An update on Multiple Sclerosis, NMO, and MOG
Diagnosis and Treatments

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Objectives

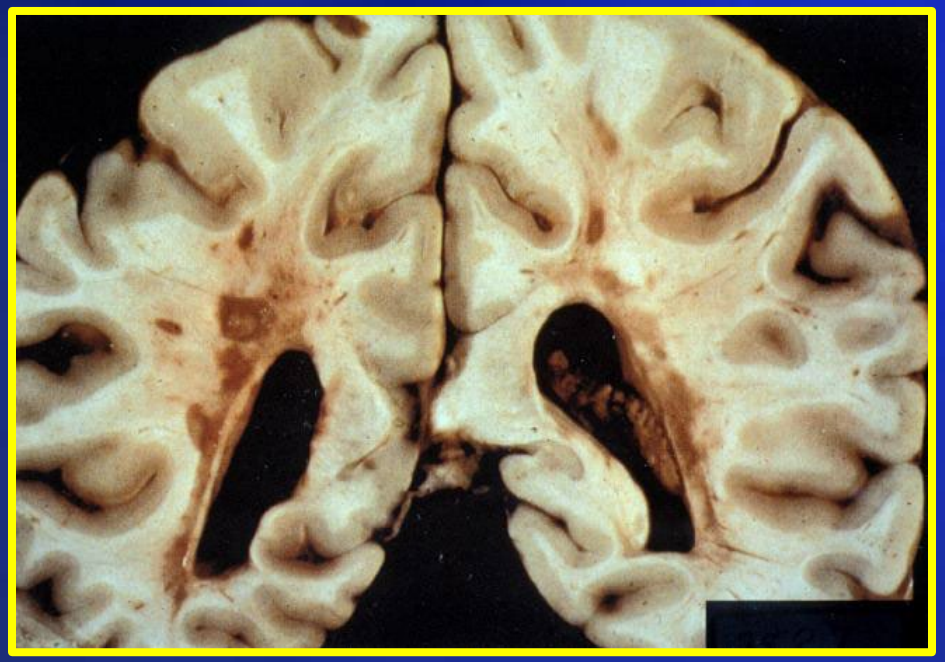
- 1. Learn to diagnosis MS
- 2. Recognize the various treatments and their potential side effects
- 3. Become aware of the need for a NEDA approach to MS
- 4. Quick overview of NMO and MOG

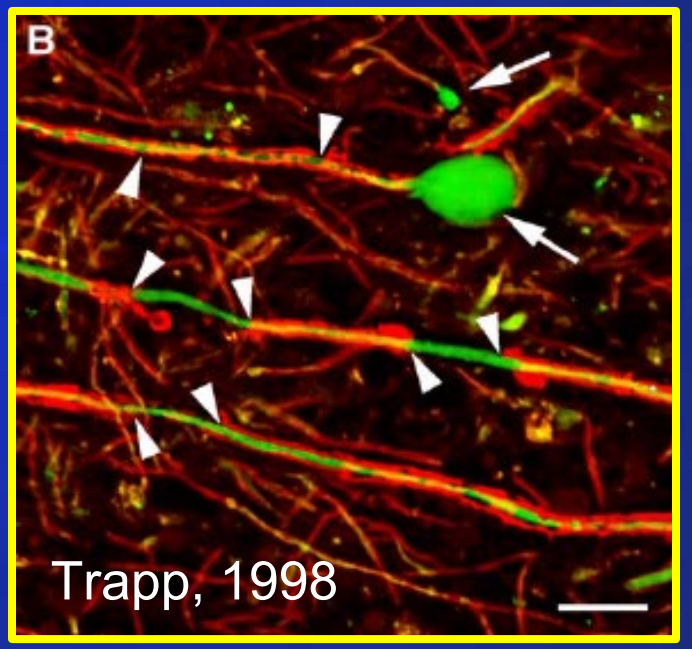
Introduction

- MS is one of the most common central nervous disease (CNS) diseases.
- Characterized by appearance of patches of demyelination in the white matter of the CNS, generally starting in the optic nerve, spinal cord or cerebellum.
- The myelin sheaths degenerate and the myelin is removed by the microglial cells. Astrocytes proliferate leading to formation of the gliotic scar.
- As demyelination occurs the conduction of the nerve impulses in the axons is impeded.

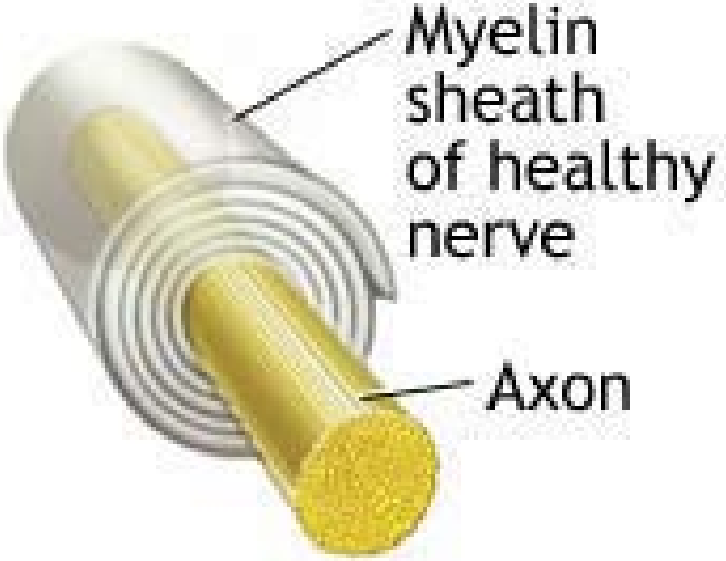
What Is MS?

- An chronic inflammatory demyelinating disorder of the CNS of uncertain etiology, lautoimmune, associated with destruction of myelin sheaths and axons, Dawson's fingers



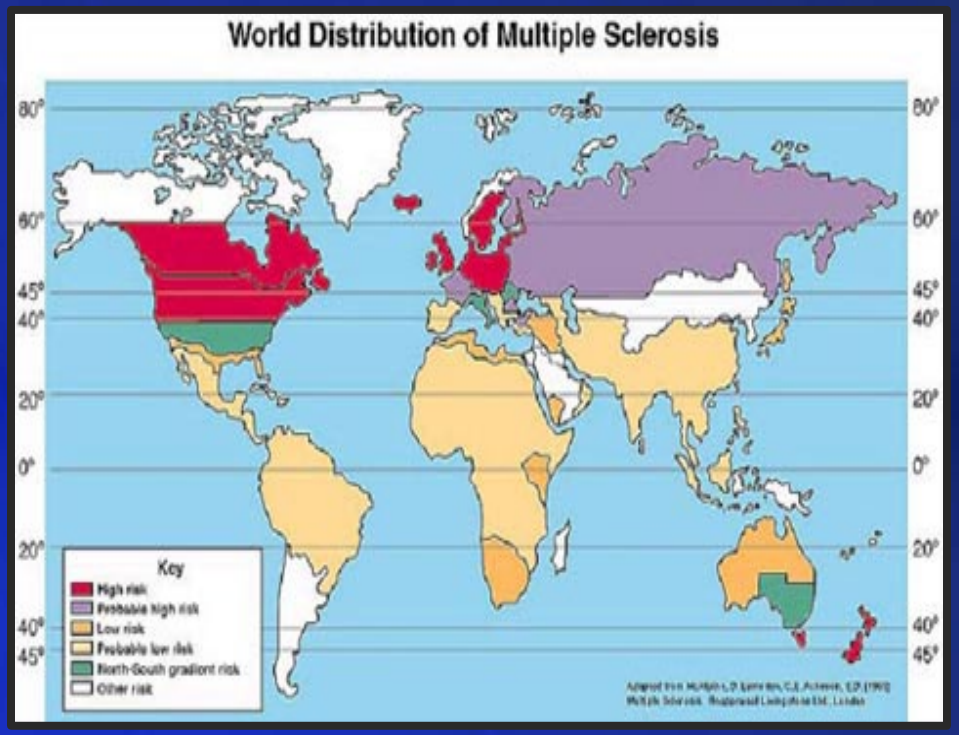


Central nervous system
(brain and spinal cord)

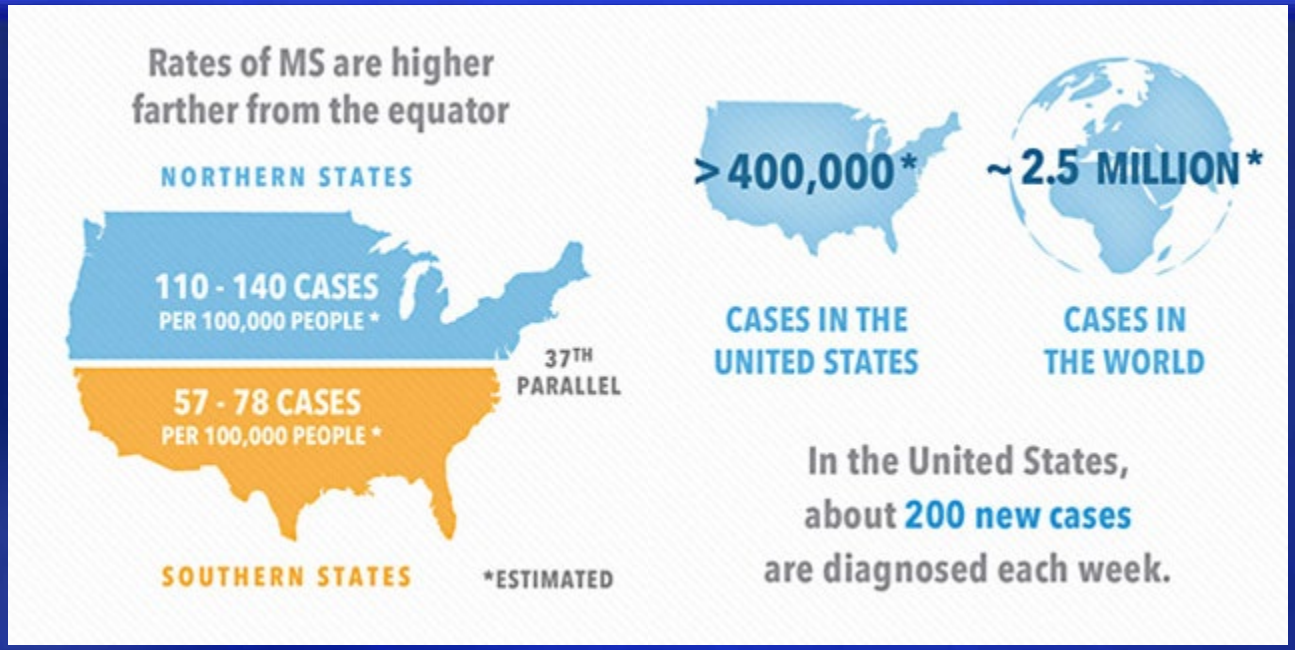


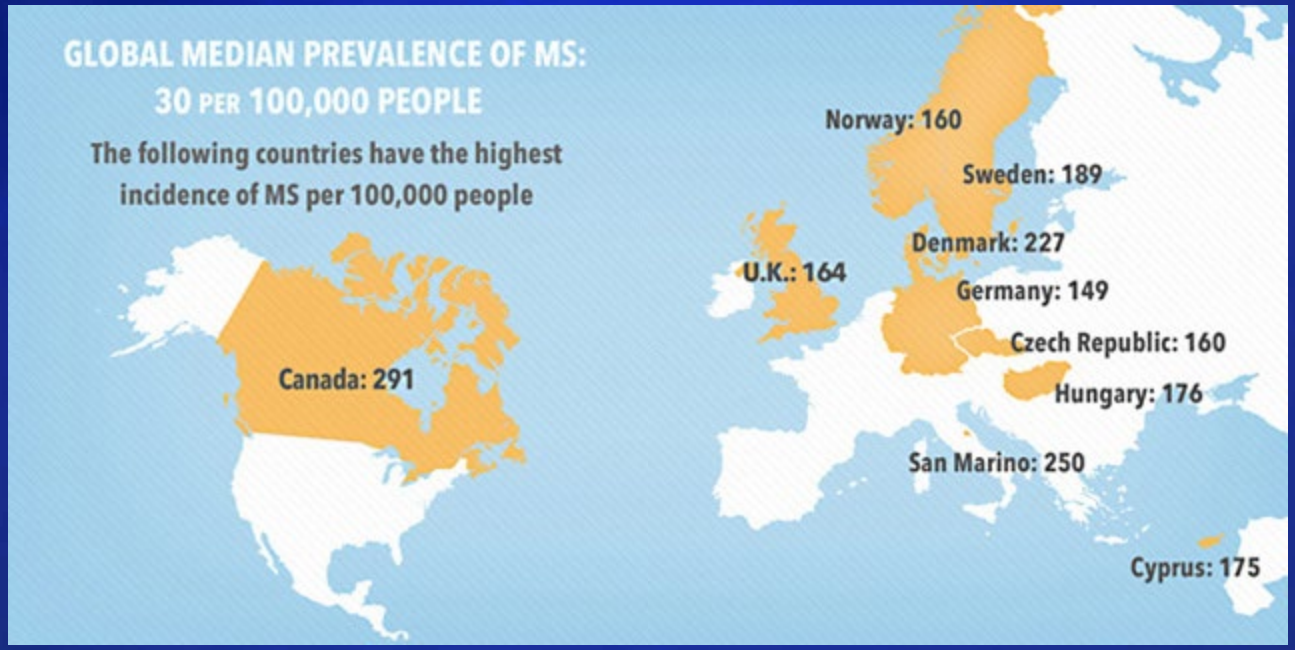
In multiple sclerosis the myelin sheath, which is a single cell whose membrane wraps around the axon, is destroyed with inflammation and scarring

Epidemiology



- Peak age 15 to 45
- Women : Men 2.5 : 1
- Geographic variation
- USA prevalence 0.1%
- Approx 1 million MS patients in USA
- Life expectancy near normal
- Total lifetime cost > $2,200,000

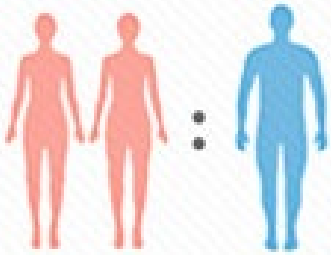

Rates of MS are higher farther from the equator
NORTHERN STATES
110 - 140 CASES
PER 100,000 PEOPLE *
37TH PARALLEL
57 - 78 CASES
PER 100,000 PEOPLE *
SOUTHERN STATES
*ESTIMATED
>400,000*
CASES IN THE UNITED STATES
~2.5 MILLION*
CASES IN THE WORLD
In the United States, about 200 new cases are diagnosed each week.

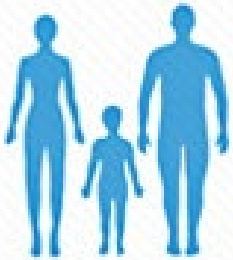

GLOBAL MEDIAN PREVALENCE OF MS:
30 PER 100,000 PEOPLE
The following countries have the highest incidence of MS per 100,000 people
Canada: 291
Norway: 160
Sweden: 189
Denmark: 227
U.K.: 164
Germany: 149
Czech Republic: 160
Hungary: 176
San Marino: 250
Cyprus: 175

YOU CAN GET MS AT **ANY AGE,**

BUT MOST PEOPLE
ARE DIAGNOSED
BETWEEN THE
AGES OF

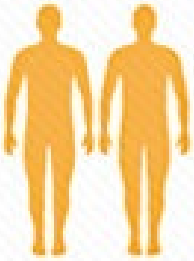
The ratio of
women with MS to
men with MS is 2 : 1.





If you have a **parent or sibling** with MS, you have a **1 - 3% chance** of developing it.

An **identical twin** with MS raises your risk to **30%.**



Pathophysiology

- MS is confined to the CNS, causing demyelination of ascending and descending tracts.
- Blood brain barrier breach results in invasion of brain and spinal cord by some membrane alteration allowing leukocytes to enter normally immunologically protected CNS.
- The inflammation and demyelination with loss of myelin sheath results in breakdown of the insulation around the axons and the velocity of AP is reduced and ultimately becomes blocked.

- The course of MS is chronic with exacerbations and remissions. Due to the widespread involvement of the different tracts at different levels of neuroaxis, the signs and symptoms are multiple.

- Remissions/stabilization in MS occurs due to the remodeling of the demyelinated axonal plasma membrane so that it acquires a higher than normal number of sodium channels which permit AP conduction despite myelin loss.

- In the progressive form of disease without remissions patients have substantial damage to the axons as well as myelin suggesting MS has axonal pathology.

- Myelin is relatively rich in lipid (70-80%), it also contains proteins that play a role in it's compaction.

- Many of the proteins found in CNS differ from those in peripheral nervous system (PNS).

- It is possible that mutations in the structure of the myelin protein can occur and be responsible for some inherited forms of demyelination. It is also possible that autoantigens develop in MS.

Types of MS

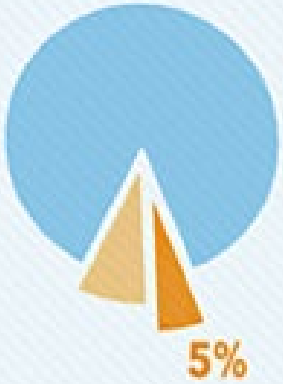
- The disease has several forms which change the course of the management. Most patients will have a months-long to year-long disease free period after their first exacerbation.

- *Clinically isolated syndrome*: single clinical attack
- *Relapsing remitting disease*: progression is characterized by relapses of active disease with incomplete recovery during periods of remission.
- *Secondary progressive disease*: progression becomes more aggressive so that a consistent worsening of function occurs.
- *Primary progressive disease*: symptoms are progressive from the onset of disease with the early onset of disability.

Percentage of patients diagnosed with **relapsing-remitting MS (RRMS)** at onset

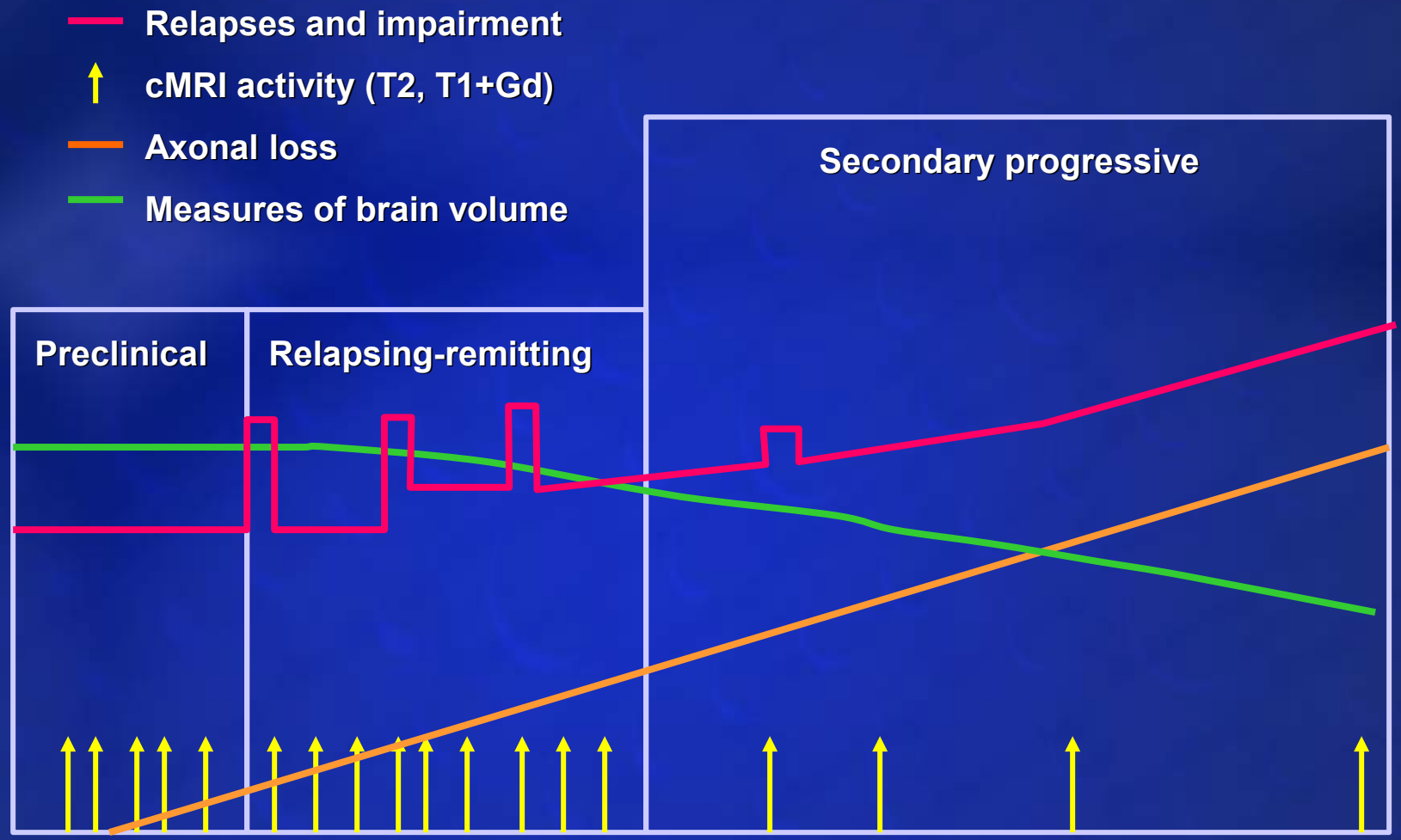
Percentage of people with **RRMS** who transition to **secondary-progressive MS (SPMS)** within a decade of initial diagnosis

Percentage of people diagnosed with **primary-progressive MS (PPMS)** at onset



Percentage of people with **progressive-relapsing MS (PRMS)**, the rarest form of MS

Natural History of Multiple Sclerosis



Adapted from Goodkin DE. UCSF MS Curriculum. January 1999.

Rx Response

Pre-Clinical

Clinically Isolated Syndrome

Relapsing-Remitting

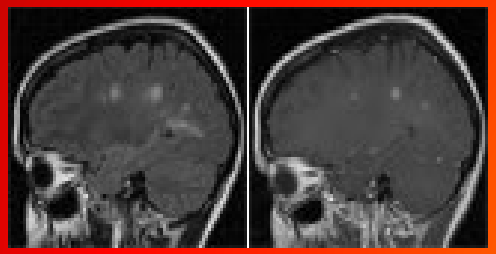
Secondary Progressive

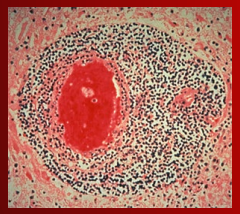
INFLAMMATORY ACTIVITY

Relapses

Active WML

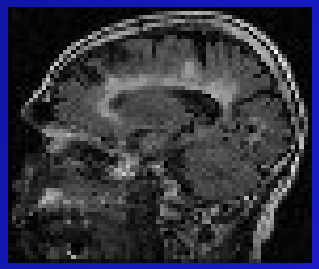
Rx effect





Atrophy

Poor Rx effect



No New WMLs

PROGRESSION

NEURODEGENERATION

Time (Years)

Clinical presentation

- Weakness, numbness, tingling or unsteadiness of the limbs is the most common sign.
- Ataxia due to involvement of the tracts of cerebellum may occur, spastic paralysis may also be present.
- Urinary urgency or retention, blurry vision and double vision are all common initial manifestations of the disease.
- Symptoms may persist for several weeks or may resolve spontaneously over a few days.

The most common early symptoms of MS are:

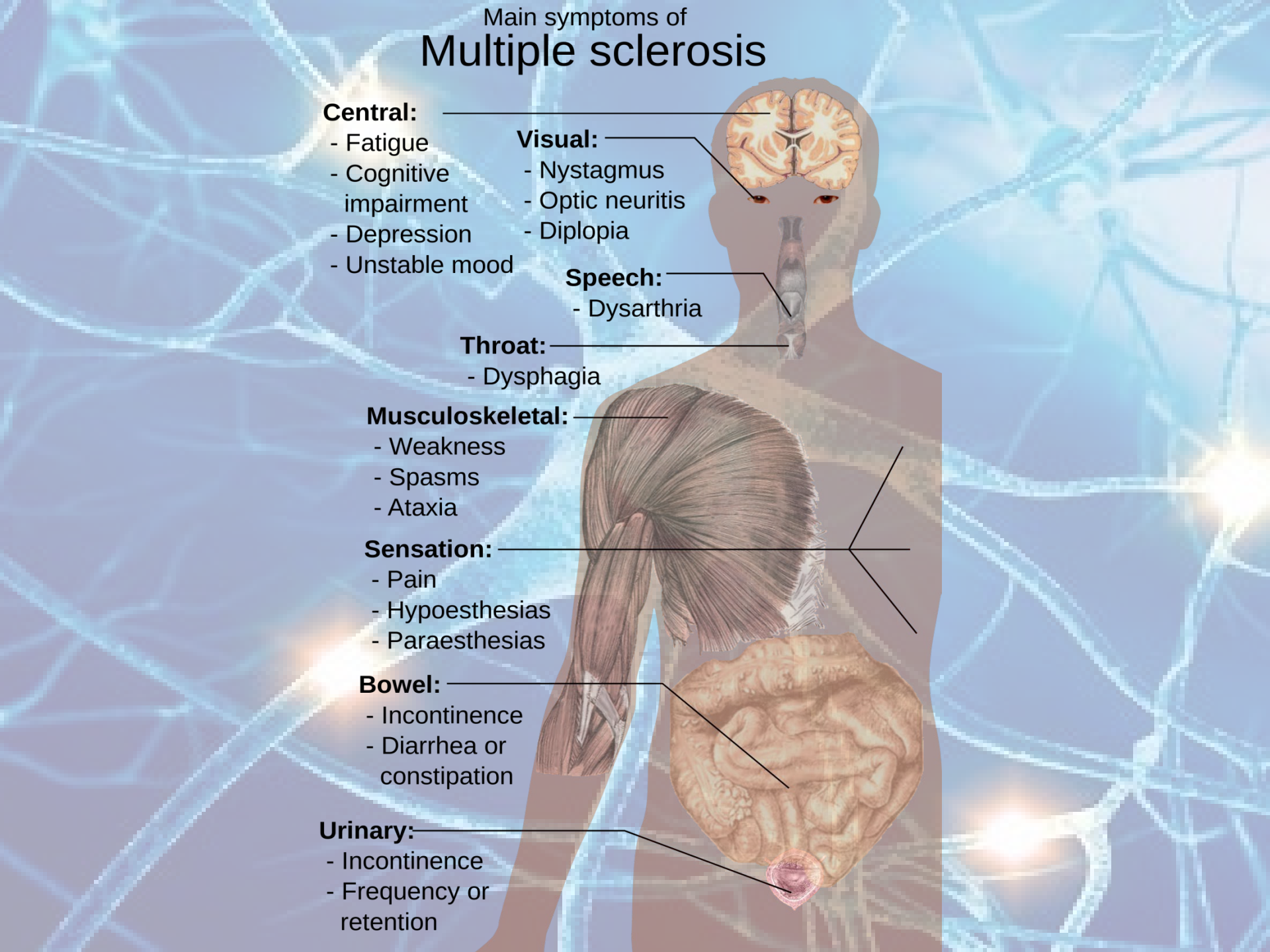
- fatigue
- vision problems
- tingling and numbness
- vertigo and dizziness
- muscle weakness and spasms
- problems with balance and coordination

Other, less common, symptoms include:

- speech and swallowing problems
- cognitive dysfunction
- difficulty with walking
- bladder and bowel dysfunction
- sexual dysfunction
- mood swings, depression

Main symptoms of

Multiple sclerosis



Central:
- Fatigue
- Cognitive impairment
- Depression
- Unstable mood

Visual:
- Nystagmus
- Optic neuritis
- Diplopia

Speech:
- Dysarthria

Throat:
- Dysphagia

Musculoskeletal:
- Weakness
- Spasms
- Ataxia

Sensation:
- Pain
- Hypoesthesias
- Paraesthesias

Bowel:
- Incontinence
- Diarrhea or constipation

Urinary:
- Incontinence
- Frequency or retention

Triggers that exacerbate MS

- Since raising the temperature shortens the duration of action potential(AP) one of the early signs is improvement on cooling and worsening by hot bath.
- Infections or trauma may acutely worsen the disease.
- Pregnancy especially the 2 to 3 months following birth.

MS Diagnosis

"Dissemination in space and time"

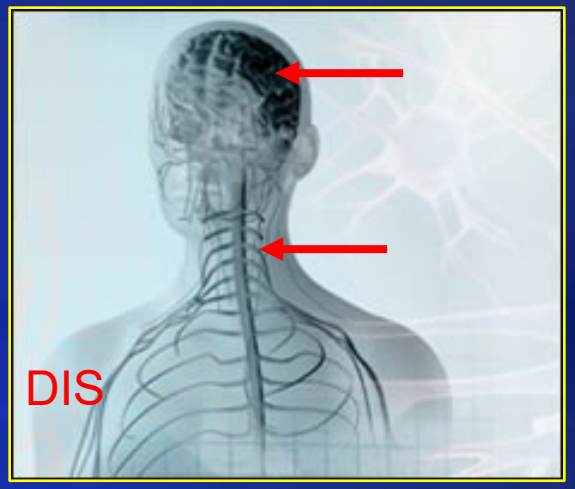
Diagnostic Criteria

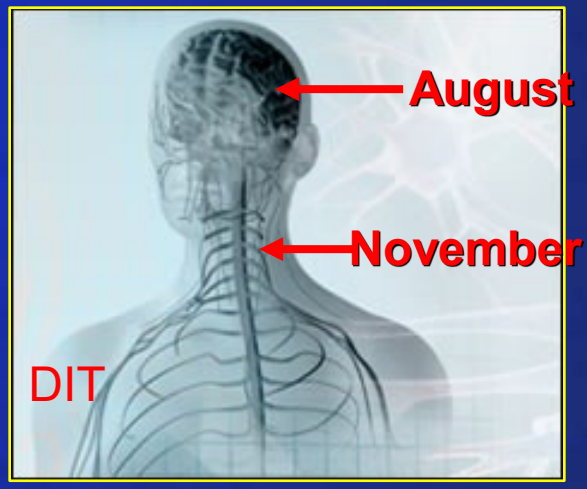
- Dawson criteria: 1916
- Schumacher criteria: 1965
- Poser criteria: 1983
- McDonald criteria: 2001
- Revised McDonald criteria: 2005,2017

- All criteria require dissemination in time and space

New Diagnostic Criteria

- Incorporate use of MRI
- Clinically Isolated Syndrome+ MRI Dissemination in space + MRI Dissemination on time = Earlier MS Diagnosis

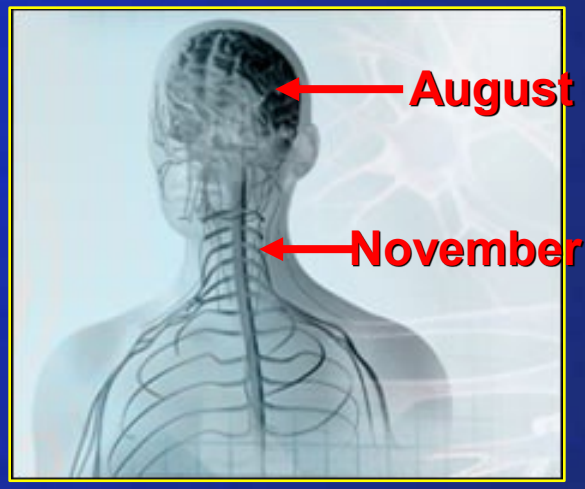




Summarized Diagnostic Criteria

1. Dissemination in space:
   Objective evidence of neurological deficits localized to two separate parts of the CNS

2. Dissemination in Time:
   Onset of neurological deficits separated by at least one month



3. Rule out other explanations!

DIAGNOSTIC WORK UP

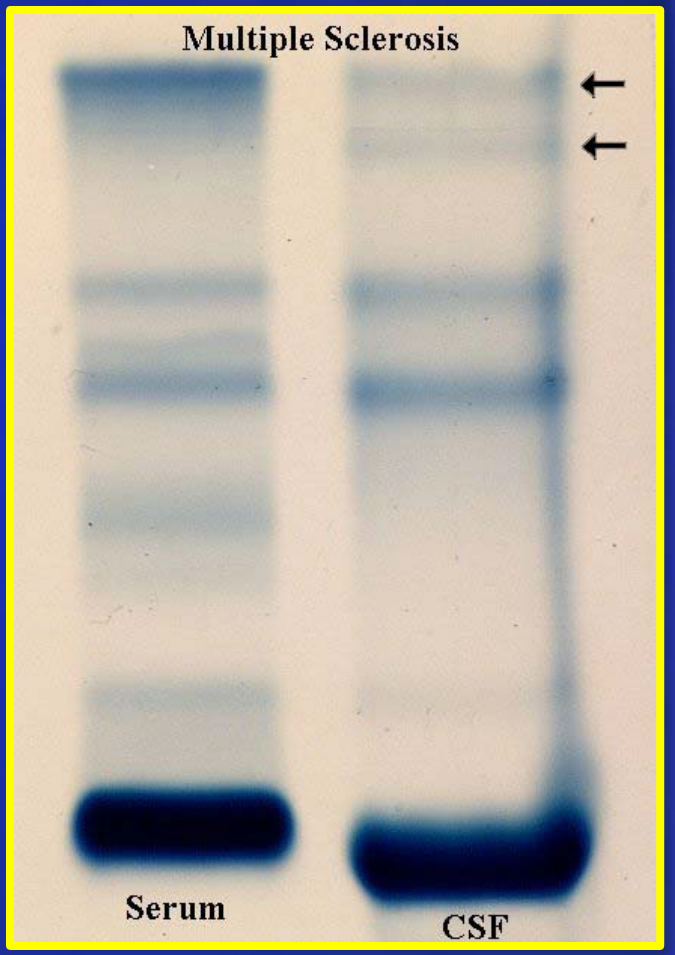
- History & Physical Exam
- Brain and Spinal Cord MRI
- Labs: rule out mimics of MS
  - Connective tissue diseases, infections, metabolic disorders
- Cerebrospinal Fluid
- Evoked Potentials:
  - Identify damage to visual, auditory, & touch perception systems
  - Less sensitive than MRI or cerebrospinal fluid

CSF Analysis

- **Most helpful for suggesting an alternative Dx**
  -high protein, marked pleocytosis, PMNs

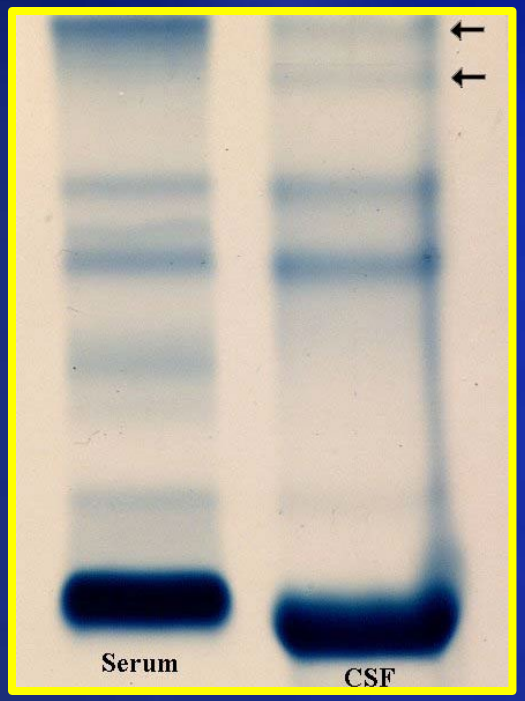
- **Elevated IgG Index ≥0.7**
  - Increased CNS IgG synthesis, with normal serum IgG *consistent with MS*

- **Oligoclonal Bands**
  - Presence of ε4 distinct bands in CSF is *consistent with* MS
  - Sensitivity 96% and the specificity 68-85%



CSF OCB are not specific to MS!

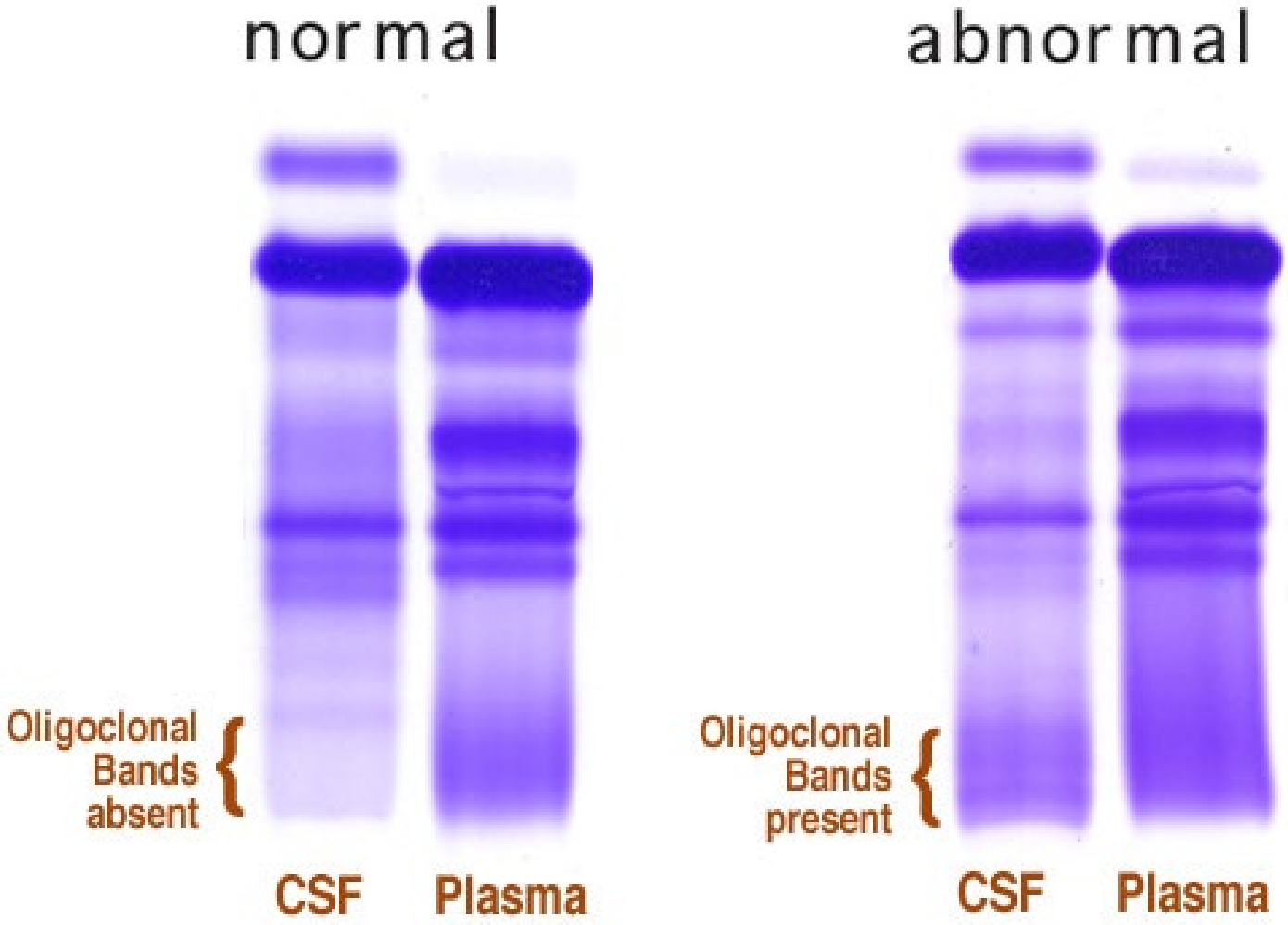
- Lupus 25%
- Sarcoidosis 51%
- Behcet's dz 8%



- Syphillis
- CJD
- Whipple's disease
- Lyme disease
- Vaculitidies
- Devic's disease
- Healthy siblings of MS patients

adapted from a lecture by Peter Riskind MD PhD 11/19/05

Oligoclonal Bands in CSF



Investigations

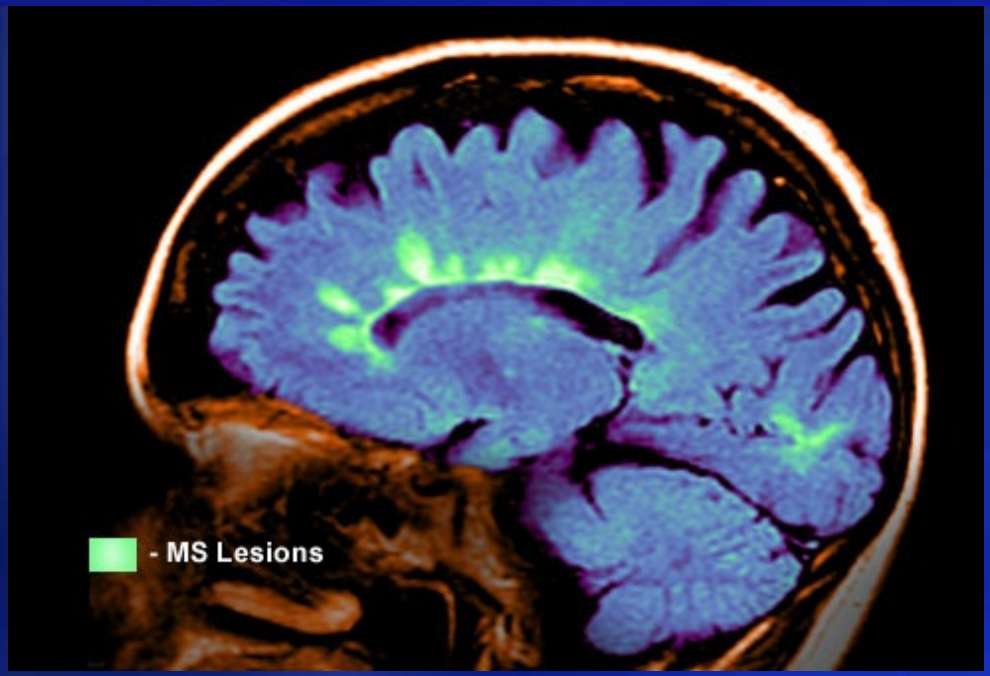
- MRI of the brain is the most accurate test to diagnose MS, reaching a sensitivity of 95% to 98% in symptomatic persons.
- Increased T2 and decreased T1 intensity represent the increased water content of demyelinated plaques in the cerebrum and spine.
- Enhancement of lesions with gadolinuim indicates active MS lesions that may enhance for up to 2 to 6 weeks after an exacerbation.

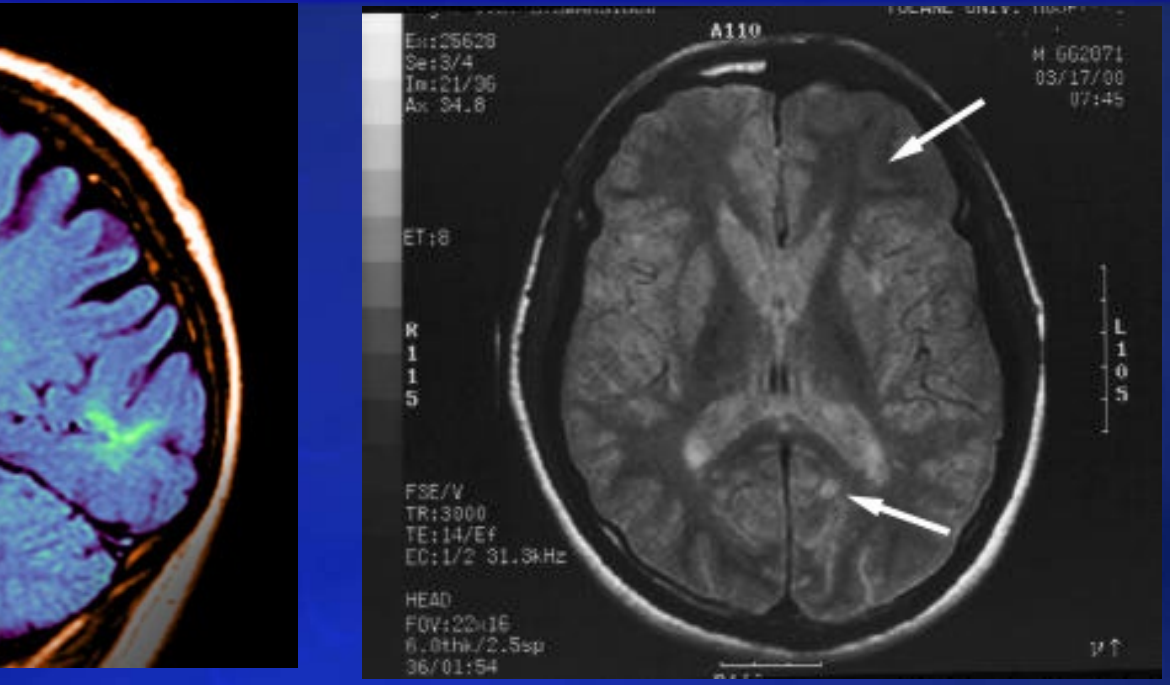
- Evoked response potentials detect slow or abnormal conduction in response to visual, auditory or somatosensory stimuli.

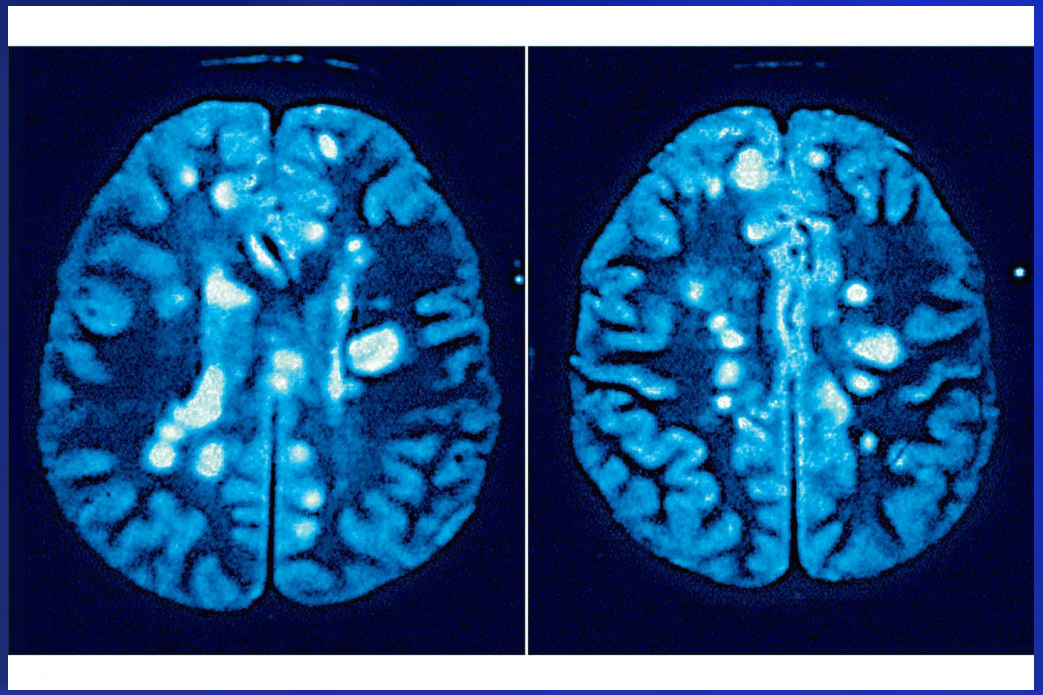
- The limitations of this test for the diagnosis of MS is that many other neurologic diseases can give an abnormal result.

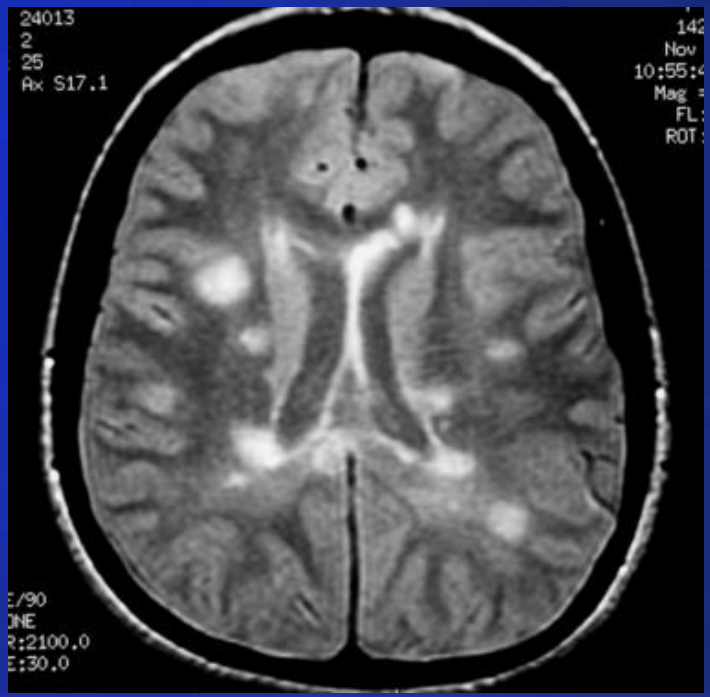
- CSF analysis usually reveals a mild pleocytosis and a total protein that is mildly elevated. A protein level exceeding 100mg/dl is unusual and should be considered as evidence against the diagnosis of MS.

- An elevated IgG index is found in 85% to 90% of patients with MS. The finding is non specific.


- MS Lesions


A110
FSE/V
TR:3000
TE:14/Ef
HEAD

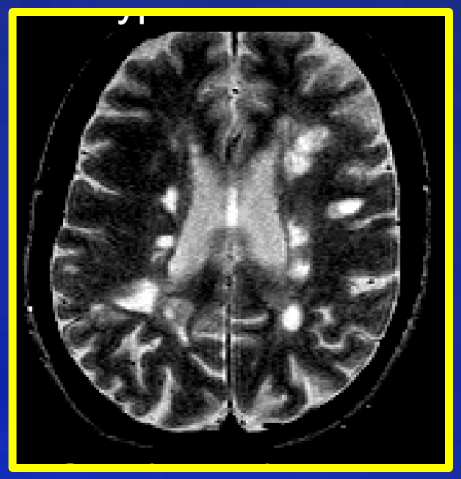


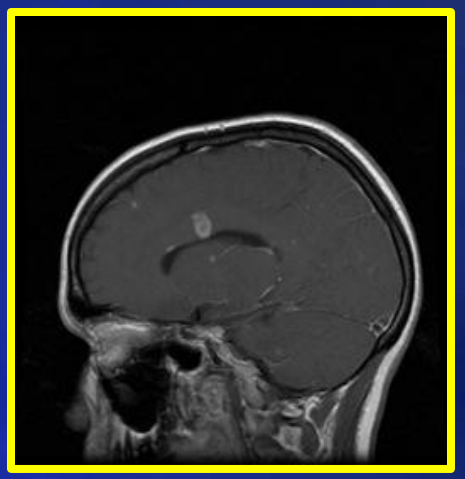

24013
Ax S17.1

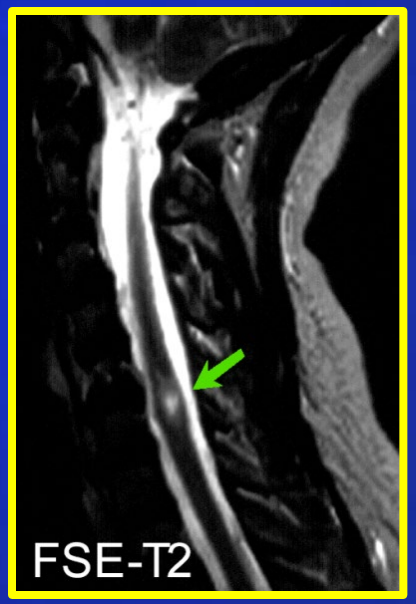
MRI - Dissemination in Space

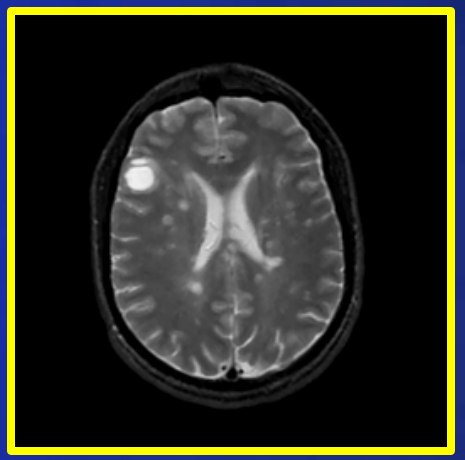
3 of the following:

- 9 T2 or 1 Gd+
- 3 Periventricular
- 1 Infratentorial
- 1 Juxtacortical lesion









CASE 1
20yo WF ICU Nurse

- 2 years ago, right foot dorsiflexion weakness and bilateral foot numbness with frequent tripping
- 9 months ago, 2 week history of clumsy gait and poor balance, abnormal handwriting
- 1 month history of blurry vision with right gaze only

CASE 1 EXAM

- Left intranuclear ophthalmoplegia (INO)
- Hyper-reflexia of the bilateral legs
- Bilateral upgoing toes (+ babinski)
- Absent vibration, poor proprioception in feet
- Mildly dysmetric finger-nose-finger and decreased fine finger movements R>L
- + Rhomberg
- Ataxic gait

CASE 1

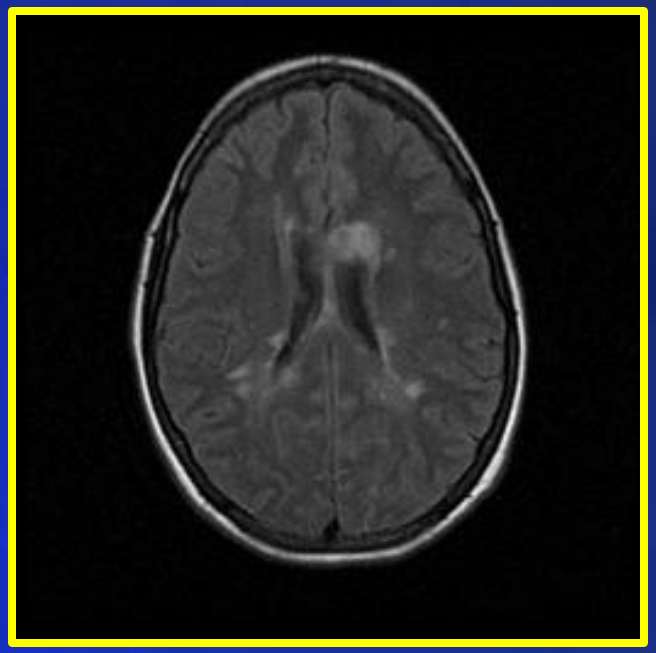
- Does she have demyelinating disease
- What is in the differential?
- How do we diagnose MS?

Differential Diagnosis

- Metabolic: SCD (B12 def), Adrenomyeloneuropathy
- Connective Tissue Diseases: Sjogren's, SLE
- Infectious: HIV, HTLV1, Lyme disease, Syphillis
- Structural: Chiari malformation, spinal cord compression
- Genetic: ataxias, paraplegias, mitochondrial
- Neoplastic: CNS lymphoma, paraneoplastic
- "MS variants": ON, TM, ADEM, NMO
- Other: Neurosarcoidosis, CNS vasculitis
- Psychiatric

CASE 1 **NEWLY DIAGNOSED RRMS**

- > 2 historical events with objective findings on examination
- MRI consistent with MS
- Normal “rule out labs”
- CXR normal

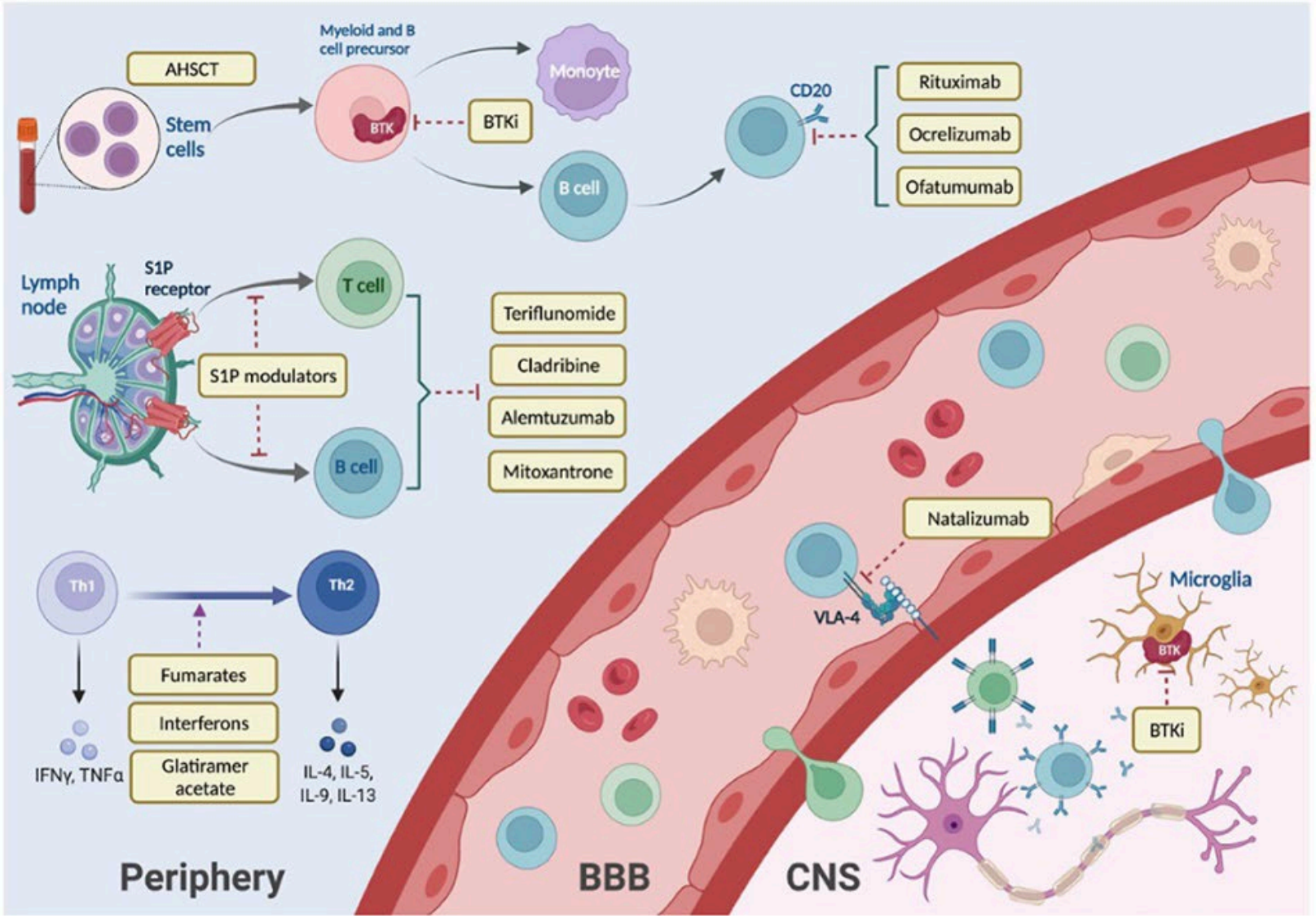


Treatment

- The treatment of MS can be divided into disease modifying therapy and treatment of symptomatic relief during an acute exacerbation—usually with steroids although there has been peaked interest in using ACTH for those intolerant to IV steroids. Cost has precluded this but there is a less expensive alternative.

- In relapsing remitting disease, there are a multitude of treatments that range from immunomodulation to immunosuppression to intermittent suppression and re-population

These medications decrease relapses, decrease active lesions and the volume of new T2 lesions and lesson disability.


AHSCT
Stem cells
Myeloid and B cell precursor
Monoyte
BTK
BTKi
B cell
CD20
Rituximab
Ocrelizumab
Ofatumumab
Lymph node
S1P receptor
T cell
S1P modulators
B cell
Teriflunomide
Cladribine
Alemtuzumab
Mitoxantrone
Natalizumab
VLA-4
Microglia
BTK
BTKi
Th1
Th2
Fumarates
Interferons
Glatiramer acetate
IFNγ, TNFα
IL-4, IL-5, IL-9, IL-13
Periphery
BBB
CNS

Oral Therapy

- Cladribine (Mavenclad)
- Teriflunomide (Abagio)
- Fingolimod (Gilenya)
- Dimethyl fumarate (Techfidera) (Vumerity)
- Ozinimod (zeposia)

- AMPYRA—WALKING AID—NOT A DMT

Infusion/injection therapy

- Tysabri—natalizumab
- Lemtrada—alemtuzumab
- Ocrevus---- Ocrelizumab
- Kesimpta---Ofatumunab
- Briumvi---ublituximab
- ABCR therapies—our mainstay for years.
  - Subcutaneous/IM

- For patients with spasticity, baclofen is the most effective medication. Tizanidine and diazepam are useful for nocturnal spasticity but are limited in their use for daytime symptoms because they cause intense somnolence.

- Pain secondary to trigiminal neuralgia and dysthesias responds well to carbamazepine, gabapentin, phenytoin, pregabalin or tricyclic antidepressants and radiosurgery

- Bladder hyperactivity is treated with oxybutynin, whereas urinary retention is treated with bethanecol. Fatigue may be treated with amantadine or fluoxetine.

- Erectile dysfunction can be treated with sildenafil acetate, etc

- Disease modifying therapies are contraindicated in pregnancy.

CASE 2

- 18 y/o senior in HS
- Cheerleader
- Swim Team Medalist

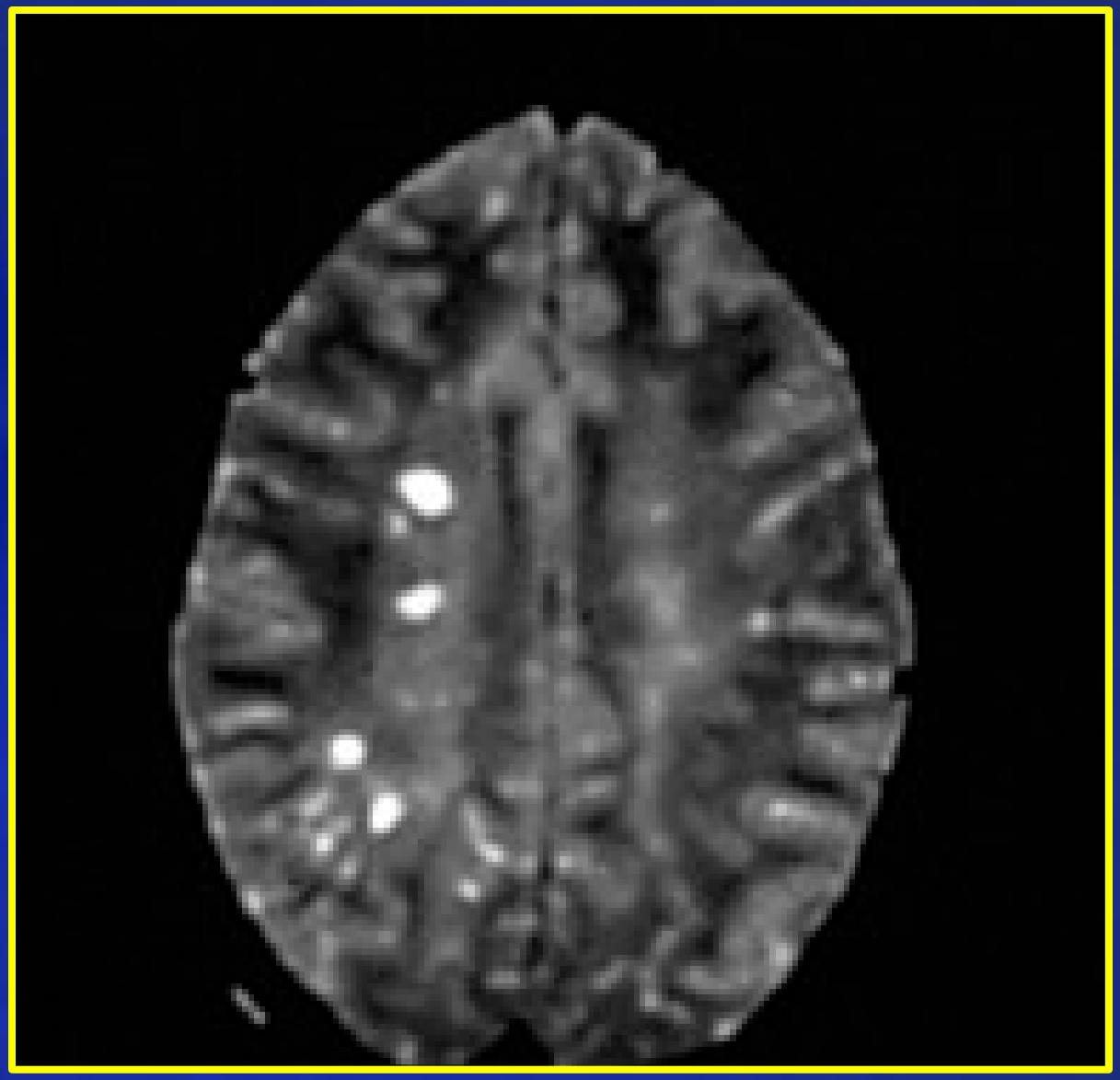
CASE 2 -

Optic Neuritis, a Clinical Isolated Syndrome

- History: Woke blind in left eye, complains of pain with extra occular movements

- Exam: Va OD 20/20, OS 20/200.
- Left disk pallor, Left Afferent pupillary defect.

CASE 2

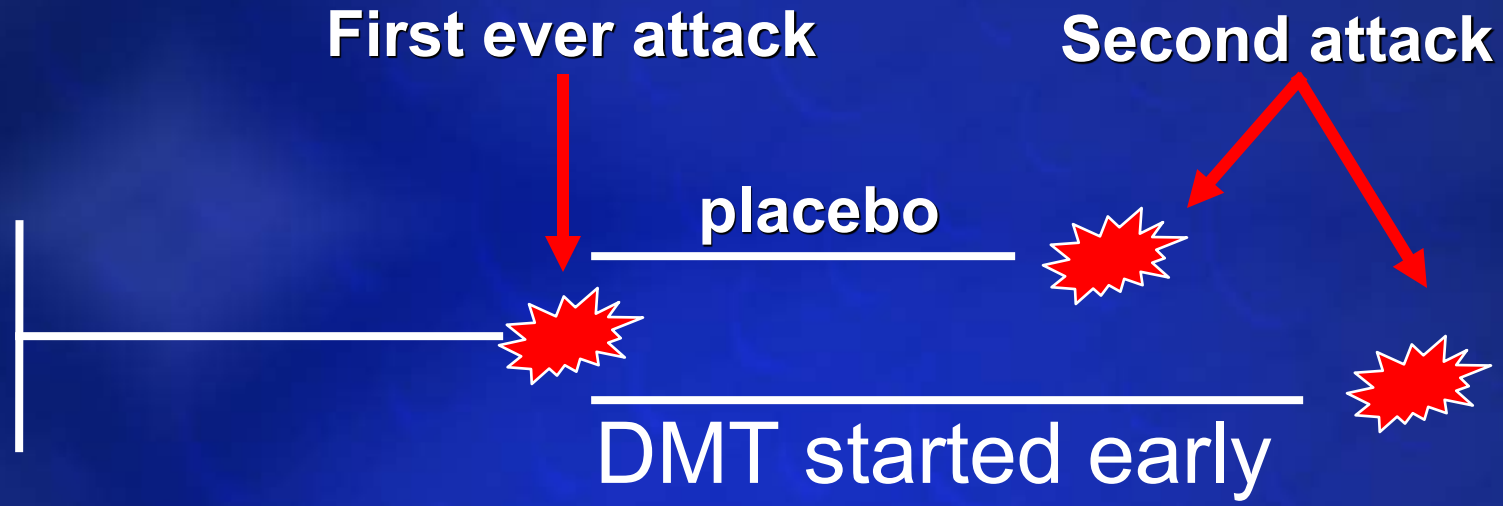


Optic Neuritis, CIS

- MRI Brain & C spine
- CSF: IgGI, OCB,
- IVMP 1gm daily x 5 days

WHAT ABOUT EARLY DMT?

CHAMPS, ETOMS, BENEFIT, PRECISE STUDIES



Time to Second Attack Delayed with Treatment

What makes you worry

- Race
- Family history
- Location of Lesions
- Number of Lesions

- How close do I perform survellience?

CASE 3

- 26yo medical student

CASE 3

- 26yo LH WF with RRMS diagnosed 2yrs ago
- 3 day history of difficulty writing, clumsy and numb left hand

- No signs/symptoms of infection
- No prior history of similar symptoms

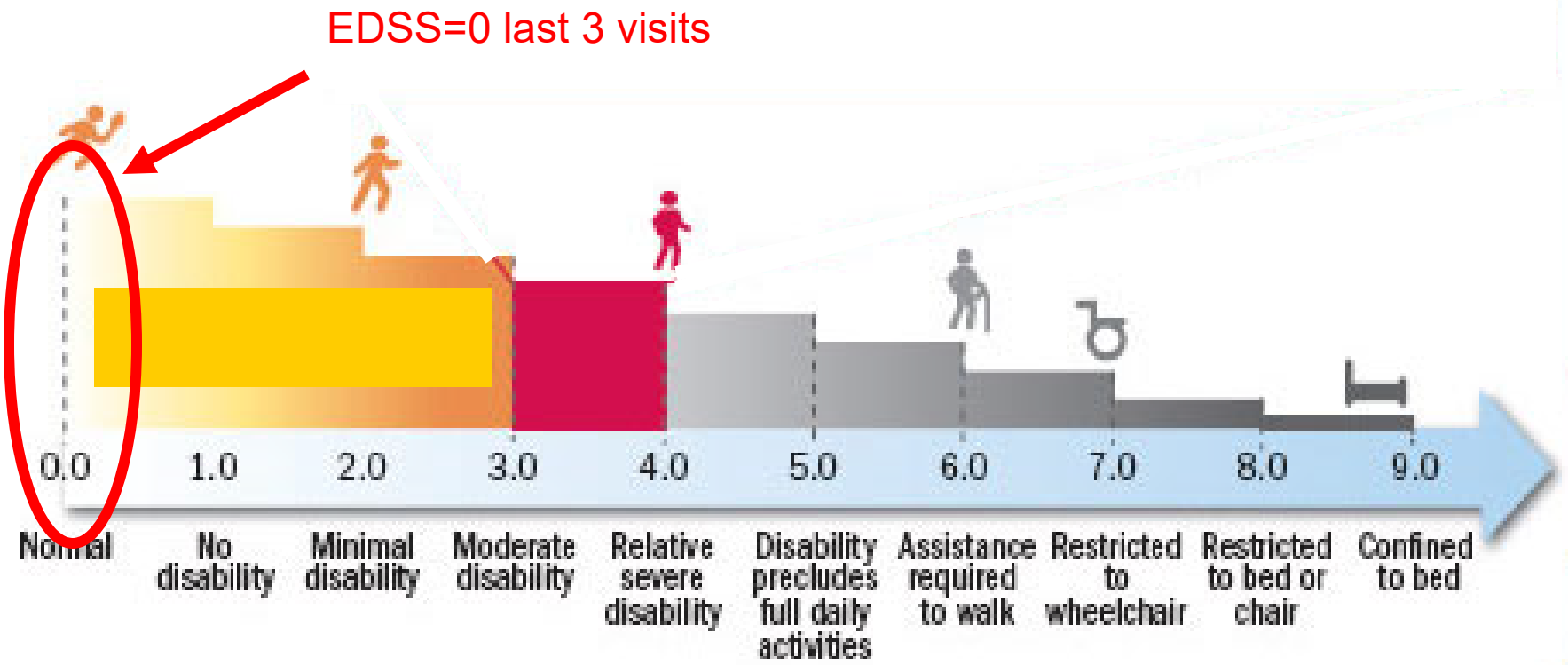
CASE 3 **ACUTE MS RELAPSE**

- 4/5 on left hand
- Hyper reflexia of left arm
- Decreased FMM & dysmetric FNF on left
- Decreased LT on left face, arm, leg
- EDSS change in gait

- Is this a relapse??

CASE 3

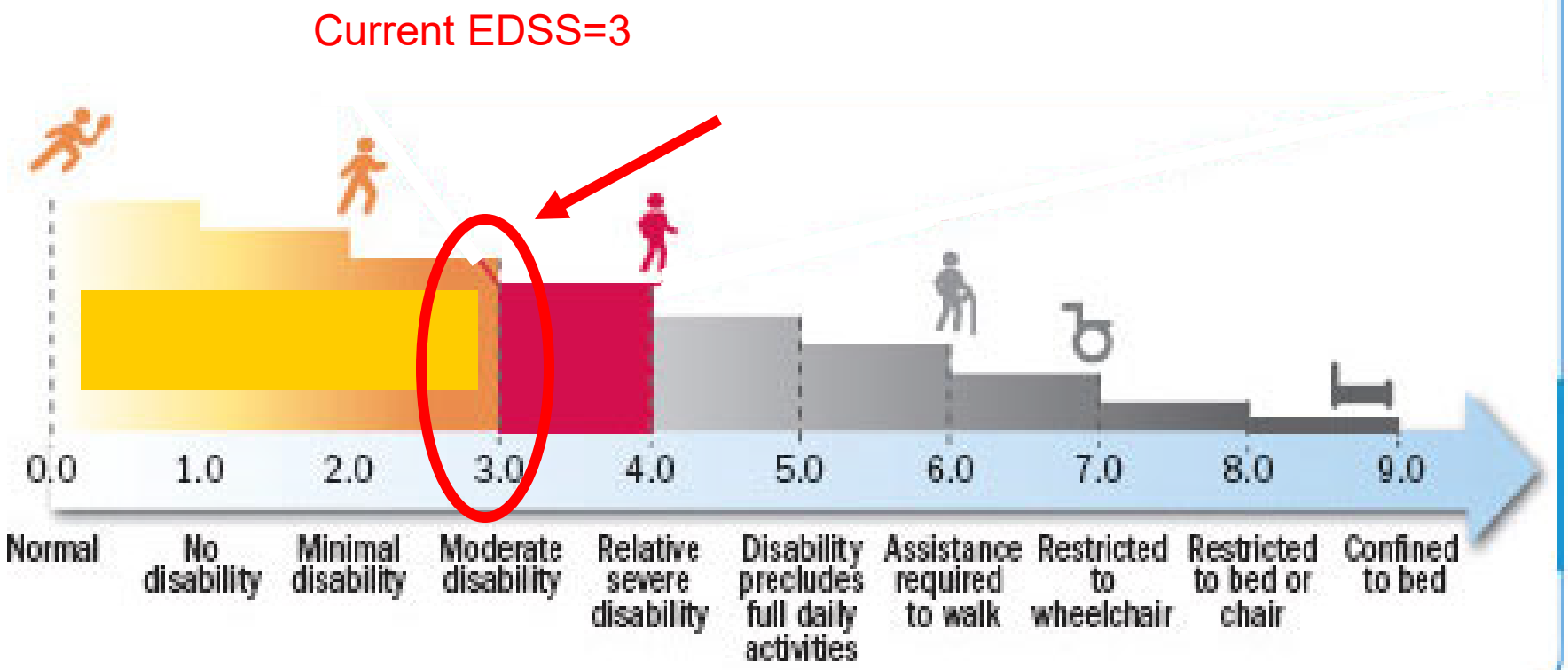
Expanded Disability Status Scale



Acute MS Relapse

CASE 3

Expanded Disability Status Scale



HOW TO IDENTIFY A RELAPSE?

- *CRITICAL*,
- compare with previous examinations (history and examination), when ever possible*;*

- *Symptoms must be present 24/7 for 24 hours*

Relapses can be precipitated by infections and fever

– Check U/A for occult UTI

ACUTE TREATMENT OF RELAPSE:

- IV Solumedrol one gram daily for 3-5 days
- Steroid alternative with ACTH
- Severe cases: up to 2 grams qd x 7 days

Steroid intolerance –ACTH/Acthar gel

- Corticotropin repository treatment

CASE 5

- 36yo Physician

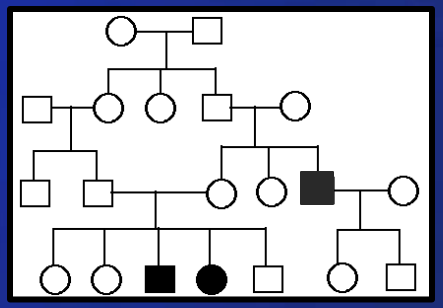
CASE 4

- 36yo WF with 4yr history of RRMS
- Oral therapy for past 3.5 years
- Last MS relapse 1 year ago
- EDSS 2, unchanged for past year

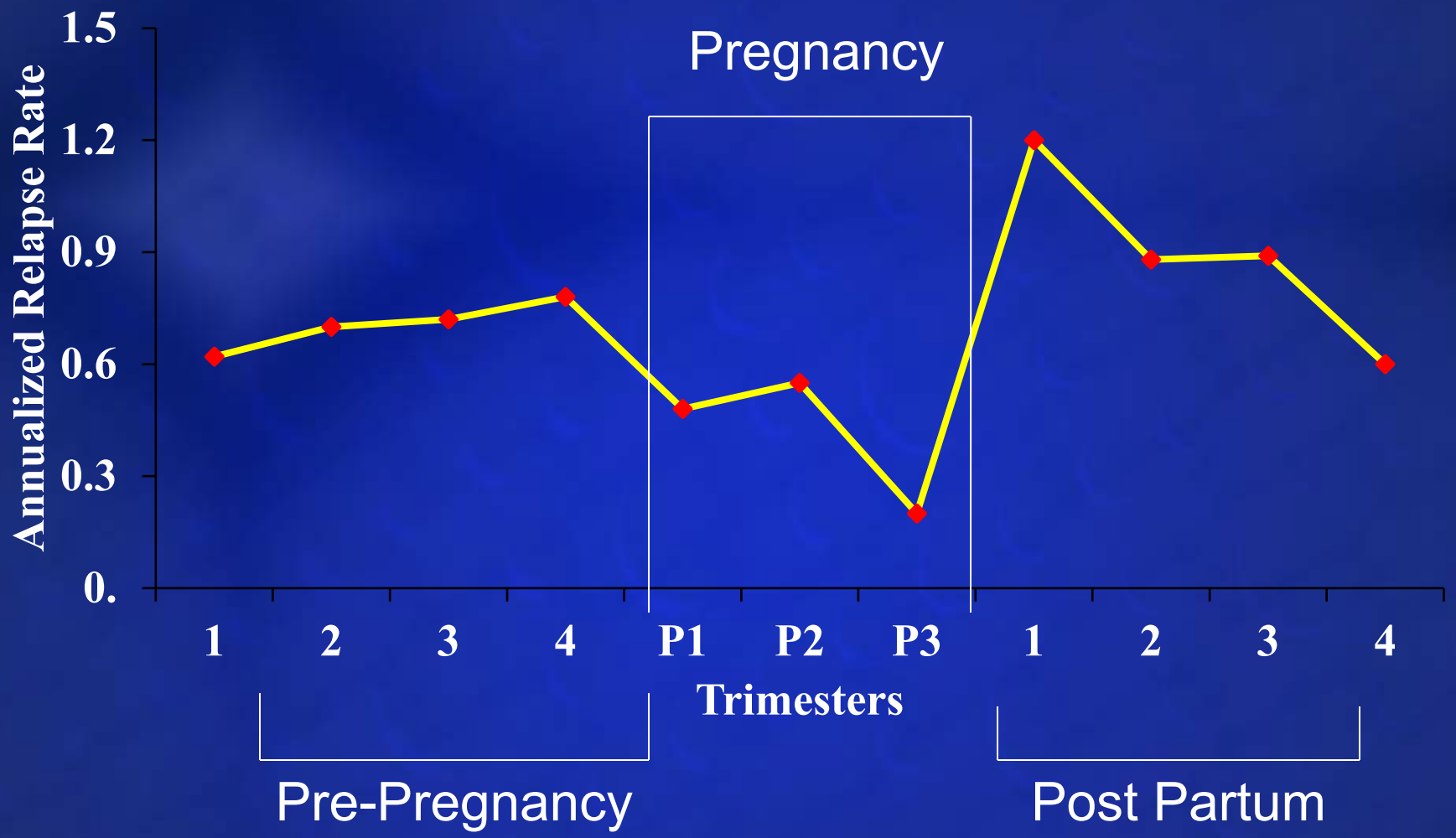
Wants to become pregnant

Pre-pregnancy Counseling

	Lifetime Risk of MS (%)
General population	F 0.5 ; M 0.3
Child of MS patient	3-5
Sibling of MS patient	3
Monozygotic twin of MS patient	25-30



Pregnancy and Relapse Rate

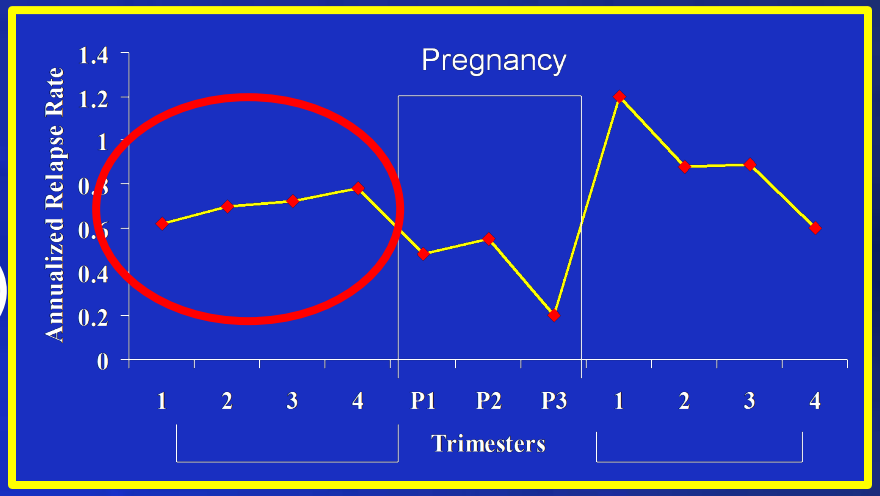


PRIMS, n=254

Pre-Pregnancy Planning

Planned Pregnancy

- Discontinue DMT before planned conception (recs)
- Brain MRI Scan



Unplanned Pregnancy

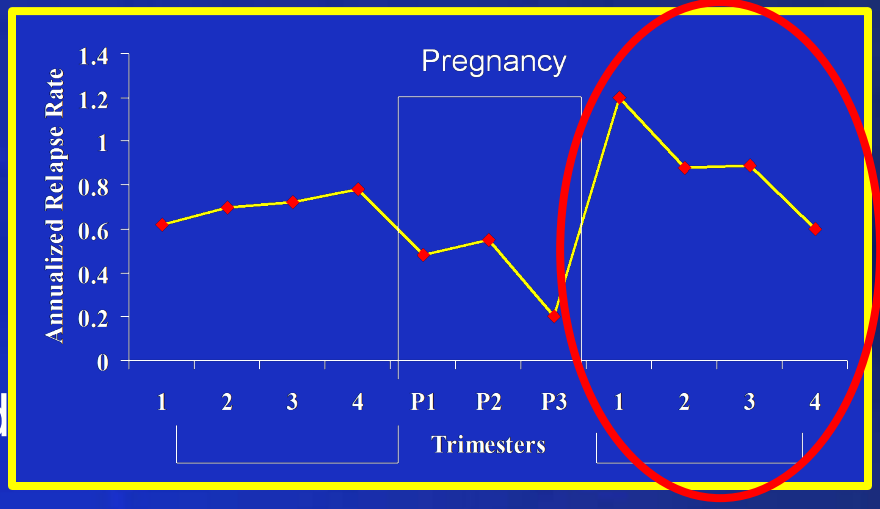
- First Trimester: Discontinue DMT
- Second Trimester: Review safety data

Post-Partum Management

Post-Partum DMT

- Resume soon after delivery

or after breastfeeding



Breastfeeding

- Not contraindicated; discouraged
  - But DMT pass into breast-milk
- May decrease relapse rate

Post-Partum Relapses (~30%)

- Treat with IVMP (PE or IVIG)
  - IVMP may impair wound healing
  - ? Prophylaxis with IVIG,Steroids

CONCEPT OF NEDA

- Same physician returns with her 18 month old in tow
- She has a stable normal exam
- Surveillance MRI with 3 new lesions
- What is your advice for change in treatment

Understanding NMO and MOG

neuromyelitis optica
myelin oligodendrocyte glycoprotien

NMOSD

Epidemiology

- Prevalence of NMO in various studies ranges from 0.5 to 10 per 100,000
- Female: male – 9:1
- Median age of onset is 32 to 41 years,
- NMO is usually sporadic, though a few familial cases have been reported.
- Other population studies of HLA in NMO indicate that the DRB1*0301 and DRB1*1037 alleles are associated with increased risk.

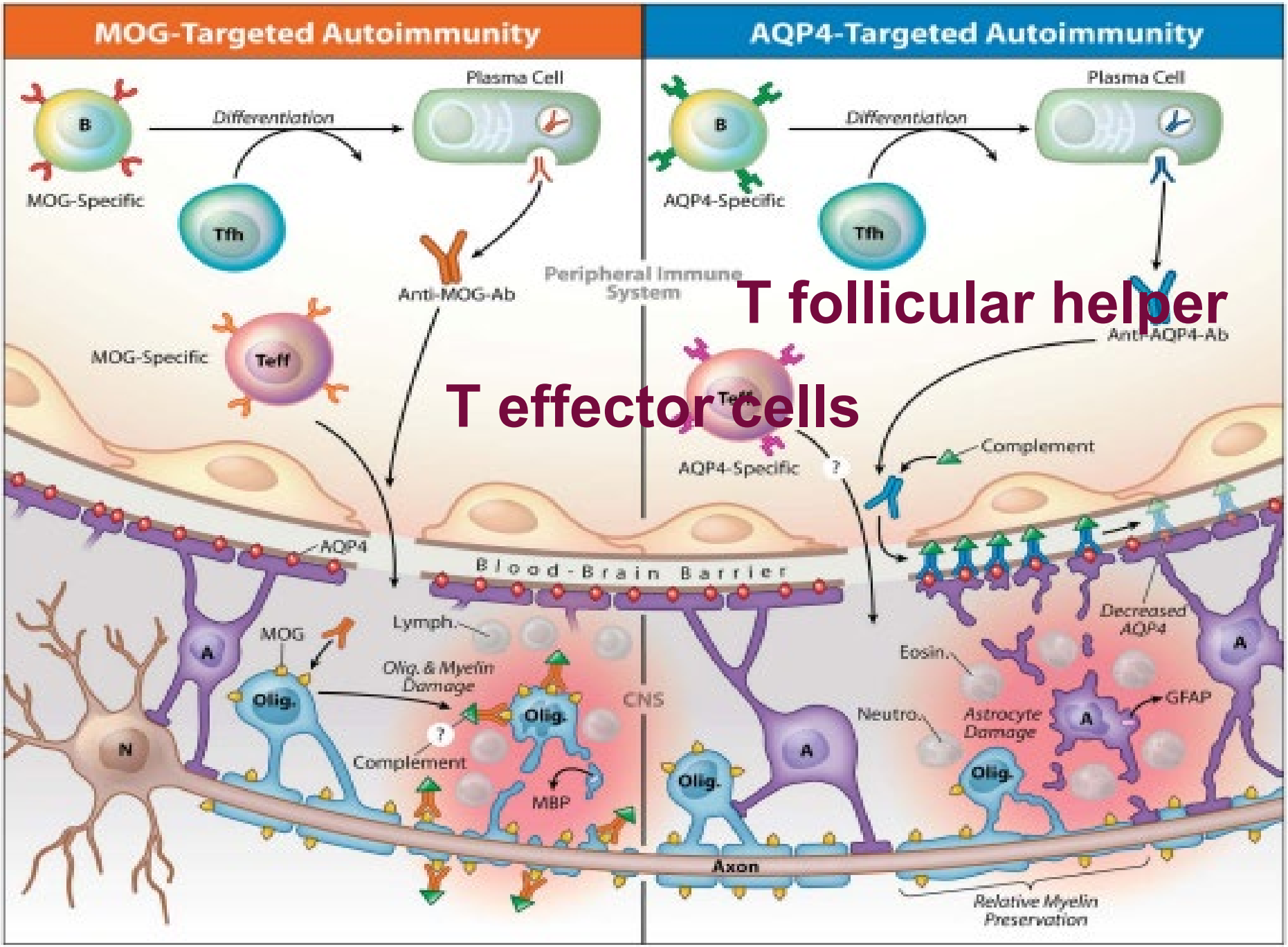
Clinical Features

Cardinal Clinical Features

- Transverse myelitis, typically longitudinally extensive (≥3 vertebral segments; often followed by tonic spasms and occasionally accompanied by pain or pruritus)
- Optic neuritis (often severe; may be bilateral)
- Episodes of intractable nausea and vomiting or hiccups from area postrema involvement

Other Clinical Features

- Narcolepsy
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Other hypothalamic presentations (eg, anorexia)
- Acute myopathy with hyperCKemia
- Brainstem syndromes (eg, ophthalmoplegia, hearing loss [possibly related to inner ear damage] opsoclonus/myoclonus)
- Myeloradiculitis
- Encephalopathy (PRES-like; ADEM-like)
- Cognitive dysfunction (subcortical pattern [inattention, executive dysfunction, reduced speed of processing])


MOG-Targeted Autoimmunity
AQP4-Targeted Autoimmunity
B
MOG-Specific
Differentiation
Plasma Cell
Tfh
Anti-MOG-Ab
Peripheral Immune System
T follicular helper
MOG-Specific
TeM
T effector cells
AQP4-Specific
Anti-AQP4-Ab
Complement
AQP4
Blood-Brain Barrier
Lymph.
MOG
Olig.
Olig. & Myelin Damage
CNS
Complement
MBP
Decreased AQP4
Eosin.
Neutro.
Astrocyte Damage
GFAP
A
N
Axon
Relative Myelin Preservation

Clinical features

- **Optic neuritis:-**
  - Severe
  - May not respond to steroids
  - Trend for recurrence
  - Progression beyond 2 weeks
  - Bilateral simultaneous or sequential
  - Usually retro bulbar
  - Papillitis and peripapillary hemorrhage

Clinical features

- **Transverse myelitis:-**

- Symmetric/Asymmetric paraparesis or quadriparesis, bladder dysfunction, and sensory loss below the level of the spinal cord lesion.

- Accompanying symptoms may include paroxysmal tonic spams of the trunk or extremities, radicular pain, or Lhermitte sign.

- Typically have a longer extent of spinal cord demyelination often involving three or more vertebral segments , a condition termed longitudinally extensive transverse myelitis (LETM)

Brain Involvement

- 50 to 60% of NMOSD patient has brain involvement.
- 40% brain lesions are symptomatic .
- 15-20% brain lesions are present during first clinical attack.
- Common sites involved are:-

1. Medulla(34%)
2. Supratentorial (29%) and infratentorial white matter (23%)
3. Midbrain (21%)
4. Cerebellum(18%)
5. Thalamus (13%) and hypothalamus (5%).

Brainstem symptoms

- Brainstem is rich in AQP4 antigen
- Involvement of the brainstem occurs in almost one-third of patients
- Common in AQP4 Ig G Ab positive patients.
- Mc brainstem symptoms :- vomiting and hiccups.
- Due to area postrema involvement.(10% as presenting symptom)
- Only Small percentage of NMOSD patients with this symptoms have lesion in area postrema on conventional imaging.

Natural History And Prognosis

- Monophasic -10-20%
- Relapsing – 80-90%
- Cumulative disability is more severe than MS
- Secondary progressive disease course is uncommon
- Relapse occurs within first year in 60 percent of patients and within three years in 90 percent

uk et al. Neurology 2017; 68: 603–605.

Recently Approved Drugs

DRUG (trade name)	APPROVAL	MECHANISM	COST	AVAILABLE IN INDIA	AVAILABLE as
Inebulizumab (Uplizna)	12/6/2020	anti-CD19 humanized monoclonal antibody	Rs 35lac	NO	Single dose vial(100mg/10ml)
Satralizumab (Enspryng)	16/8/2020	anti-IL-6R monoclonal antibody	Rs 11lac	NO	Single dose prefilled syringe (120mg/ml)
Eculizumab (Soliris) Ultimaris (very recent)	June 2019	humanized monoclonal antibody against complement protein C5	Rs 2,10,000/ vial	YES	300mg/30ml vial

MOG
MYELIN OLIGO
GLYCOPROTEIN ANTIBODY

Clinical Course

- Monophasic or relapsing
- 50% relapse in first two years after presentation
- 75% relapse by five years
- Titers higher at time of relapse
- Up to 50% become antibody negative after relapse
- Persistent positivity indicates higher risk of relapse

Disability

- Outcomes better than NMO
- Severity of relapse may be the same but relapse outcome better than NMO
- Severe persistent disability in 40-75%
- Sphincter>cognitive>visual>mobility
- Disability driven by severity of first attack (70%) and frequency of attacks.
- Progression not described to date

Phenotype

- ON 41-63%
- TM 30%
- ADEM-like varies based on age(common in pediatric age)
- Brainstem syndromes (incl. area postrema) up to 30%
- Many do not fulfill 2015 diagnostic criteria for NMOSD

PRESENTATION AS ADEM

- Common in pediatric age group
- ADEM symptoms: systemic (fever, headache, nausea, vomiting, malaise, altered mental status) and more specific, which vary based upon the locations of the lesions within the CNS (vision impairment, ataxia, hemiparesis, hemisensory loss)
- Anti-MOG antibodies present in 40–68% of children with ADEM diagnosis.
- In adults with the positive anti-MOG test, ADEM presentation is less frequent, varies from a few up to 18% of cases.

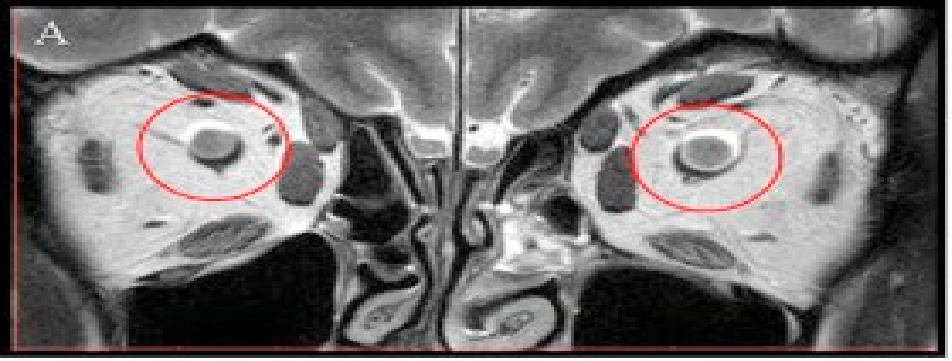
MOG Optic Neuritis

- Most frequent clinical phenotype in older age patients
- Disc swelling common and may be severe
- Often bilateral
- Chronic Relapsing form
- Longitudinally extensive, anterior part on MRI
- Optic nerve head swelling
- Perineuritis common
- Good outcome

Ciotti, J. et al A. Clinical and laboratory features distinguishing MOG antibody disease from multiple sclerosis and AQP4 antibody-positive neuromyelitis optica. Mult. Scler. Relat. Disord. 2020, 45, 102399.

Spine MRI

- Isolated transverse myelitis (TM) as initial presentation of MOGAD in about 20% patients, but a combination of TM and ON occurred in 8 to 15%
- 80% longitudinally extensive
- Multiple lesions including conus (75%)
- Urinary retention/incontinence and/or bowel and/or erectile dysfunction developed at least once in almost 70% patients with TM
- Often confined to grey matter
- Usually enhance acutely, but less commonly than NMO and MS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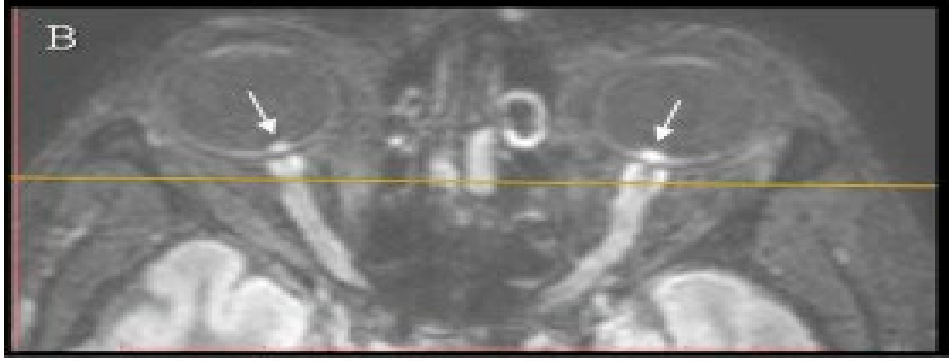
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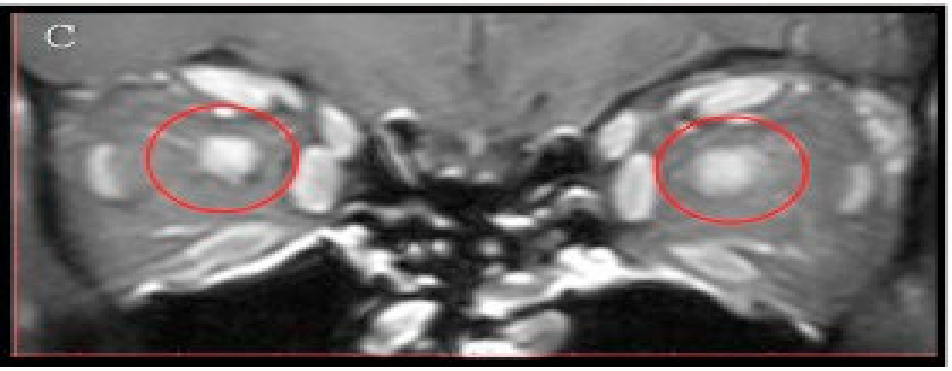
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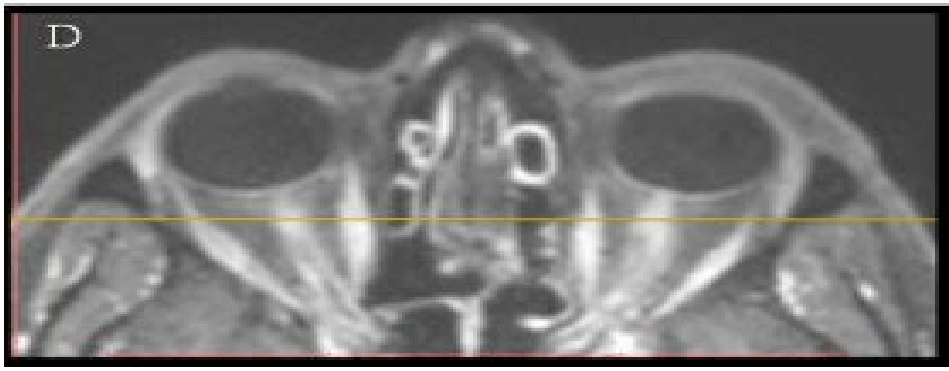
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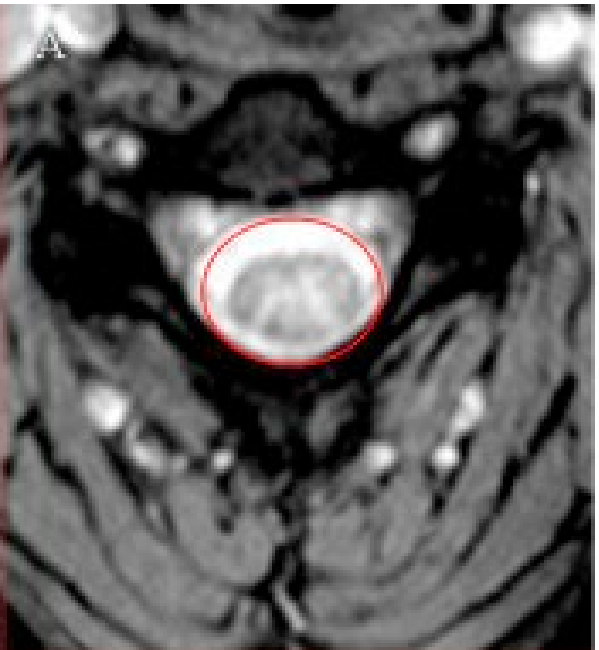
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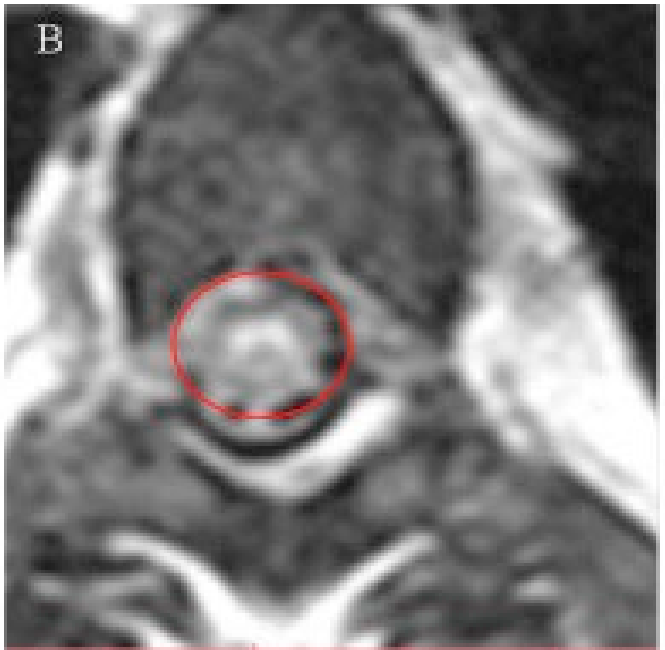
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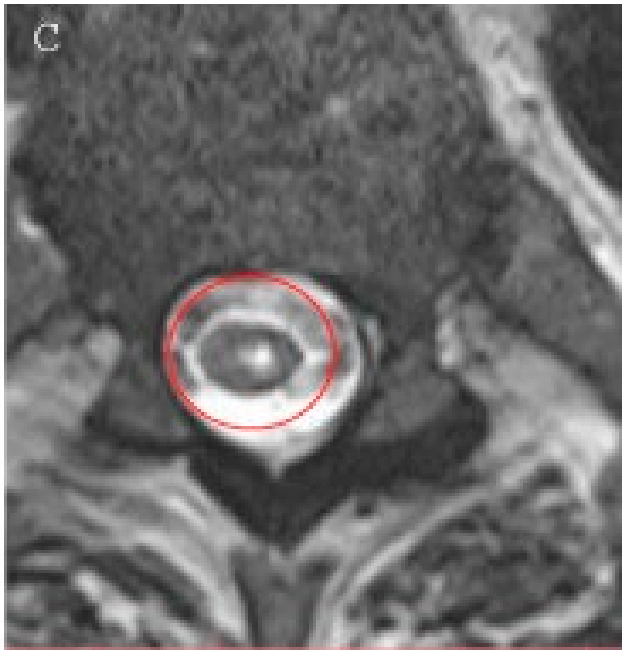
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Brain MRI

- More brainstem and cerebellar than supratentorial lesions.
- Area postema seen in about 15% of the anti-MOG positive patients
- Thalamic and SUBcortical lesions common
- Less demarcated and more fuzzy compared to NMO and MS
- Cortical inflammation associated with the MOGAD manifests mostly with epileptic seizures (20 times more common then NMOSD)

Shen, C.H.; et alSeizure Occurrence in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease: A Systematic Review and Meta-Analysis. Mult. Scler. Relat. Disord. 2020, 42, 102057

MS Overlap

- 5% of MS patients are MOG-IgG positive
- Mostly severe, relapsing brainstem and spinal syndromes
- Atypical lesion
- May show evolution in space and time on MRI

M Spadaro et al. Neurol Neuroimmunol Neuroinflamm 2016;3:e257.

CSF

- Pleocytosis 40-50%
- Neutrophil predominance
- Elevated protein 33-40%
- OCB rare(<15%), Ig index usually normal
- MOG IgG in CSF in 70% of seropositive subjects

Proposed Diagnostic Criteria MOGAD (must meet all three criteria)

1. Clinical findings: any of the following presentations:
   - ADEM
   - Optic neuritis,
   - Transverse myelitis (LETM or SSTM)
   - Brain or brainstem syndrome compatible with demyelination
   - Any combination of the above

2. Serum positive for MOG-IgG by cell-based assay

3. Exclusion of alternative diagnosis

To Summarise

Characteristics	MS	NMO	MOG
Antecedent infection/ immuninization	Rare	Rare	common
Epidemiology	Prevalence : common Ethnicity: whites more predisposed Geographic regions: farthest from equator	Rare African-Americans, Afro-Caribbeans Near to equator	Unknown Unknown Unknown
Clinical onset and course	85% remitting-relapsing/ 15% primary-progressive Not monophasic	Typically relapsing, no secondary progression	Monophasic or relapsing , No secondary progression

Characteristics	MS	NMO	MOG
Gender (M:F)	1:2	1:9	M<F
Functional outcome	variable	poor	good
Age of onset	3rd decade	4th decade	1st to 3rd decade
Optic Nerve MRI	Uninalteral, enhancement of <50% of nerve affected, middle of optic nerve	Bialteral, enhancement of >50% of optic nerve, posterior optic pathway involving chiasma	Bilateral, enhancement of >50% of optic nerve, anterior optic pathway with optic nerve head swelling
MRI: BRAIN	Oviod Periventricular, Dawson fingers, juxtacortical, cortical, infratentorial peripheral, ring/ open ring enhancement	Usually normal or non-specific WM lesions; if present , area prostrema, perithird/ fourth ventricle, splenium, diffuse corpus callosum, pencil thin ependymal or cloud enhancement.	ADEM like fluffy WM, deep GM, diffuse/confluent brainstem including cerebellar peduncles.

	MS	NMO	MOG
MRI:SPINE	Short-segment peripheral WM lesions	LETM (≥3 vertebral segments) central GM lesion. 85% LETM	Distributed in the lower parts of the spinal cord, conus involved, central cord involved, 75%LETM
CSF:CELLS	Mild pleocytosis Lymphocyte predominant	Occasional prominent pleocytosis PMN cells and mononuclear cell	Pleocytosis 40-50% neutrophil predominant
CSF:OCBs	85%	15-30%	Rare(10-15%)
AB	Absent	AQ-4 Present in 70-80%	MOG +ve in 70%
Acute t/t Maintenance t/t Prognosis	IV/ steroid; plasma exchange(rarely required) Immunomodulation Majority Ambulatory after 20 yrs; most disability occurs in 2nd progressive phase	IV/ steroid; plasma exchange (often required) Immunosupression Attack-related accumulationof disability;	IV/ steroid; plasma exchange (often required); IVIG in children Immunosupression Most disability after 1st attack; transient seropositivity predicts monophasic course; persistent seropositivity and high titre predict

	FEATURE	NMO	MS
1.	Demographics	Mixed race	Whites
2.	Age at onset	40yr	30yr
3.	Gender	Female in AQP4+ Equal in sero-	Female
4.	Clinical phenotype • Relapse • Recovery • Progression	 Severe Poor -	 Mild Generally good +
5.	Optic neuritis • Simultaneous B/L • Altitudinal defect • RNFL thinness	 Upto 20% cases + Widespread and more thin	 Rare - Temporal and less thin
6.	Transverse myelitis	LETM, centally located	Small segment, peripheral
7.	Devic type presentation	4-6% in AQP4+ 24-32% in sero-	Atypical
8.	Intractable nausea/vomiting/hiccough and SIADH	Well described	Atypical

PATHOLOGY

	FEATURE	NMO	MS
1.	Involves	White and gray matter	Predominant white matter
2.	Edema	Striking	Less
3.	Necrosis	+	Not striking
4.	Cavitations	+	-
5.	Myelin	Relatively preserved	Severe demyelination
6.	Axon damage	+	+
7.	Leukocyte infiltrates	Neutro/eosinophils	T and B lymphocytes
8.	Aquaporin 4	Loss	Upregulation
9.	GFAP	Loss	Upregulation
10.	Complement deposits	+	Less marked
11.	Vascularity	+	uncommon

Jarius S *et al*. (2008) Mechanisms of Disease: aquaporin-4 antibodies in neuromyelitis optica *Nat Clin Pract Neurol* 10.1038/ncpneuro0764

MOC question

Which statement is false:

A. Multiple Sclerosis is a disorder of lesions over time and space
B. Oligoclonal bands are 100% diagnostic of MS
C. NMO is a monophasic illness associated with the AQ4 antigen
D. There is no benefit to treating CIS early in MS