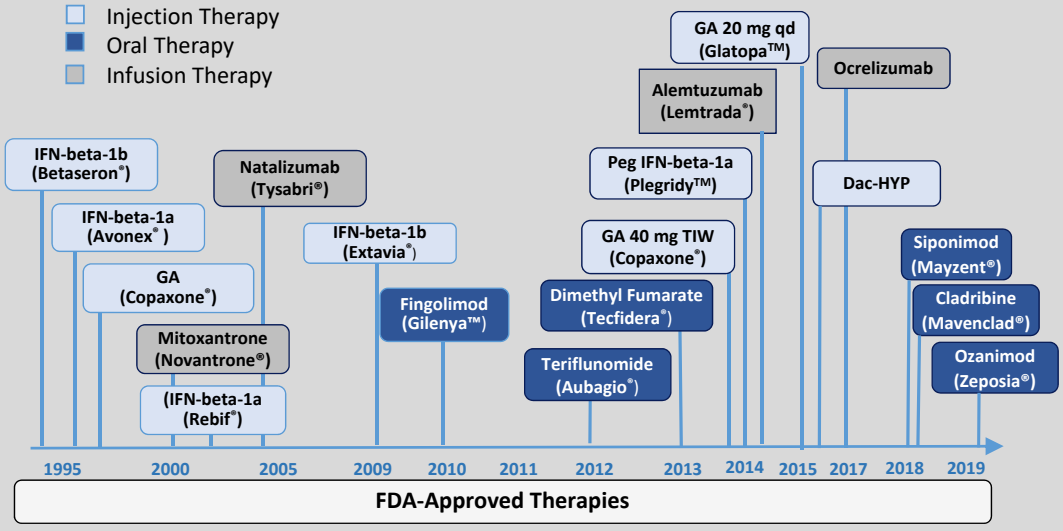


Neuroimage. 2018; 168:477-489

Disease Modifying Therapies in MS

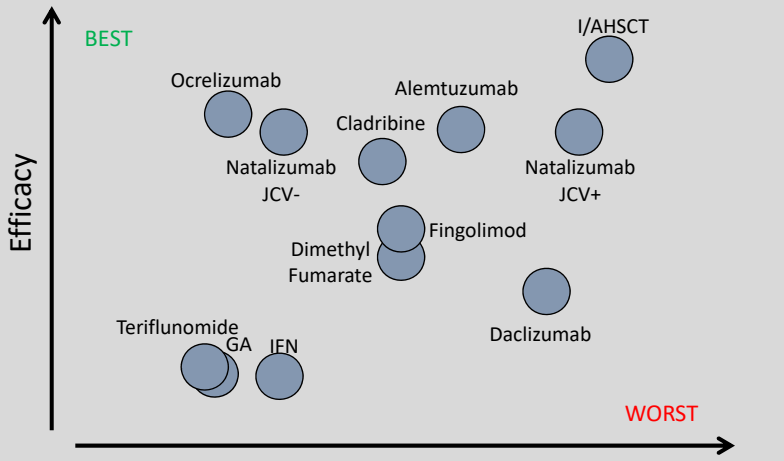
- There are currently over 15 DMTs that are FDA approved for the treatment of relapsing or "active" forms of MS
- These drugs significantly reduce the annualized relapse rate (ranging from 25 to 80% or higher) and the frequency of gadolinium enhancing or new T2 white matter lesions
- Many have been shown to slow disability accumulation, cognitive decline and rates of cerebral atrophy
- The introduction of DMT has represented a major advance in the treatment of individuals with RRMS and has had a profound impact by mitigating morbidity and enhancing quality of life.
- However, each of these drugs has a unique side effect profile. Rare serious infections can occur, with individual drugs increasing the risk for specific infections. The higher efficacy agents tend to impose greater risks.

Evolving relapsing MS treatment landscape



Adapted from Wingerchuk DM, Weinshenker BG. *BMJ* 2016;354:13518

Overview of RRMS DMTs



Challenges

None are cures.

There is a paucity of effective treatments for PMS

New generation DMT in RRMS are designed to target lymphocytes

- Natalizumab (Tysabri™) is a monoclonal antibody against α4 integrin that blocks lymphocyte trafficking across the blood-brain-barrier
- Fingolimod (Gilenya™), Siponimod (Mayzent™), and Ozanimod (Zeposia™) are sphingosine-1-phosphate receptor modulators that inhibit the egress of lymphocytes from lymph nodes to the circulation, thereby curtailing their migration to the CNS
- Alemtuzamab (Lemtrada™) is a monoclonal antibody against CD52 that depletes lymphocytes
- Ocrelizumab (Ocrevus™), Rituximab, and Ofatumamab are monoclonal antibodies that deplete B cells
- Cladribine (Mavenclad™) is a purine analog and global immunosuppressant

Two general approaches to disease modification in MS

Escalation approach

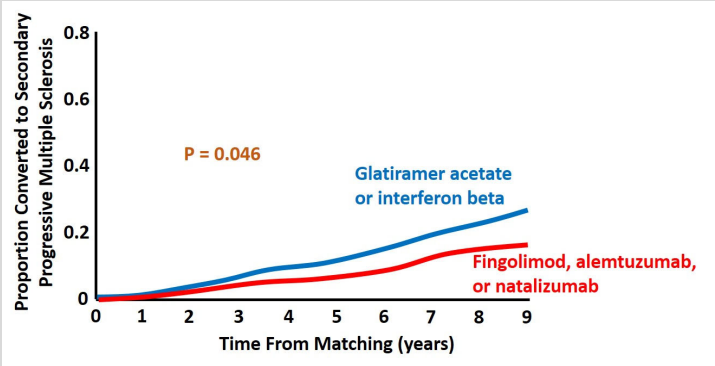
- Initiate therapy with a safe medication, albeit with modest efficacy
- Escalate to more efficacious therapies based on presence of on-going disease activity
- Minimizes risk overall by limiting exposure to medications with greater risk to cases where disease characteristics warrant it

Early high-efficacy approach

- Initiate therapy with or switch early to one of the high efficacy medications
- To minimize risk, based on demographics, comorbidities, other risk factors, special circumstances
  - Select the specific high efficacy medication
  - Identify selected patients for whom a lower efficacy agent is more appropriate
- Maximizes exposure to potent anti-inflammatory effects early in the disease when it is most likely to be beneficial

Adapted from J. Cohen, Cleveland Clinic

Initial DMT and rate of conversion to SPMS



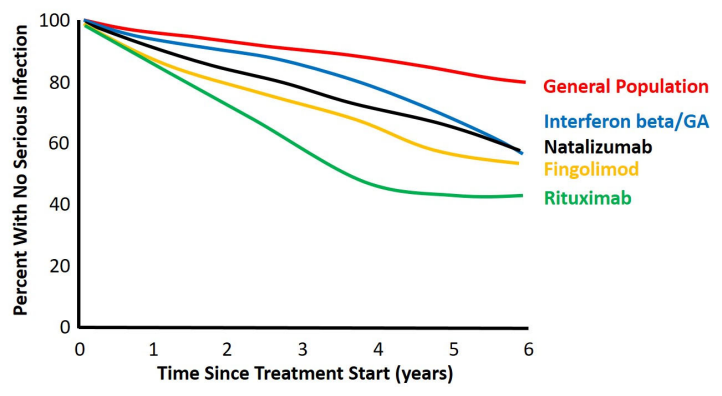
- Propensity matched cohort of 1555 patients RRMS at 68 centers commencing DMT or monitoring 1988-2012 with 4-yrs followup
- Lower risk of SPMS in patients treated initially with fingolimod, alemtuzumab, or natalizumab vs IFN/GA HR=0.66

Brown JWL et al. JAMA 2019;321:175-187

DMT side effect profiles

- IFNβ- injection site reactions, flu-like SX, depression, elevated LFTs
- Glatiramer Acetate- injection site reactions, lipoatrophy
- Teriflunomide- hepatotoxicity, teratogenicity
- Dimethylfumarate- flushing, GI upset, PML (very rare)
- Fingolimod, siponimod, ozanimod- Atrioventricular conduction slowing, macular edema, herpes infections, cryptococcal meningitis, atypical mycobacteria, PML (very rare)
- Cladribine- herpes zoster, ?malignancy
- Natalizumab- PML
- Alemtuzumab- Autoantibody mediated diseases (Grave's, ITP, anti-GBM), cervicocepahlic arterial dissection/ stroke, Listeria meningitis, herpes infections, fungal infection, ?malignancy
- Ocrelizumab, rituximab- Hepatitis B reactivation

Increased risk of serious infection with MS DMTs

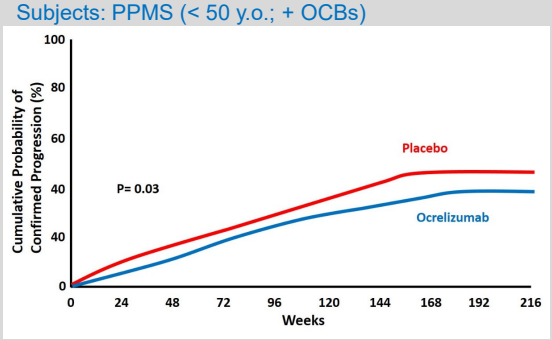


- 6421 patients with RRMS in Swedish registry initiating DMT Jan 1 2011 – Dec 31 2017
- Crude rate of infections:
  General population 5.2
  IFN/GA 8.9
  Natalizumab 11.4
  Fingolimod 14.3
  Rituximab 19.7
- After confounder adjustment, the rate was higher for **rituximab vs IFN/GA (HR=1.70)** but not for natalizumab or fingolimod

Luna G et al. JAMA Neurol 2020;77:184-91

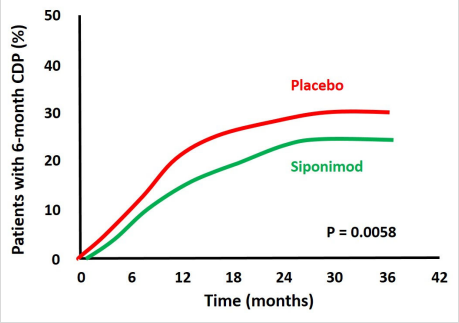
DMT for progressive MS

Oratorio
Tx: Ocrelizumab
Primary Endpoint: 12-Week Confirmed Disability Worsening
Subjects: PPMS (< 50 y.o.; + OCBs)



Montalban X et al. NEJM 2017;376:209-20

EXPAND
Tx: Siponimod
Primary Endpoint: 6 month Confirmed Disability Worsening
Subjects: SPMS (mean age 48, mean time since conversion- 3.9 y)



Kappos L et al. Lancet 2018;391:1263-73

Both studies indicate that patients with progressive MS who are younger, with shorter disease duration, and signs of active inflammatory activity (superimposed relapses, gad enhancing lesions) are more likely to benefit.

Symptomatic Management of MS

- **Fatigue**- Rule out sleep disorders
- **Cognitive deficits-** Neuropsychological assessment; cognitive rehabilitation therapy
- **Paroxysmal Sx** (vertigo, ataxia, dystonia)
- **Pain**
- **Urinary urgency/ retention**
- **Spasticity**
- **Mood disorders**
- **Gait imbalance**

Take Home Messages

- MS is a heterogeneous disease with neuroinflammatory and neurodegenerative components. It is the most common cause of non-traumatic CNS disability among young adults in the Western hemisphere. Recent epidemiological studies show that the prevalence of MS in the United States is higher than previously appreciated.
- Disease modifying therapies (DMT) are effective in suppressing MS relapses and new inflammatory lesion formation. Individual DMTs vary in efficacy and side effect profiles. A growing body of evidence indicates that early initiation of higher efficacy DMT may slow disability accumulation and conversion to progressive MS.
- High efficacy DMTs also slow disability accumulation in some individuals with progressive forms of MS (particularly those who are younger and have evidence of ongoing inflammatory activity). However, the effects are modest. There is a dire need for more effective treatments in progressive MS.
- There does not appear to be an increased risk of contracting COVID19 among individuals with MS, including those on DMT. Preliminary studies suggest that IFNβ might decrease, while rituximab might increase, the likelihood of severe complications from COVID19 infection. Otherwise, no association has thus far been identified between DMT use and COVID19 severity.