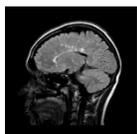


Multiple Sclerosis and Other Demyelinating Masqueuraders



A. Paul Chous, M.A. O.D., FAAO
Tacoma, WA

Disclosure

- I have been a consultant for, been on advisory boards or spoken on behalf of the following:
AI Optics, American Diabetes Association, Apellis, Asta Real, LKC Technologies, Regeneron, Zeavision



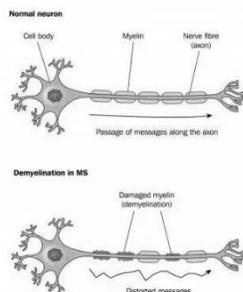
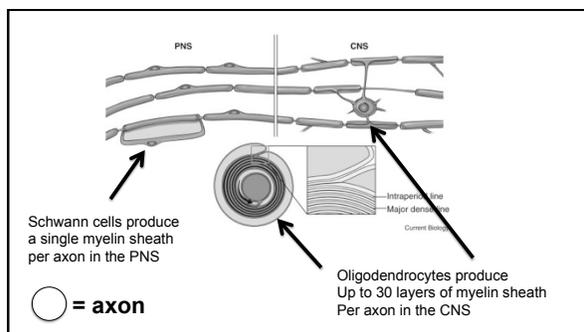
My affiliations with these companies have not affected the materials within this lecture

"Try it in—I just bought a hundred shares."

Demyelination

- Loss of myelin sheath (insulation) on axons
- May be hereditary and/or acquired
- Myelin damage results from primary attack on myelin-producing oligodendrocytes (OGCs) in the CNS, Schwann cells in the PNS, or directly on the myelin sheath**
 - may or may not lead to total demyelination

Exp Neurol. 2016 Sep;283(Pt. B):452-75.

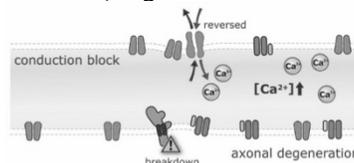


MS is the most common demyelinating disease

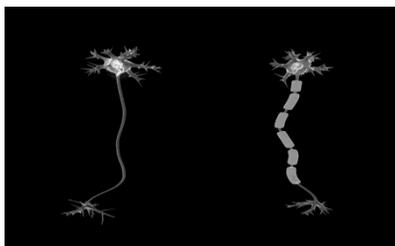
BUT...Many inflammatory, autoimmune, infectious, granulomatous & metabolic disorders can mimic MS demyelination & symptoms

Demyelination

- Disruption of Na^+ , Ca^{++} , K^+ ion channels causes ATP-depletion, excess intracellular Ca^{++} and axonal block/degeneration



Loss of 'saltatory conduction' along nodes of Ranvier



There are a Plethora of Demyelinating Disorders
Demyelinating Diseases

Inflammatory	Infectious	Granulomatous	Other
<ul style="list-style-type: none"> MS ADEM NMO Paraneoplastic Sjogren's Polyarteritis nodosa SLE 	<ul style="list-style-type: none"> HIV Lyme Neurosyphilis PML HTLV-1 Human T-lymphotropic virus type 1 	<ul style="list-style-type: none"> Lymphomatoid granulomatosis Sarcoidosis GPA Granulomatosis with Polyangiitis Formerly Wegener's Granulomatosis 	<ul style="list-style-type: none"> Vitamin B12 Spinocerebellar D/o Adrenoleukodystrophy

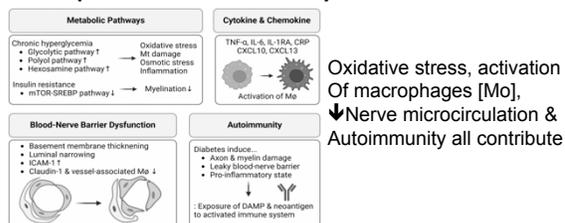
Int J Mol Sci. 2015 Sep 7;16(9):21215-36

Demyelinating Attack by Location & Entity

Oligodendrocytes	Schwann Cells	Myelin Sheaths
MS	Guillain-Barre [AI]	MS
NMO	Charcot-Marie-Tooth [genetic]	NMO
ADEM/MOGAD	Diabetic Neuropathy	ADEM/MOGAD
PML [JC Virus]	CIDP	PML
Leukodystrophies [genetic]		CIDP
Alzheimer's		
Parkinson's		

CIDP = Chronic Inflammatory Demyelinating Polyneuropathy is linked to diabetes, Lupus, Sjogren's, IBD, hyperthyroidism, HIV

Multiple Mechanisms of Demyelination in Diabetes



CIDP is 2X to 11X more common in diabetes

lin Neurol Neurosurg. 2025 Feb;249:108719. Arch Neurol. 2002 May;59(5):758-65.

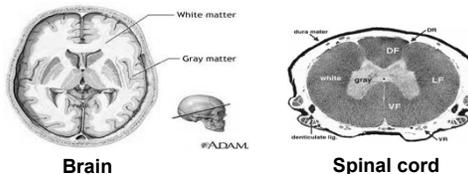
MS is the Most Common Demyelinating Disease

- DDx of MS from other demyelinating diseases requires neuroimaging, serum/CSF analysis, symptom presentation & time course



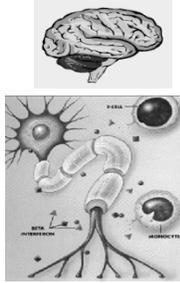
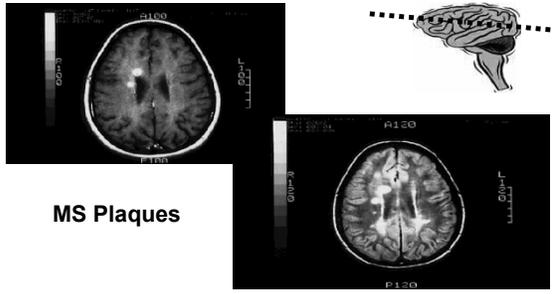
What is MS?

- Autoimmune Disease of the CNS
- Demyelination of white matter



What is MS?

- MS is an immune-mediated disease of the brain and spinal cord
 - ~ 1 million affected in US
 - ~ 12,000 new cases/yr
- Immune system attacks and destroys myelin and axons
- Characterized by demyelination and axonal loss → Demyelinating plaques

MS Plaques

Features of MS

- Demyelination results in
 - Paresthesia (numbness & weakness)
 - Loss of skeletal muscle coordination
 - Loss of autonomic function
- Multiple sites of CNS involvement
- Multiple attacks over time

Most Relevant Signs and Symptoms of MS in the Primary Care Setting

Numbness	Fatigue	Pain
Diplopia	Vertigo	Depression
Bladder Dysfunction	Bowel Dysfunction	Sexual Dysfunction
Gait impairments	Cognitive Dysfunction	Paresis

Infectious Mononucleosis Doubles the Risk of MS
 PLoS One 2010 Sep 1;5(9):e12496.

FOX 59 NEWS ▾ INDY NOW ▾ WEATHER ▾ TRAFFIC ▾ MORNING NEWS ▾ SPORTS ▾ JOBS ▾

Common 'kissing disease' among teens may trigger multiple sclerosis



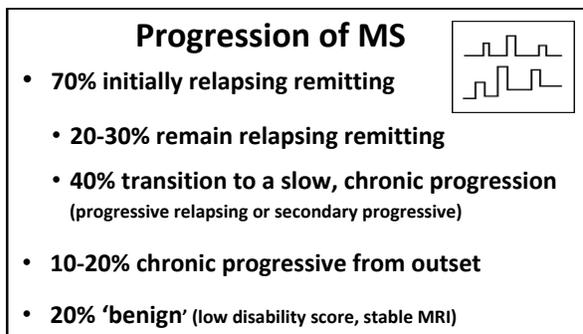
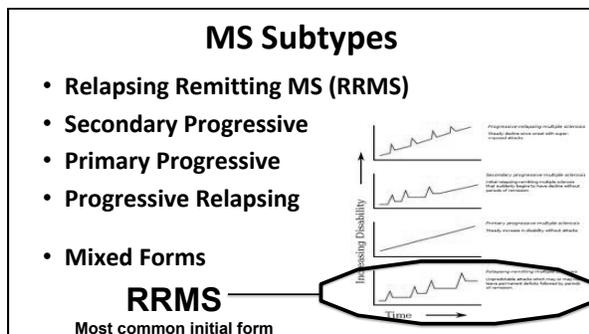
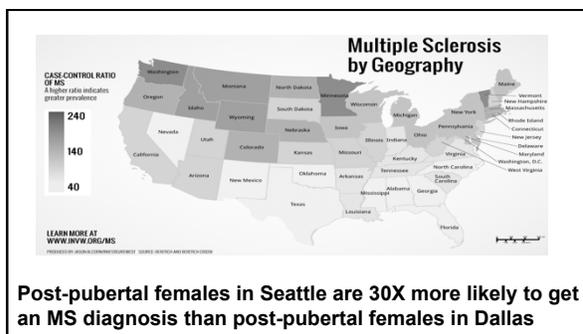
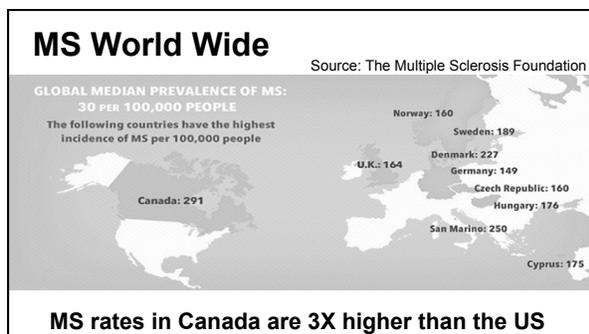
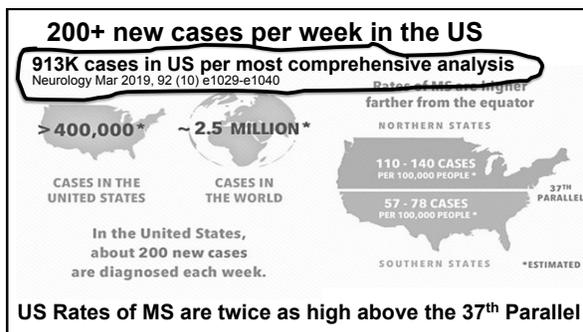
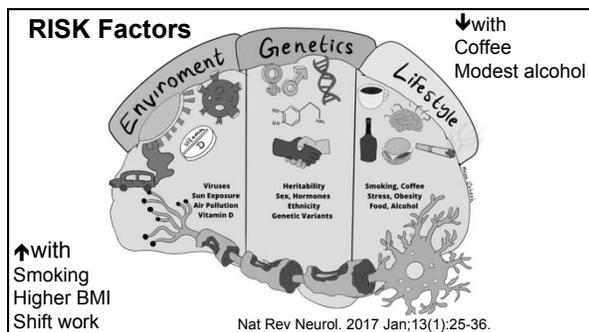


Article | [Open access](#) | Published: 14 July 2025

Early identification of individuals at risk for multiple sclerosis by quantification of EBNA-1₃₈₁₋₄₅₂-specific antibody titers

- Presence of Epstein-Barr Virus nuclear antibody-1 in this specific region cross-reacts with CNS proteins, including myelin basic protein → auto-immunity
- 324 MS patients versus 324 controls
- EBNA-1 are elevated 5.4 years prior to MS Dx

Nat Commun 16, 6416 (2025)



Genetics & Gender

- 7-20 times more common among those with an affected family member
- Identical twins = 40% concordance rate
- 10% higher risk if T1DM, autoimmune thyroid disease (Grave's, Hashimoto's), IBD
- Women 2:1

Am J Epidemiol (2005) 162 (8): 774-778.

MS Risk Linked to Breast Feeding

- Mothers who breastfed ≥ 15 months were half as likely to develop MS compared to women who breastfed ≤ 4 months
- Observational study of pts with newly diagnosed MS/ CIS (n = 397) and matched controls (n = 433)
- Adjusted OR for longer breastfeeding = 0.47
– p = 0.003 for significance

Neurology. 2017 Aug 8;89(6):563-569.

What is CIS?

- The initial demyelinating event is referred to as "Clinically Isolated Syndrome" (CIS)
- Common presentations include:
 - Optic neuritis → most common in Hispanics
 - Transverse myelitis → most common in African Americans
 - Brainstem syndromes (INO, cranial neuropathy, nystagmus)

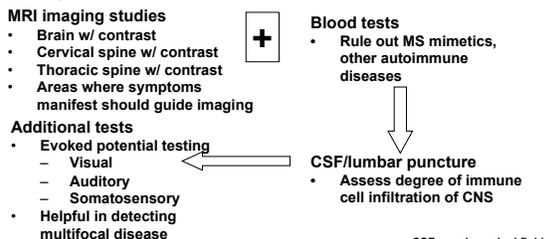
Transverse Myelitis

myelitis = inflammation of the spinal cord

- Ascending numbness from the feet up through the torso or hands to the arms
- Balance problems
- Partial or complete motor paralysis
- L'hermitte's Sign
- Bladder & sexual dysfunction are common



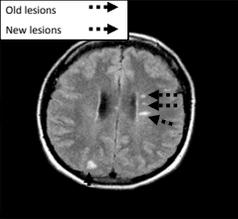
Diagnostic Work-Up for Patients With Suspected CIS and/or MS



Diagnosis of MS

- Requires multiple sites of CNS involvement over time
- MRI of brain and spinal cord
 - T2 weighted FLAIR (fluid attenuated inversion recovery) → shows old & new lesions
 - T1 weighted with gadolinium contrast → new lesions
- Number of MRI lesions is the single most important predictor of conversion to clinically definite MS (CDMS) and disability progression

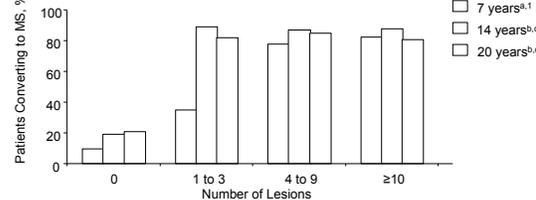
T2-Weighted/FLAIR Brain MRI¹⁻³



- Reveals hyperintense lesions
- Shows total number of lesions
- Indicative of disease burden
- Lesions may sometimes mimic brain tumors
- Available scanning protocols
 - Sagittal Fluid Attenuated Inversion Recovery (FLAIR)
 - Axial FLAIR

1. Image obtained from <http://www.mslivingwell.org/new/understanding-your-mri>. Accessed March 31, 2010.
 2. Filippi M. *Mult Scler*. 2000;6:320-326. 3. Inglesse M. *Psychiatr Times*. 2007;3(7). <http://www.psychiatrictimes.com/display/article/10168/56481?pageNumber=2>. Accessed March 31, 2010.

Baseline MRI Correlates With Risk of Conversion to MS



^a McDonald criteria. ^b Poser criteria. ^c Same patient cohort.
 1. Tintore M et al. *Neurology*. 2006;67:968-972. 2. Brex PA et al. *N Engl J Med*. 2002;346:158-164.
 3. Fisniku LK et al. *Brain*. 2008;131:808-817.

Disability from MS

- **Expanded Disability Status Score (EDSS)**
 - Scoring for each of 8 functional systems
- Pyramidal (ability to walk)
- Cerebellar (coordination)
- Brain stem (speech and swallowing)
- Sensory (touch and pain)
- Bowel and bladder functions
- Visual
- Mental
- Other (includes any other neurological findings due to MS)

Criticisms

- Inordinate emphasis on walking
- Insufficient focus on cognition
- Irregular scale

Baseline MRI Correlates With Disability Progression at 5 years

# of Lesions on Baseline MRI	Patients With EDSS ≥ 3 at 5 years
0	5.8%
1-3	8.7%
4-9	11.1%
≥ 10	25.4%

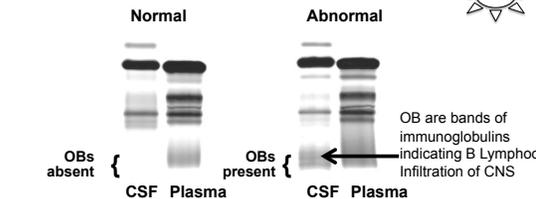
EDSS > 3 means moderate disability

EDSS: Expanded Disability Status Scale.
 Tintore M et al. *Neurology*. 2006;67:968-972.

Diagnosis of MS is Clinical

- **Lab tests to R/O mimetics**
 - Serum B12, ESR, Lyme titer, ANA, RF, anticardiolipin, TSH, NMO-IgG
- **Lumbar puncture with CSF analysis**
 - Oligoclonal banding: B-lymphocyte infiltration of CNS
 - Elevated IgG Index (antibodies typical of autoimmune disease)
- **Nerve conduction studies to confirm demyelination**
 - Reduced nerve conduction time

Oligoclonal Bands (OBs) in CSF^{1,2}

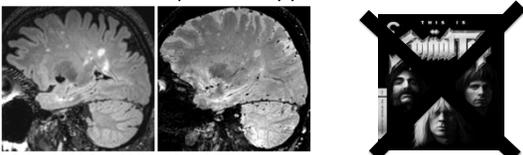


- **95% of patients with MS have CSF OBs**
- **IgG index is rarely elevated in CSF OB-negative patients**

1. Link H, Huang YM. *J Neuroimmunol*. 2005;150:17-28. 2. Image adapted from: http://library.med.utah.edu/kw/ms/ml/ml_ms_oligoclonal.html. Accessed February 25, 2010.

Central Vein Sign for MS Dx

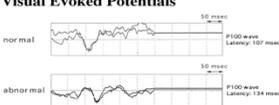
- The 'rule of 6' is an alternative to LP OBs for diagnostic sensitivity (91%)
 - ≥ 6 T2-weighted MRI lesions with a central vein
 - Faster Dx and far preferred by patients wih CIS



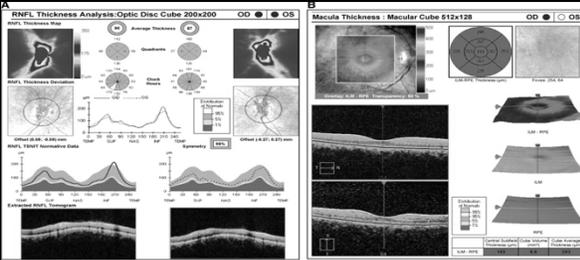
Mult Scler. 2024 Sep;30(10):1268-1277.

Other Tests

- Evoked Potentials**
 - Visual Evoked Potentials
 - Visual
 - Auditory
 - Somatosensory
- OCT: meta-analysis shows RNFL thinning and reduced low contrast acuity in pts with MS (with & w/o previous optic neuritis)**

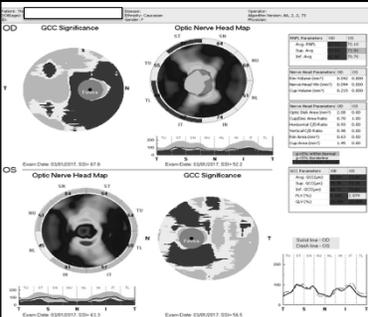


Arch Neurol. 2009 Nov;66(11):1366-72.



37 yo woman with MS diagnosed x 8 years and no Hx of Optic Neuritis

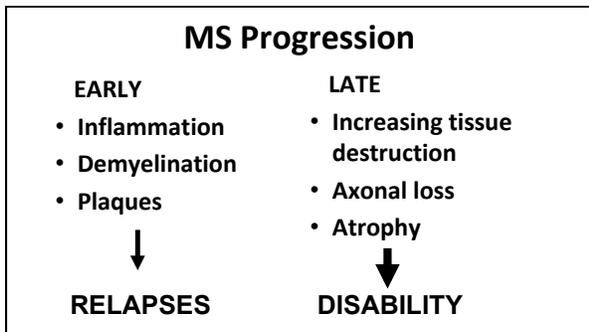
Brain January 20, 2011



67 yo female with non-progressive MS x 35 years with Hx of right-sided optic neuritis.

RNFL and Ganglion Cell Complex [GCC = thickness of GC + IPL] are grossly abnormal OD AND OS

Source: A. Paul Chous, OD

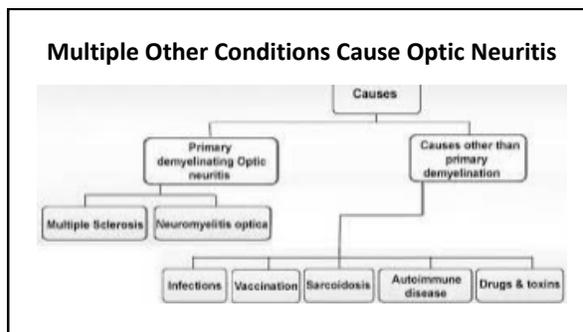


Ambulation & Mortality

- 90% of pts ambulatory at 10 years
- 75% ambulatory at 15 years
- Mean decrease in life expectancy: 5-10 years

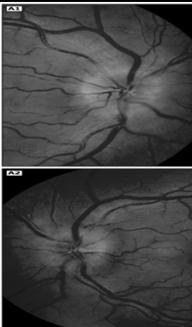
Ocular Complications

- **Optic Neuritis**
 - 40-55% of MS pts will experience (more common in Hispanics)
 - Initial event in 20% of pts
 - Sudden loss of vision in one or both eyes
 - Pain on eye movement
 - Color desaturation
 - Visual field defects
 - Recovery of acuity over days to weeks
 - DDx: neuromyelitis optica (Devic's Disease) – NMO IgG antibodies (targets cellular aquaporin receptors)

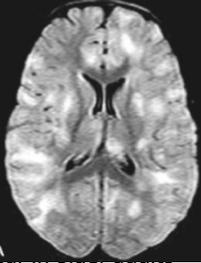
ON: What Else Could

- **MOGAD**: myelin oligodendrocyte disease – **affects children > adults**
 - MOG antibodies in serum
 - Bilateral optic neuritis (50%) often with anterior optic nerve affected (and often CF vision)
 - Good visual recovery is the rule
 - Tx : steroids, plasma exchange, IVIg
 - 50% of patients have **ADEM**



What is ADEM?

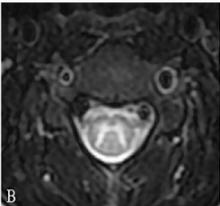
- Acute Disseminated Encephalomyelitis
 - Acute, multifocal demyelinating lesions
 - Large, ill-defined brain lesions affecting white matter
 - CN Palsy in up to 45% and optic neuritis
 - Typically monophasic (single episode)
- Behavioral changes, malaise, blurred vision
- Often follows viral infection
- 90% in people < 20 yrs but may occur in adults



Handb Clin Neurol. 2014;123:705-17.

MOGAD H-Sign

- axial MRI of spinal cord demonstrating gray matter damage highlighting the anterior and posterior horns
 - not seen in MS



Neuromyelitis Optica Spectrum Disorder (NMOSD)

- More severe optic neuritis involving the posterior ON, optic tracts and chiasm
- **Dx by aquaporin-4 antibodies in serum**
 - AQP4 provides fast water transport/homeostasis in the CNS
- MS meds can worsen (Tysabri, Gilenya, B-interferon)
- **Tx is IV methylprednisolone/plasma exchange**

NMOSD – MRI Lesions

Gd Enhanced lesions
In posterior optic N.

Area Postrema Syndrome (APS)
Nausea/Vomiting/Intractable Hiccups may be FIRST sign NMO

BMJ Case Reports CP 2020;13:e238588.

Common features of ON in MS, NMOSD and MOGAD (helping to guide clinical decision on diagnosis and course of treatment)			
Feature	MS	NMOSD	MOGAD
Paediatric presentation	Uncommon	Rare	Common
Gender	F=M	F=M	F=M
Course	Relapsing or progressive	Relapsing	Monophasic or relapsing
Visual acuity impairment	Mild to moderate	Severe	Severe
Bilateral presentation	Rare	Common	Common
Steroid response	Very good if needed	Sometimes refractory	Steroid responsive
Recovery	Very good	Risk of poor recovery	Good
ON swelling / OCT	Mild or none	Swollen but less common than MOGAD	Commonly swollen
MRI brain	Multifocal T2-hyperintense white matter lesions	May be normal	May be normal Gray matter involved in 30-50%
MRI spine	Multiple focal lesions	Longitudinally extensive lesion (conus rarely involved)	Longitudinally extensive lesion (H-sign and conus lesions)
CSF oligoclonal bands	Very common	Uncommon	Uncommon

Accessed 12/22/2025 from: <https://www.beckwith.com/1160/110/0305026>

Causes of Optic Neuritis Where Demyelination is Secondary

- Infections** ; Lyme Dz, TB, syphilis, HSV/HZV, toxoplasmosis, HIV
- Autoimmunity**: Behcet's, sarcoid, SLE, Sjogren's
 - Some neurologists recommend screening for SS in all pts with ON; 60% had abnormal VEP in one study; ON may precede visual or sicca symptoms
- Toxicity/Nutritional**: ethambutol for TB, methanol ingestion, B12 deficiency (vegans & potentially vegetarians on long-term metformin)

Vitamin B12 Deficiency vs. Multiple Sclerosis

- Vitamin B12 Deficiency**:
 - Affects central and peripheral nervous systems
 - More likely affects legs rather than arms
 - Affects both sides of the body equally
 - Muscle weakness
 - Difficulty walking
 - Cognitive dysfunction
 - Sensory disturbances
- Multiple Sclerosis**:
 - Affects only the central nervous system
 - Doesn't impair one part more than another
 - May affect just one side of the body.

Cobalamin AKA vitamin B12 is necessary for producing myelin basic protein (MBP) and myelin synthesis/repair

verywell

Relative Risk of Optic Neuritis in Various Diseases

- HSV: 1.50X
- RA: 1.57X
- Ankylosing Spondylitis: 2.02X
- Systemic Lupus: 2.38X
- TB: 4.6X
- Granulomatous Vasculitis: 14.28X
- MS and MOGAD: 140.77X NMO: 1233X**

N = 33K+ Dx with Optic Neuritis

Front Neurol. 2024 Feb 27;15:1353326.

Back to MS...

MS & BACK PAIN
REDUCING LOW BACK STIFFNESS

Lower back pain prevalence as high as 76%

ev Neurol (Paris). 2021 Apr;177(4):349–358.

Other Ocular Complications

- **Internuclear Ophthalmoplegia (INO)**
 - Brainstem demyelination (MLF)
 - Loss of adduction with intact convergence
 - + Horizontal Nystagmus of abducting eye
 - Diplopia on lateral gaze
 - 16-30% of MS → INO (44% Asymptomatic)
 - Bilateral INO is pathognomonic for MS, especially in young pts

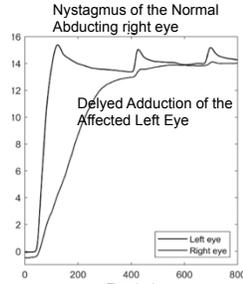
Right INO



Bull Soc Belg Ophthalmol. 2009;65-8. IOVS 2019;60(9):

Infrared Oculometry Better Detects INO

- More common in males & Black patients
- More commonly associated with poor cognition, arm weakness & higher EDSS

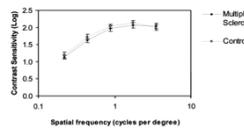


Mult Scler Relat Disord. 2022 Jul;63:103824.

Other Eye Findings

- Nystagmus with oscillopsia
- Cranial nerve palsies (typically CN VI)
- RNFL Thinning and perimetric defects
 - Reduced contrast sensitivity
- Ocular Inflammation
 - Pars planitis
 - Retinal periphlebitis
 - Granulomatous uveitis

*phosphaes
*Uthoff's sign

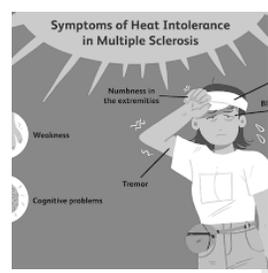


Curr Opin Ophthalmol. 2005 Oct;16(5):315-20
Ocul Immunol Inflamm. 2004 Jun;12(2):137-42

General Medicine

Uthoff's sign is seen in

A. Parkinsonism.
B. Cerebral palsy.
C. Multiple sclerosis.
D. Alzheimer's disease.



MS Treatment Goals

- Prevent relapses
- Decrease severity and shorten relapses
- Decrease disability
- Slow or prevent conversion from Relapsing Remitting (RRMS) to Secondary Progressive (SPMS)

Disease-Modifying Therapy (DMT)

Injected

- **Interferons**
 - Avonex®
 - Betaseron®
 - Extavia®
 - Rebif®
- Copaxone®

IV

- Novantrone®
- Tysabri®
- Lemtrada®

MABs

- Ocrevus® (Approved 2017)
- Kesimpta® (Approved 2020)

FDA approved Oral Agents

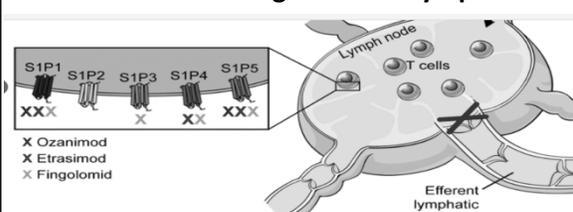
- Gilenya®
- Aubagio®
- Tecfidera®
- Mayzent®
- Zeposia®
- Vumerity® (Approved 2019)

'New' Oral Agents for MS

- **Goal:** equivalent or superior efficacy to injectable agents & convenience
- **First Oral: Fingolimod (Gilenya™)** – S1P inhibitor
 - Prevents egress of T cells from lymph nodes → auto-aggressive lymphocytic infiltration of CNS
 - Superior reduction of relapses when compared head-to-head with Interferon β-1a
 - Increased risk of infection, HTN and bradycardia
 - **0.5-1.5% incidence of CME**

Cohen JA et al. *New Engl J Med.* 2010;362:402-415. Kappos L et al. *N Engl J Med.* 2010;362:387-401.

S1P Facilitates T-cell Egress from Lymph Nodes



April 2019 *Current Gastroenterology Reports* 21(5)

Other Oral Therapies:

- **Aubagio™ (teriflunomide)** – inhibits T cell mitosis – least effective oral agent
- **Tecfidera™ (dimethylfumarate)** – inhibits CAMs and inflammation; activates Nrf2 pathway ↑ antioxidant defense
 - 4% have GI adverse events
- **Vumerity™ (diroxamel fumarate)** bioequivalent with fewer GI AEs

ARR Relative Efficacy:
S1P inhibitors = Tecfidera/Vumerity > Aubagio

Newly Dx MS & Initial Tx

- **Oral therapies were the most commonly prescribed initial treatment by 2020 (62.3%)**
 - Dimethyl fumarate most common in adults
 - Fingolimod most common in children*
- Supplanting injectables from 2001 to 2020
- Infusion therapies remain < 5% (Ocrevus ≈ 8%)

AMA Neurol. 2023;80(8):860-867.

* only FDA-approved oral Tx for MS in ages < 18

Alternative/Complementary Strategies

- **Dietary**
 - **Swank Diet:** low fat (< 20 g/d) showed 84% reduction in MS mortality over 34 years
 - **Best Bet Diet:** low saturated fat, correction of leaky gut, elimination of food allergens (gluten, eggs, added sugars) using ELISA
 - **Wahls Diet:** modified Paleo diet sans eggs & nightshades with 9+ F/V/day (berries, dark greens)
 - All three diets recommend elimination of eggs, dairy and highly processed foods
 - Recent RCT of RRMS subjects suffering chronic fatigue showed physical improvement with both Swank & Wahls diets; cognitive improvement with Wahls only

The WAVES randomized parallel-arm clinical trial. *Multiple Sclerosis Journal - Experimental, Translational and Clinical.* July 2021.

Vitamin D3 in Optic Neuritis Pts

- 30 subjects with ON were given weekly doses of 50,000 IU D3 or placebo
- **68% less conversion to CDMS in the Tx group (p= 0.007) after 12 months**
- **Vitamin D may help prevent progression from optic neuritis to clinically definite MS**

Acta Neurol Belg. 2013 Sep;113(3):257-63

New Findings on Vitamin D3 For MS

- 288 with early MS or CIS randomized 1:1 to 100,000 IU oral vitamin D3 Q14 days for 2 yrs vs placebo
 - Serum 25(OH)-D3 < 36 ng/mL (mean level in MS = 15)
- **34% less disease activity (new MRI lesions/relapse; p = 0.004) & double the time to new activity (432 vs 224 days; p=0.003) - avg 25-OH D3 ↑to 85 ng/mL**
- **Equivalent to 7,142 IU of D3 daily**

NO AEs
Reported

The D-Lay MS Randomized Clinical Trial. JAMA. 2025 Mar 10:e251604.

Re-Myelination Therapies?

- Bexarotene (skin cancer agent) → remyelination in rat models of MS
 - minimal affect on brain MRI in a small human trial
Front. Immunol., 10 August 2021 Lancet Neurol 2021 Sep;20(9):709-720.
- Metformin ↑A muciniphila, Tregs and signalling molecules that → remyelination in a mouse model
→ **Human trials underway for ProgMS in Belgium**
 - Excellent safety profile
Pharmacol Rep. 2020 Jun;72(3):641-658. Front Immunol. 2024 Feb 21;15:1362629.

Conclusions

- **Ocular findings are common in MS & other demyelinating diseases**
- **Multiple entities are associated with demyelination and can be confused with MS**
- **Clinical findings, MRI, CSF, serum and nerve conduction studies can help make the right Dx**

THANK YOU GOA!!

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