Multiple Sclerosis and related disorders

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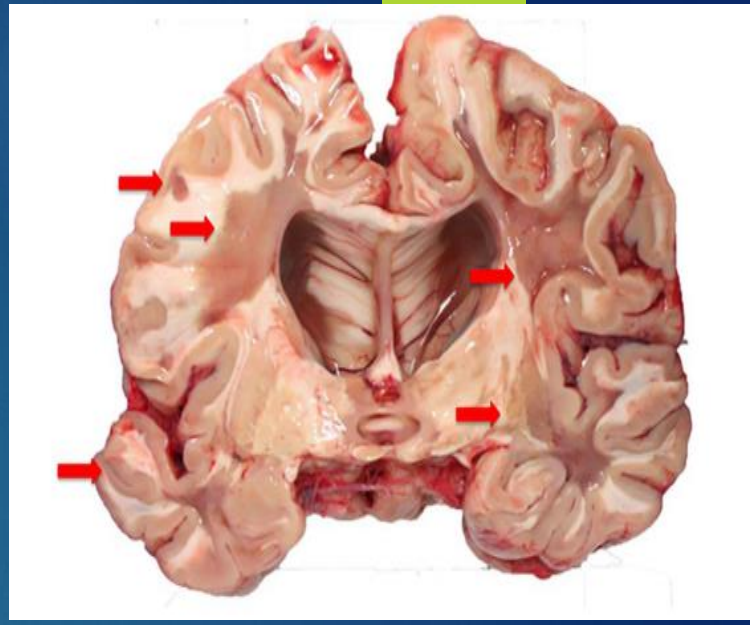
Multiple (Disseminated) Sclerosis

- Pathology
- Pathogenesis
- Epidemiology/Etiology
- Clinical course and stages / Prognosis
- Diagnosis/ Differential diagnosis
- Approach to treatment/ Disease-modifying therapy/ Prognostication

Pathology



- Unique Dual pathology- Inflammation and degeneration

- MS is a chronic inflammatory disease of the **CNS** that leads to focal destruction of myelin , axonal damage and reactive gliosis of astrocytes in the white and grey matter .
- MS is characterised by multifocal demyelinating lesions or ‘plaques’
- Plaques are due to focal loss of myelin (oligodendrocytes), with relative preservation of axons and astrocytic gliosis

- Plaques are most commonly seen in the spinal cord , optic nerves , brainstem/cerebellum and periventricular white matter.

Pathophysiology

Multiple sclerosis is an autoimmune disease in which lymphocytes migrate out of lymph nodes into the circulation, cross the blood–brain barrier, and aggressively target putative myelin antigens in the CNS , causing inflammation, demyelination , neuroaxonal injury, astrogliosis, and ultimately neurodegeneration

- It is considered an immune-mediated disease in genetically susceptible individuals.
- The immune attack is triggered by an environmental agent that is acquired in childhood (<15 yrs).

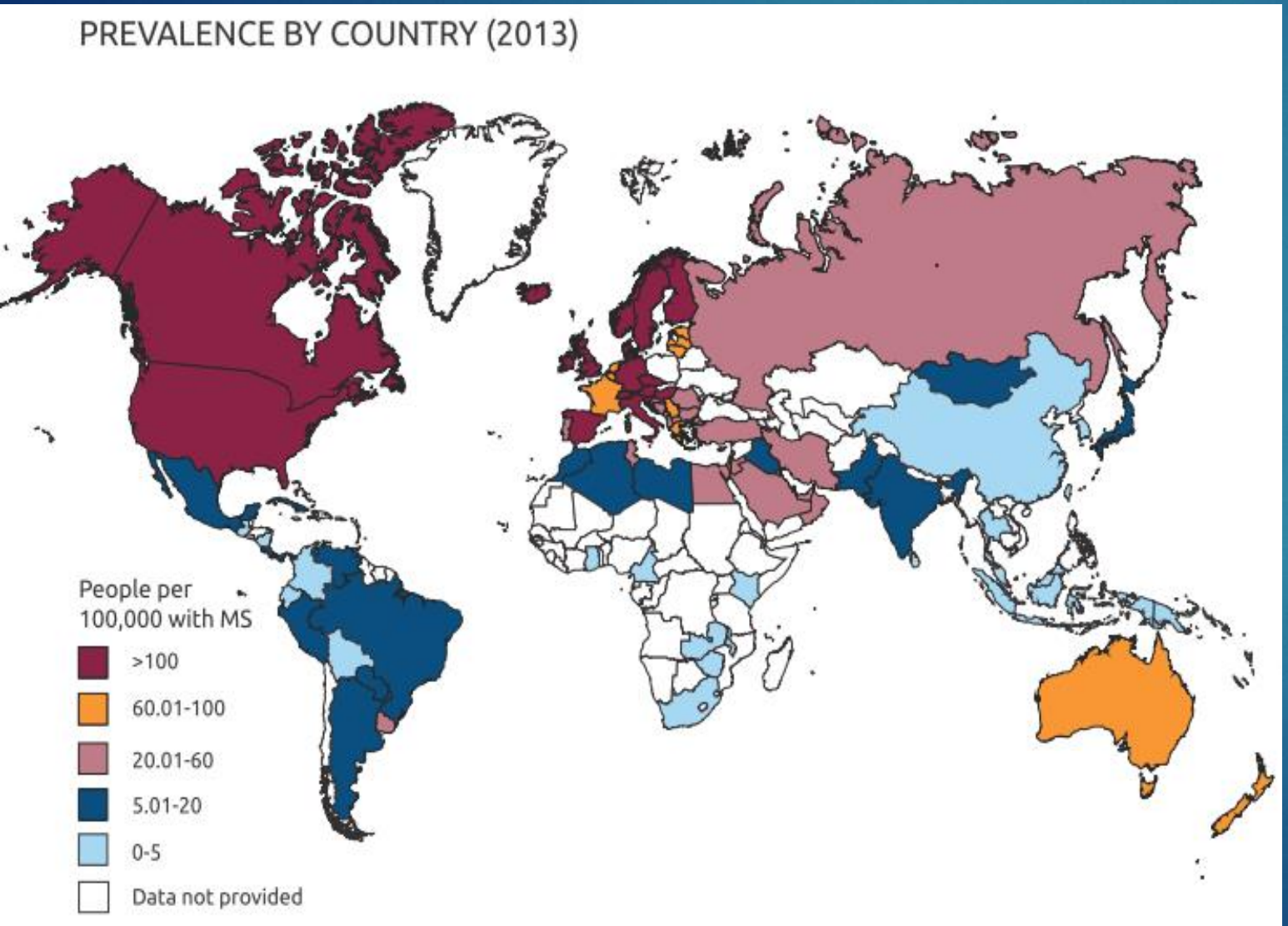
Epidemiology

- MS is the most common inflammatory demyelinating disease of the CNS and is the most common disabling neurological disease to afflict young adults
- The mean age of onset is approximately 30 years.
- Almost 70% of patients manifest symptoms between ages 20 and 40.
- Disease onset rarely occurs prior to 10 or after 60 years of age. However, patients as young as 3 and as old as 67 years of age have been described
- There is clear gender difference with females being more frequently affected than men (2.5 :1)

MS Epidemiology

- There is a clear trend towards increased prevalence over the last few decades- according to the MSIF , the global median prevalence of MS increased by 10% in the last 5 years (from 1.8 million in 2008 to 2.5 million in 2017)
- This increase is quite gender-specific, and seen mostly in females.
- Increasing prevalence is multifactorial..

MS Epidemiology- Geographical distribution



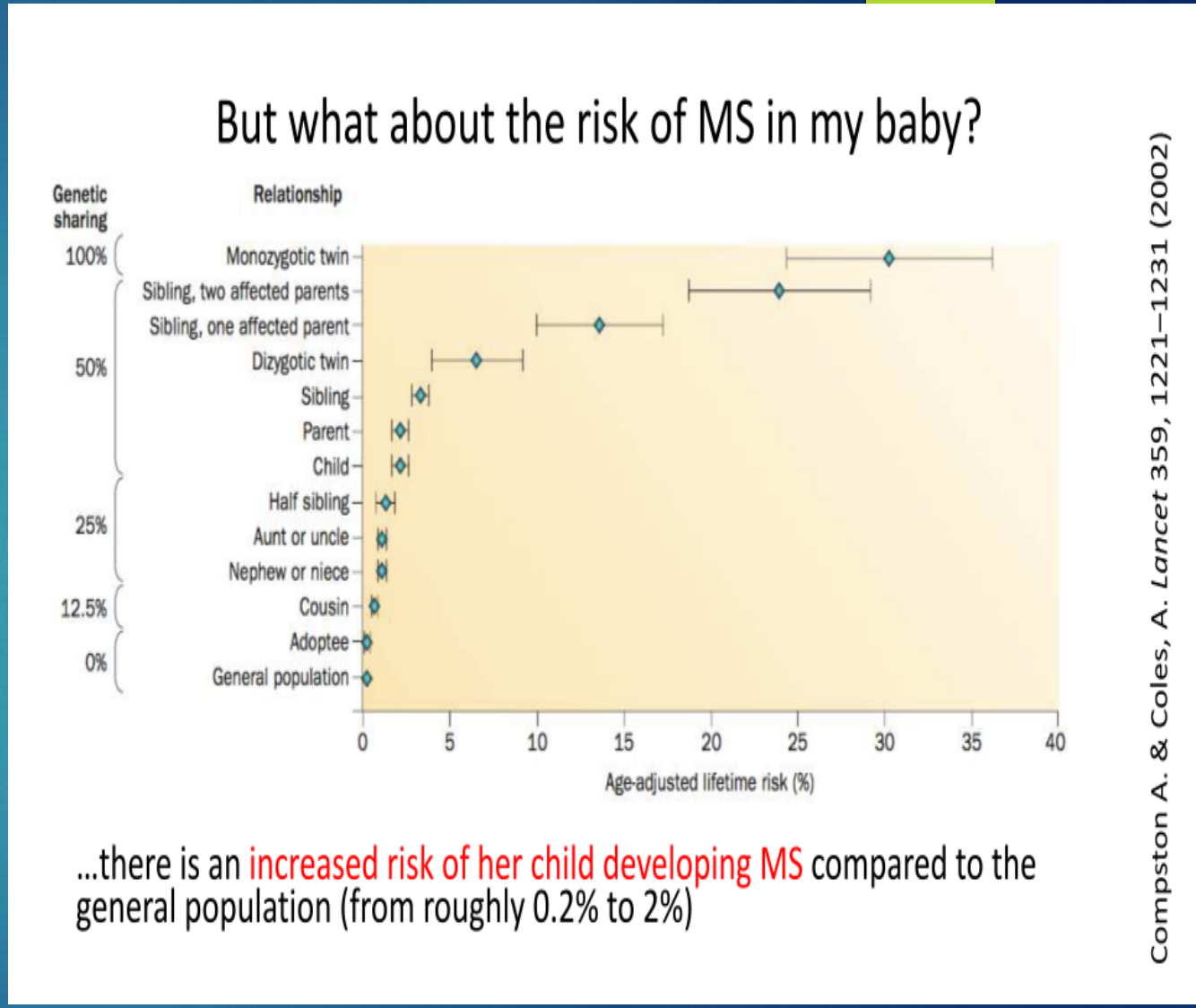
- A very specific geographic distribution around the world – the effect of latitude
- Epidemiology studies in the Middle East show an intermediate prevalence of around 40/100000.

Genetic factors

The incidence of MS in first degree relatives is 20-40 times higher than in general population, suggesting the influence of genetic factors on the disease.

- Monozygotic twins: 30% concordance
- Dizygotic twins: 5% concordance
- 1 parent has MS: 2%-4%
- Second degree relative: 1%

Lifetime risk of developing MS: 0.1%-0.2%



Risk factors/Triggers of MS

- Epstein – Barr virus (EBV) infection
- Decreased sun exposure/vitamin D deficiency.
- Smoking (Active and passive)
- High salt intake
- High BMI (Diet)
- Increased physical and emotional stress ?
- Improved hygiene
- Other viral infections (HPV)

"Urbanization and western life-style"

EBV theory

- Exposure to EBV at an early age in children has been linked to reduced incidence of MS, while exposure in the form of infectious mononucleosis later in life (late adolescence) is linked to an increased risk.

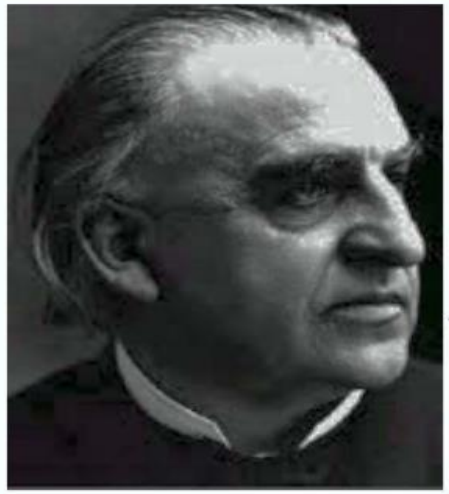
- EBV prevalence also appears to correlate with the observed differences in MS based on latitude and socioeconomic structure

Establishing a diagnosis of Relapsing MS

- Classically, a diagnosis of relapsing MS is made when a patient exhibits typical inflammatory neurologic episodes (relapses) disseminated in time and space.

- Relapses are defined as new or worsening neurologic symptoms that occur in the absence of fever or infection, last over 24 hours, and are preceded by 30 days of relative neurologic stability

- No alternative explanation for the episodes.

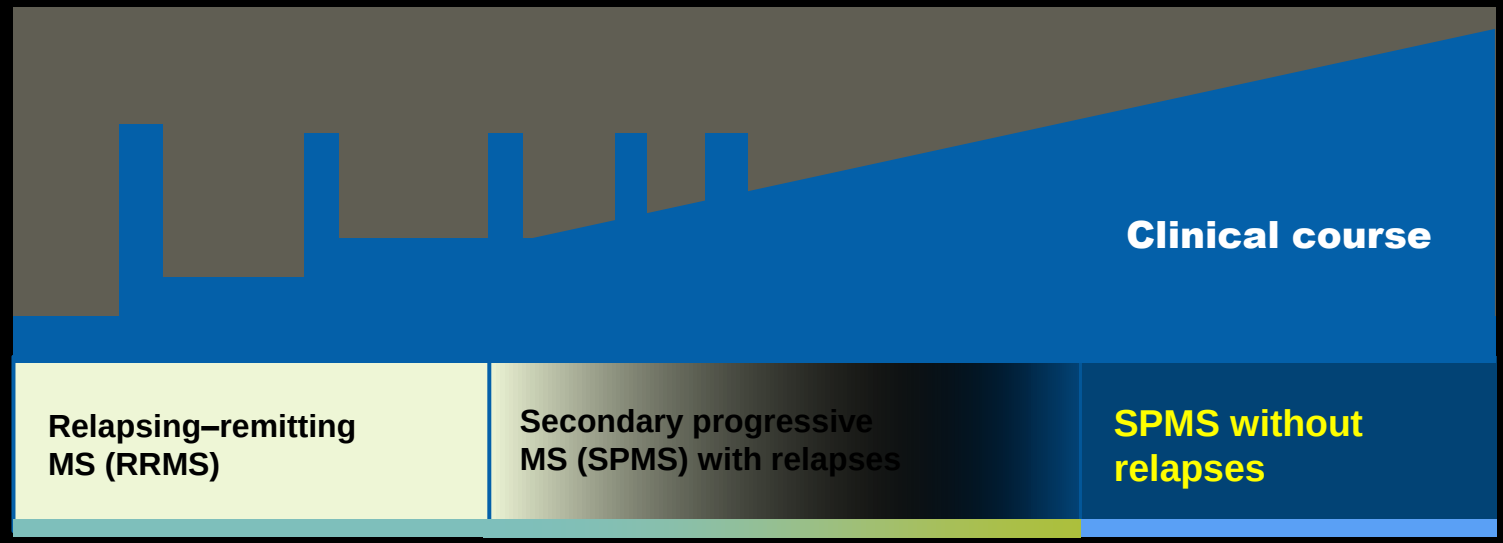


To learn how to treat disease, one must learn how to recognize it. The diagnosis is the best trump in the scheme of treatment.

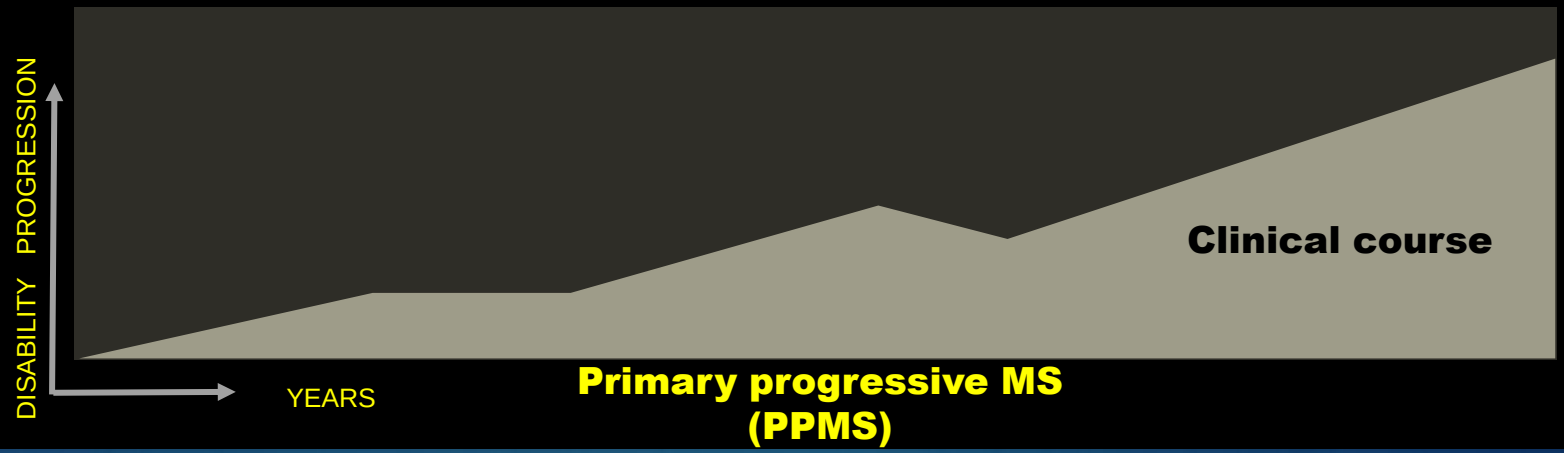
Jean Martin Charcot
1825-1893

MS disease continuum

~90%
of patients have relapsing–remitting onset of MS



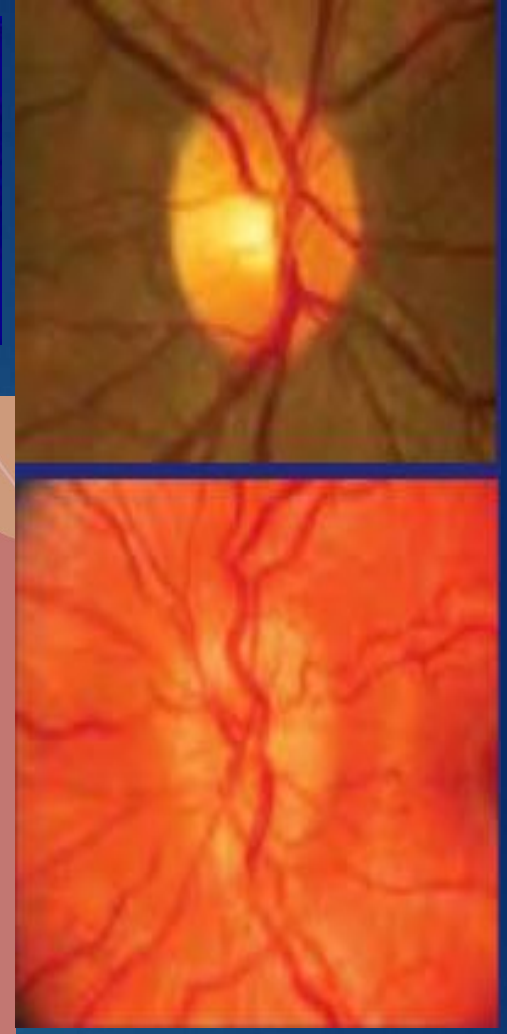
~10%
of patients have primary progressive onset of MS



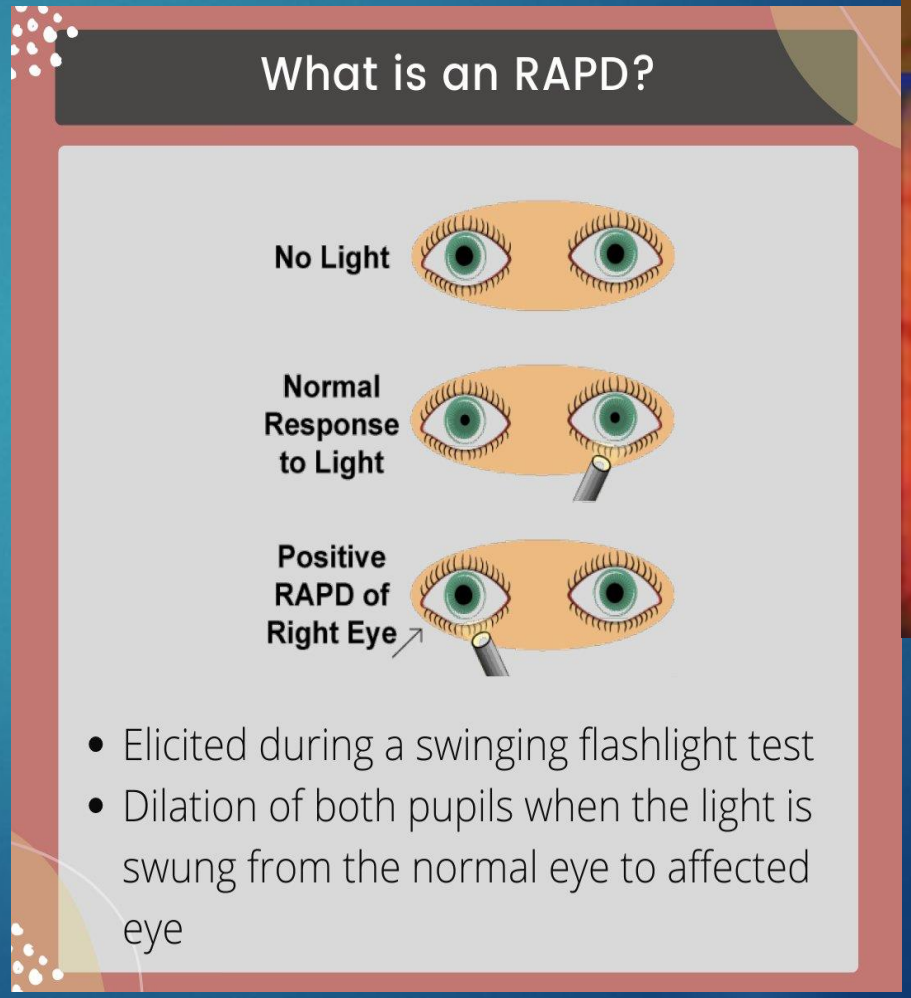
Common Relapses

Part of CNS affected	Clinical Presentations
Optic nerve	Optic neuritis
Spinal cord	Numbness/tingling (partial myelitis) Hemi or paraparesis Bowel/bladder dysfunction Lhermitte's sign
Brain stem	Diplopia/ Internuclear ophthalmoplegia (MLF) Dizziness/vertigo Trigeminal neuralgia Facial palsy

Typical MS-related Acute Optic Neuritis



- Unilateral
- Onset over few days to 2 weeks
- Classic triad of visual loss, periocular pain esp. on moving the eye and dyschromatopsia,
- Visual acuity- variable (not very severe)
- Relative Afferent Pupillary Defect (RAPD)
- Red desaturation
- Central visual field loss (scotoma)
- Good recovery >90% starting within 2-3 weeks
- Normal OD in 70%
- Optic atrophy after 4-6weeks



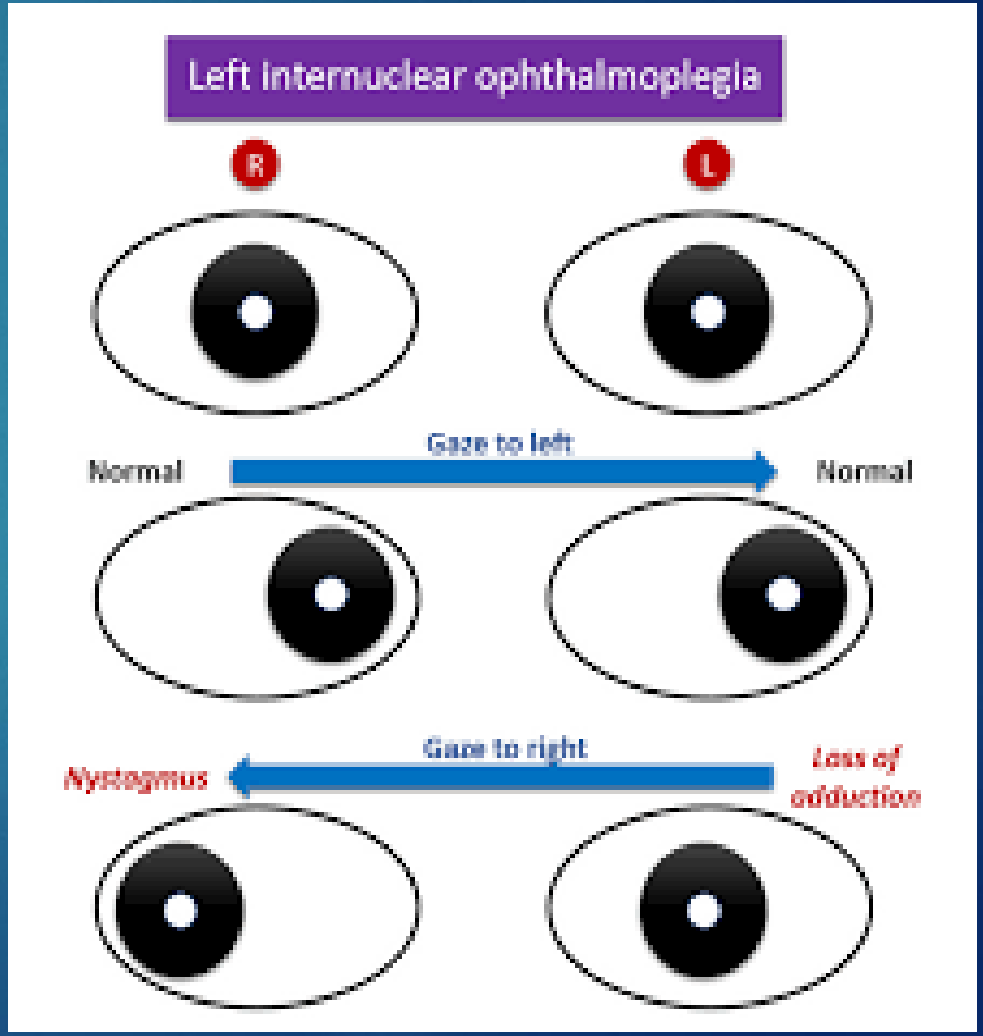
Red Flags: Myelitis

- Hyper-acute non progressive onset
- Symmetrical symptoms
- Complete involvement of the spinal segment
- Progressive myelopathy with absence of bladder involvement
- Anterior spinal artery territory lesion
- Localized or radicular spinal pain
- Cauda equina Syndrome
- Co-existing lower motor neuron (LMN) signs

- **Compression** (eg, intervertebral disk, tumor)
- **Ischemia/infarction**
- **Other inflammatory** (eg, neuromyelitis optica, sarcoid, lupus, Sjögren syndrome)
- **Infection** (eg, syphilis, Lyme, virus, tuberculosis)
- **Toxic/nutritional/metabolic** (eg, vitamin B_{12} deficiency, nitrous oxide toxicity, copper deficiency)
- **Arteriovenous malformation**
- **Noncord "mimics"** (eg, Guillain-Barré syndrome, myasthenia gravis)

Brainstem/Cerebellar

MS	*Less common*	*Atypical*
Internuclear ophthalmoplegia	Facial palsy, facial myokymia	
Ataxia and multidirectional nystagmus	Deafness	Vascular territory syndrome, e.g., lateral medullary
Sixth nerve palsy	One-and-a-half syndrome	Third nerve palsy
Facial numbness	Trigeminal neuralgia	Progressive trigeminal sensory neuropathy
	Paroxysmal tonic spasms	Focal dystonia, torticollis



MS symptoms (not relapses)

Residual symptoms from previous relapses or non-relapse-related symptoms:

- Fatigue
- Pain, spasticity ,spasms, Ataxia
- Uhthoff's phenomenon- Pseudo-relapses
- Depression, anxiety, rarely psychosis
- Bladder dysfunction
- Seizures
- Memory problems, cognitive issues

Clinical features atypical for MS

- Onset before age 10 or after age 50
- Deficit developing within minutes
- Cortical deficits such as aphasia, apraxia, alexia, neglect
- Rigidity, sustained dystonia
- Early seizures
- Early dementia

Para-clinical tests

- MRI

- CSF
- Visual-evoked potentials

- Other evoked potential (Brainstem,auditory,somato-sensory)
- Specialized blood/CSF biomarkers (Neurofilament Light)
- Optical Coherence Tomography
- Specialized MRI techniques

Blood tests to exlude other diseases

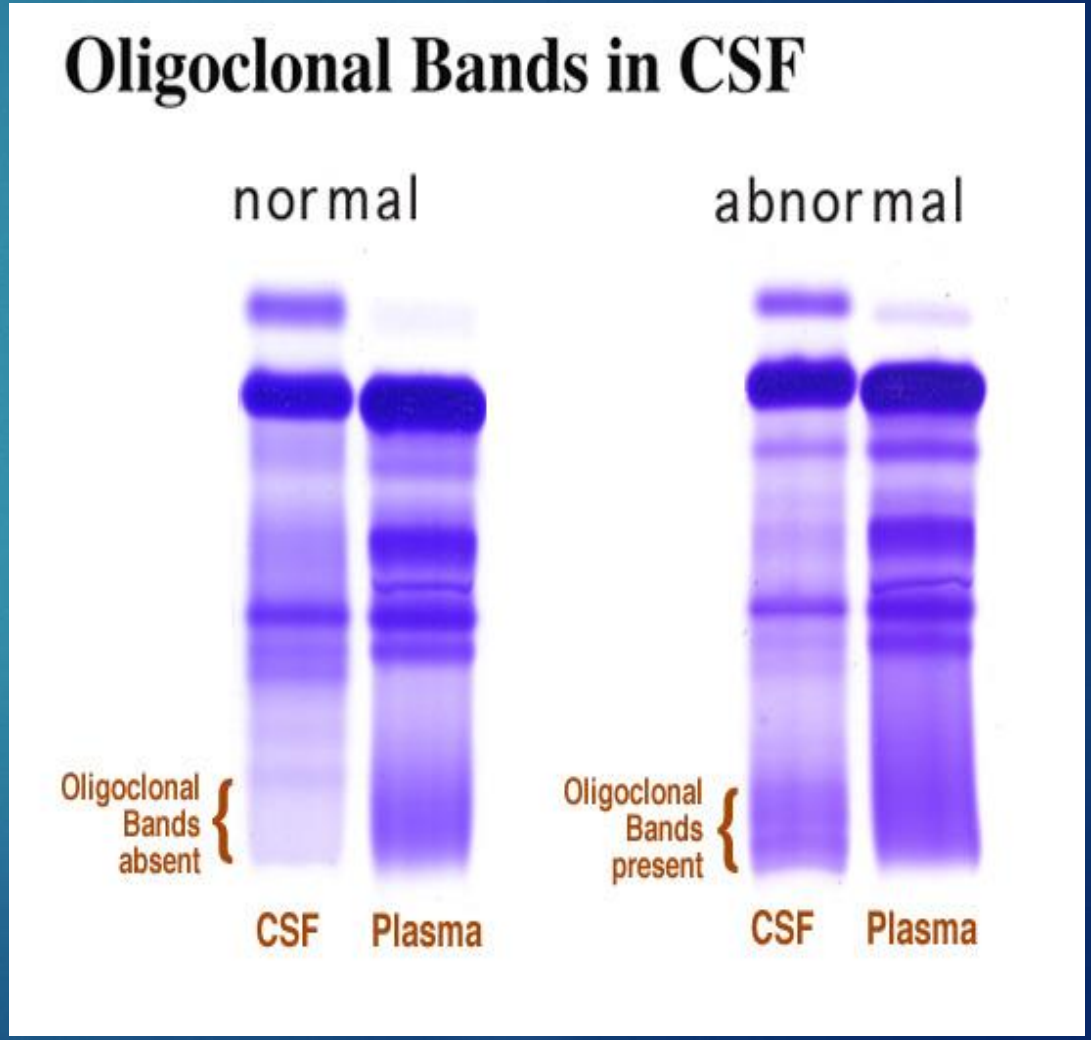
- Normal systemic inflammatory markers (ESR, CRP).

- Autoantibodies (Low-titre ANA may occur)

- Vasculitis screen, B12, TFT, LFT, serum ACE/CXR

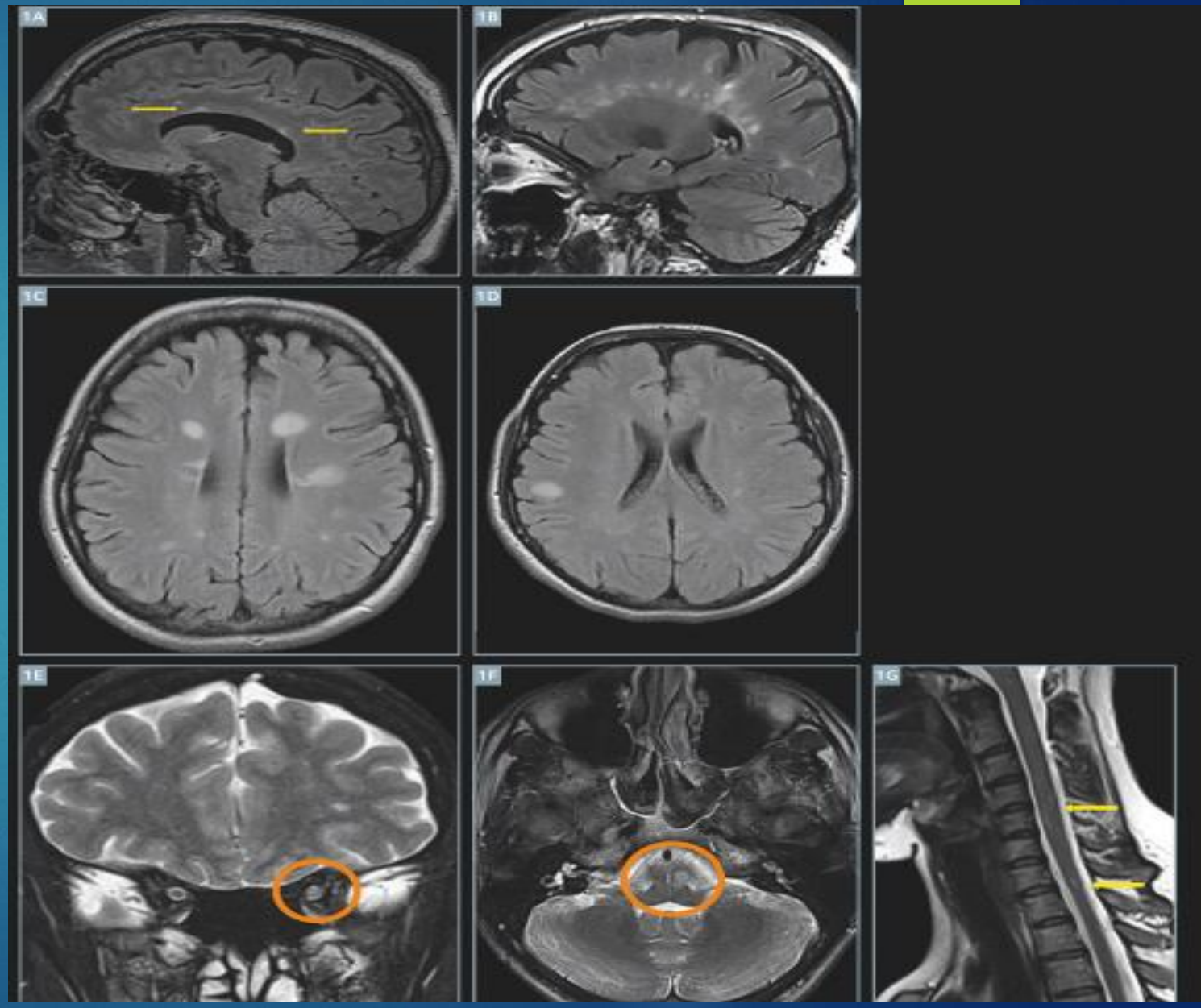
Frequencies of abnormal CSF variables in clinically definite MS

- Oligoclonal IgG bands >95% by isoelectric focusing technique
- Increased IgG index 75%
- Increased WBC count > 5 cells in 1/3 of patients (very rarely > 35)
- Mildly increased protein in 1/2 of patients (very rarely> 70)
- If protein >100 and/or low glucose unlikely to be MS



MS brain lesion characteristics

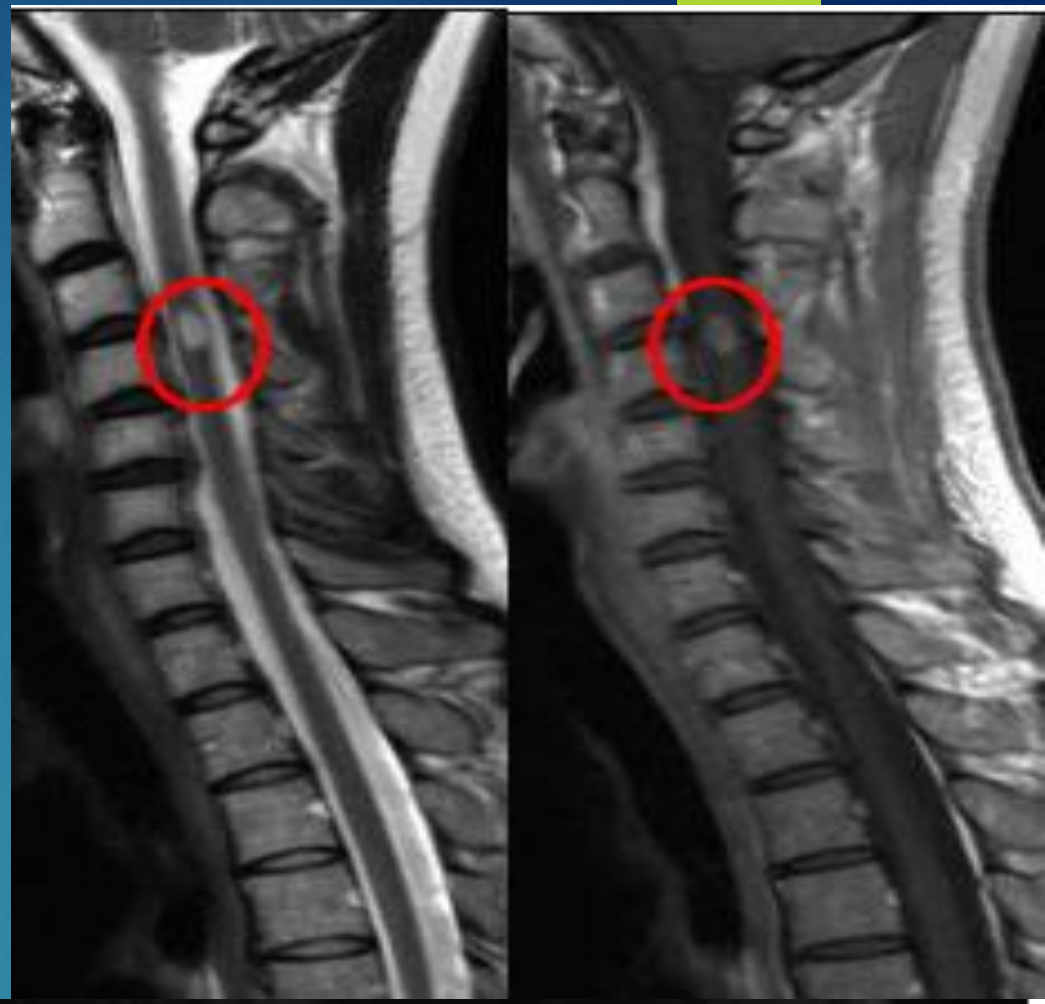
Lesion configuration	ovoid (round shape)
Size of lesions	> punctate
Typical lesion location	periventricular, juxtacortical, infratentorial
Lesion pattern	random, asymmetric
Tissue destruction	variable
Contrast enhancement	frequent

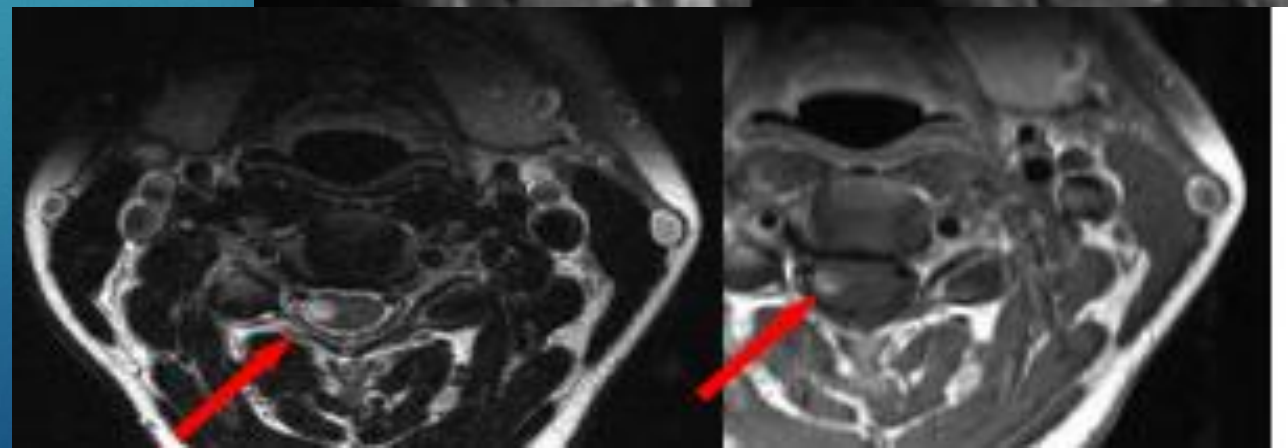


MS spinal cord lesion characteristics

- Cigar shaped (in sagittal plane)
- Extension < 2 vertebral bodies in length and < ½ spinal cord diameter
- Eccentric location
- Mass effect rare
- Cervical cord and posterior columns preferentially affected

No incidental age-related / vascular spinal cord lesions





Differential Diagnosis

- Excluding diseases that can mimic MS clinically **or <u>radiologically</u>** is very important and can be very challenging.

- Over-diagnosis of non-specific MRI changes !!

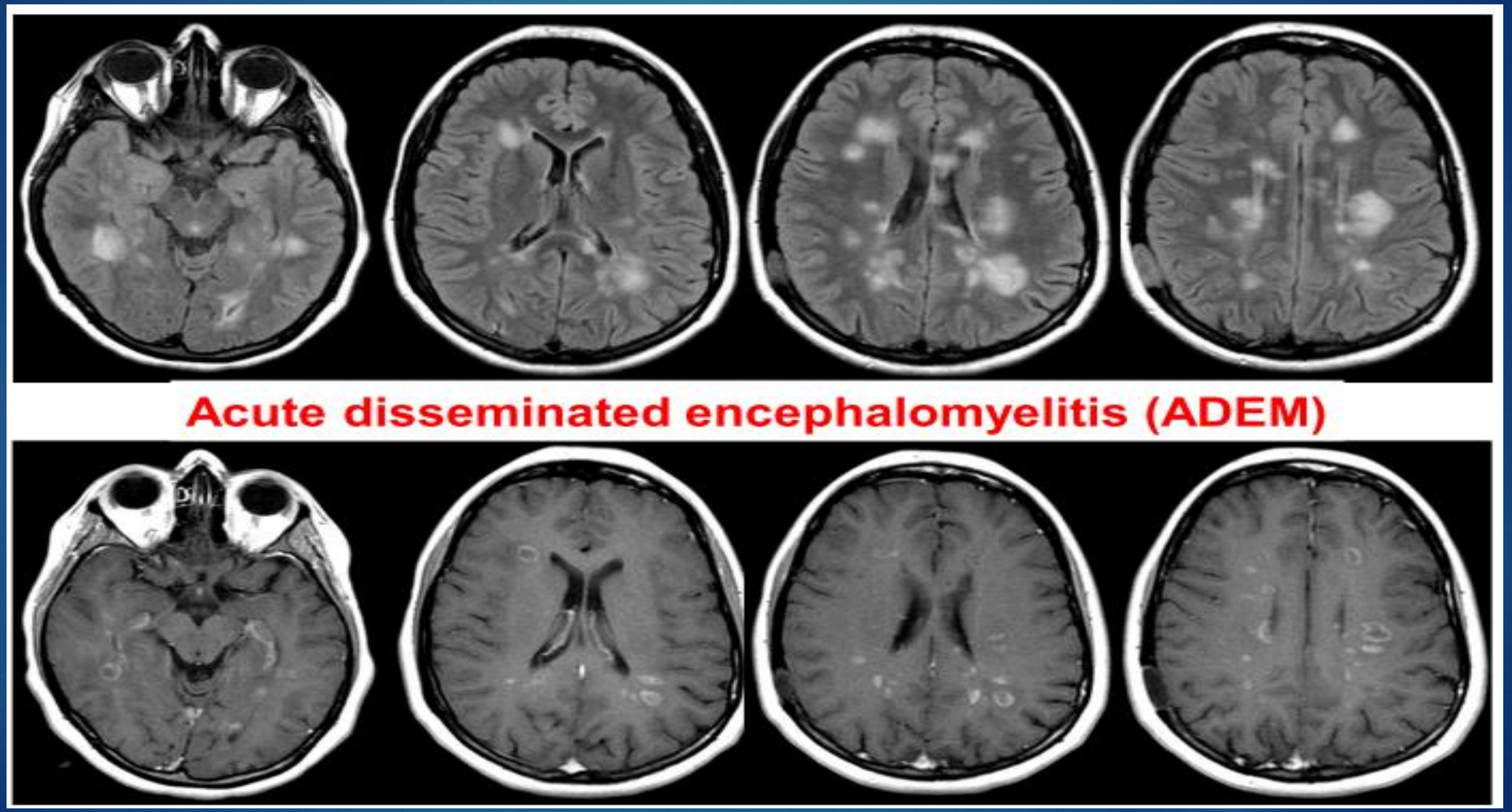
Differential Diagnosis

- MS is the most common primary demyelinating disease of the CNS, but other other primary demyelinating disorders should be considered

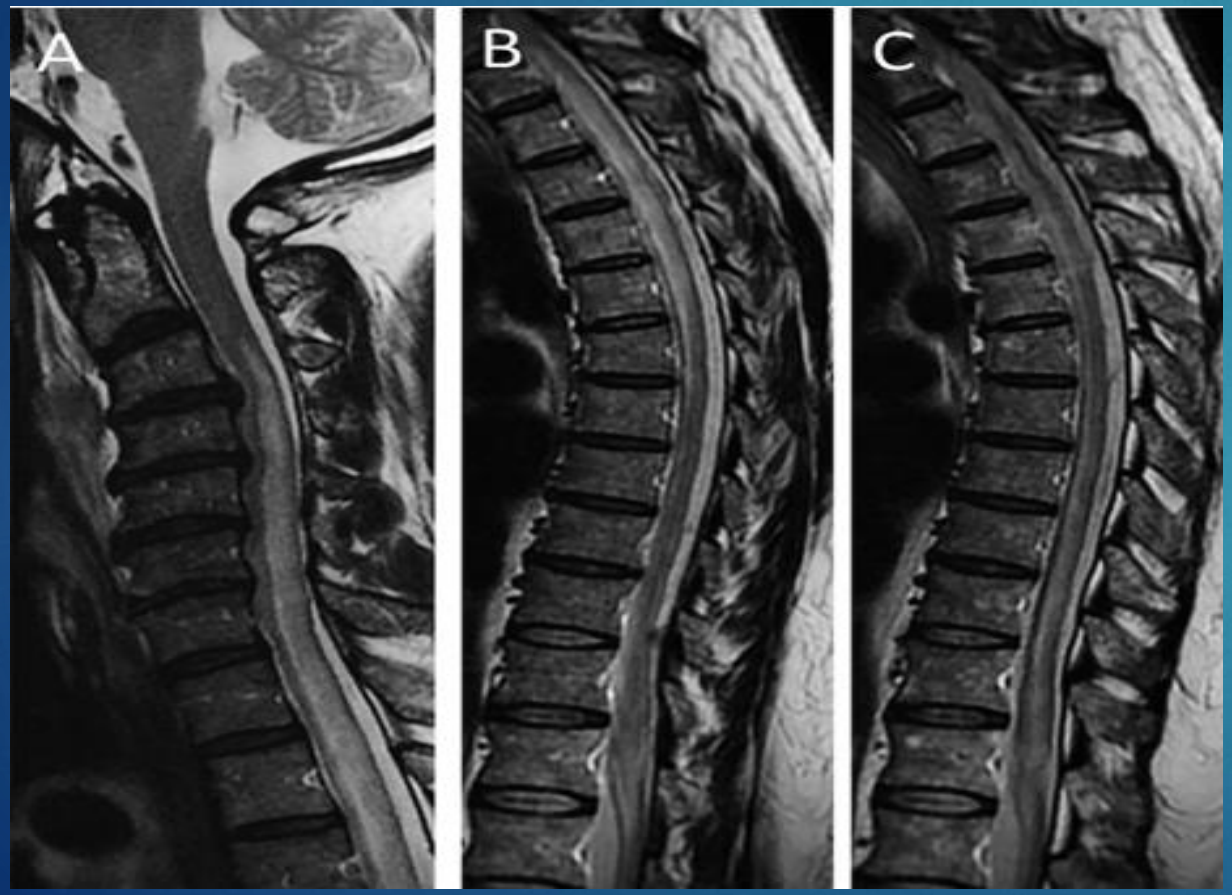
- Acute Disseminated Encephalomyelitis (ADEM)

- Neuromyelitis Optica /NMO spectrum disorder (NMOSD)
- Myelin Oligodendrocyte Glycoprotein-associated Demyelination (MOGAD)

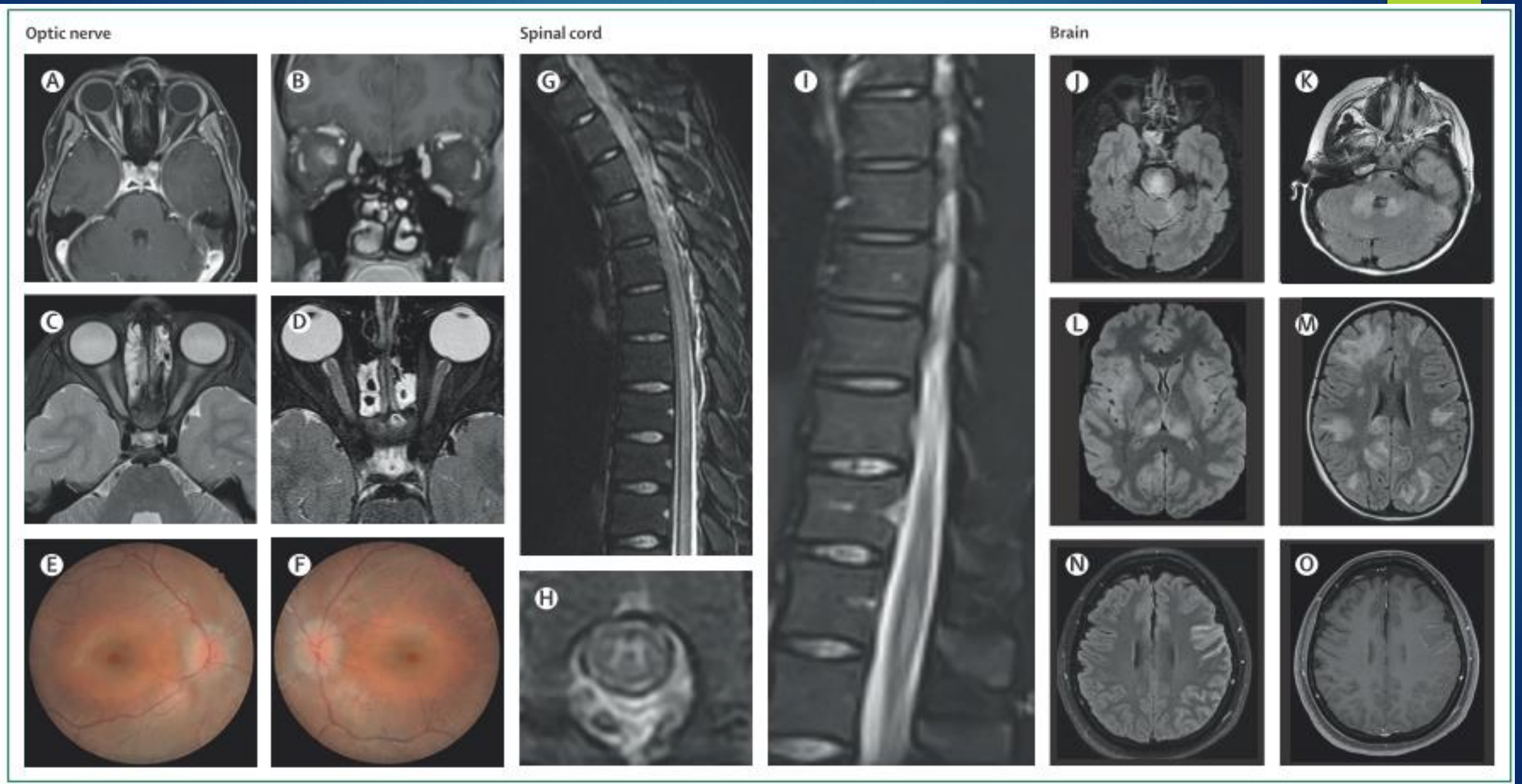
ADEM



NMOSD

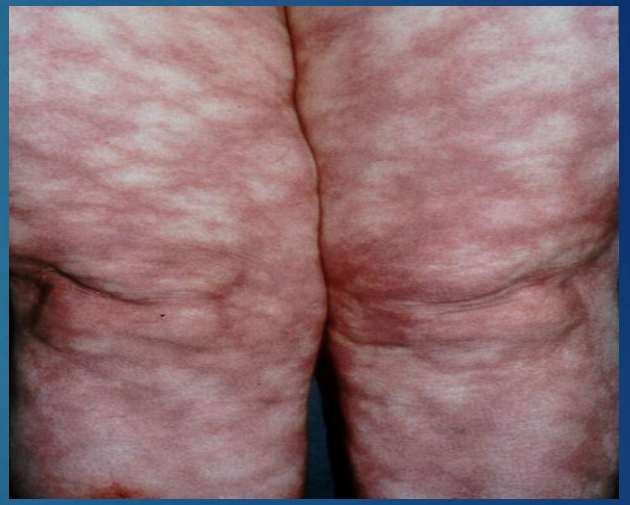


MOGAD



Demyelination Secondary to systemic diseases Ischemic/inflammatory…

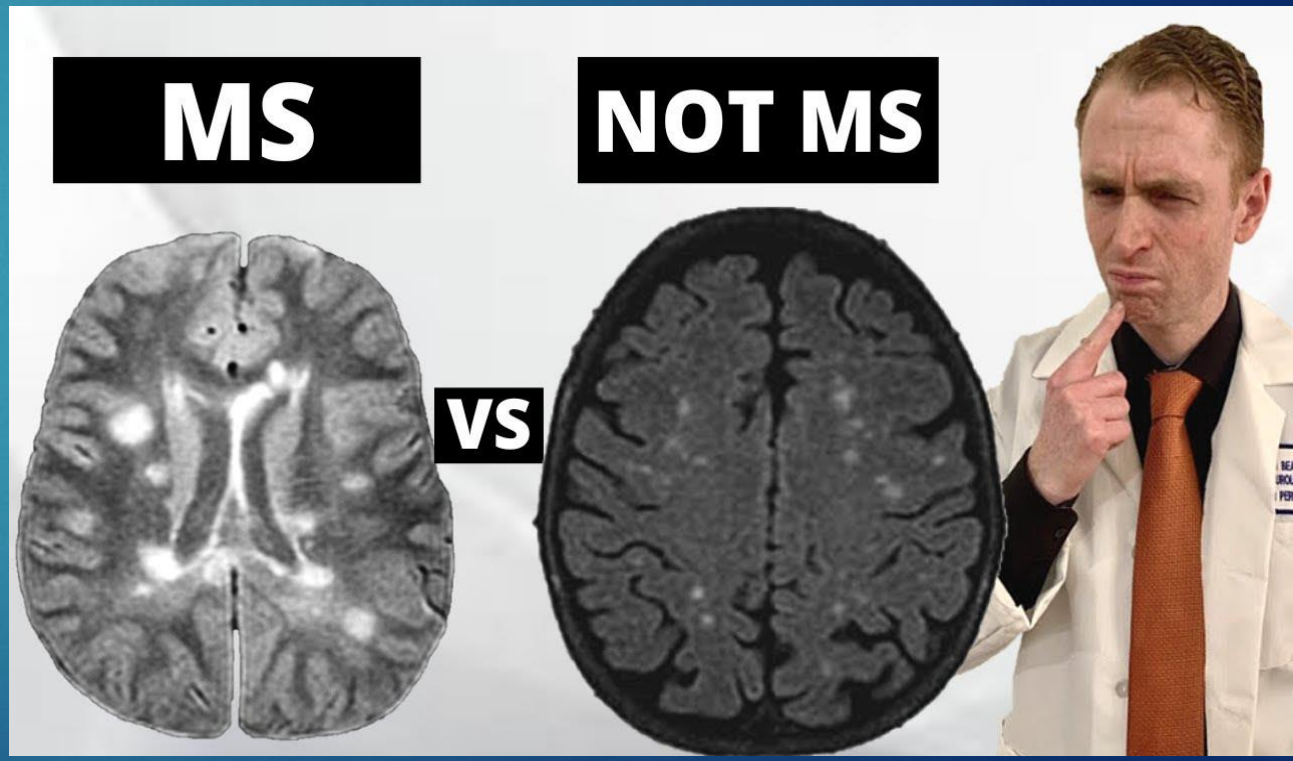
- Non-specific WM lesions
- Small vessel disease
- Migraine,
- Vasculitis (SLE, APLA syndrome*, Sjogren's , Behcet's)
- Infection (Lyme disease)
- Sarcoidosis, Susac's syndrome
- B12 deficiency/ Hyperhomocystinemia



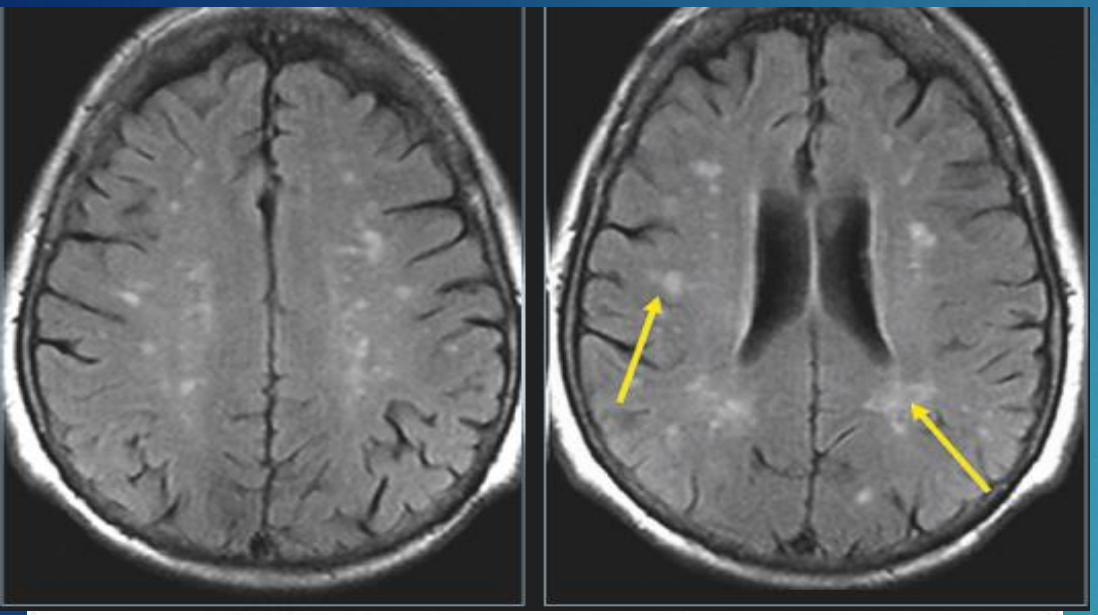
*Livedo reticularis

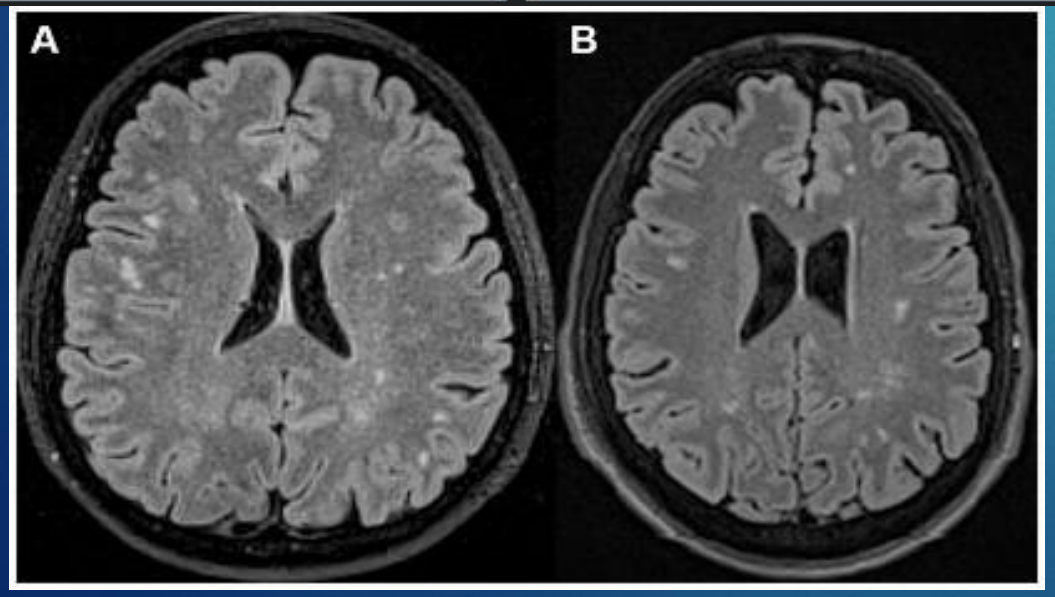
Non-specific WM lesions
UBO’s (Unknown Bright Objects)

- Multifocal areas of T2 hyperintensity in the periventricular or deep white matter have been reported in around 35% of healthy individuals over the age of 60 years.
- Lesions may be small, multiple and punctuate or large and confluent.
- These non- specific, age-related, asymptomatic foci of ischemic demyelination may lead to misdiagnosis of MS especially in patients over 50 years old

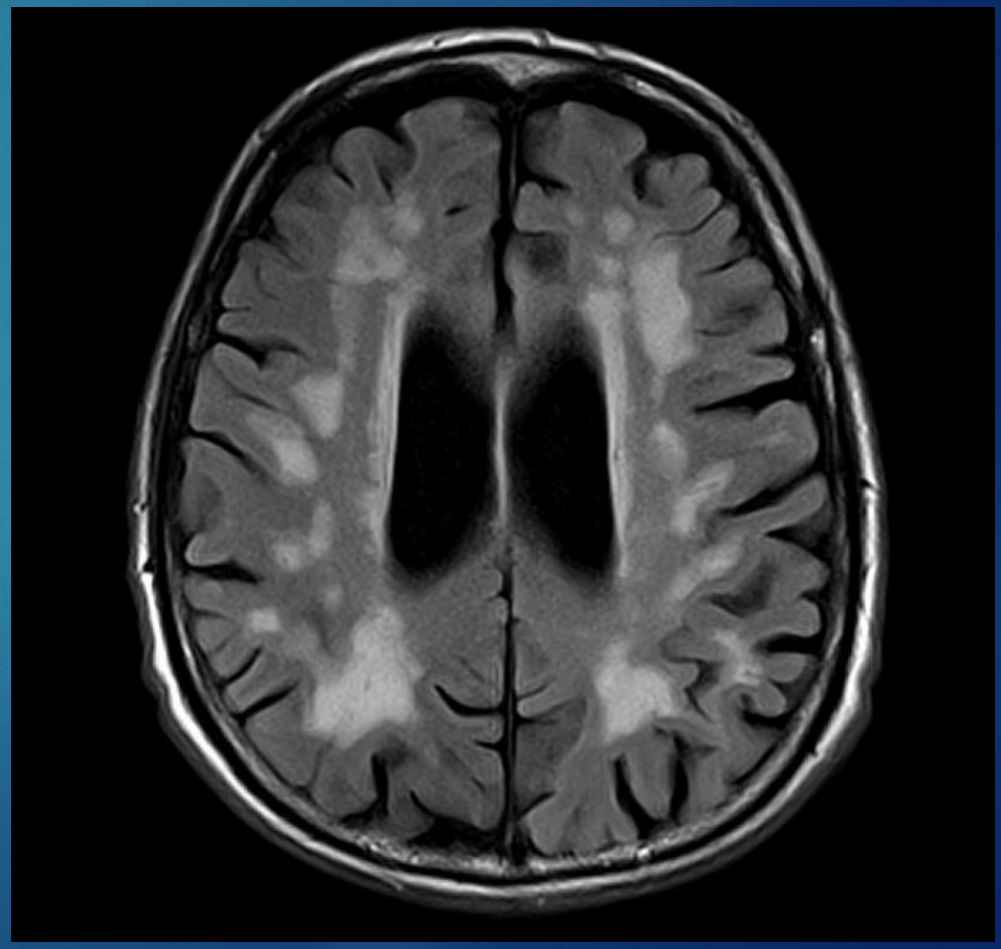


Non-specific WM lesions (UBO's) in Ageing/Migraine





Ischemic lesions/Small vessel disease



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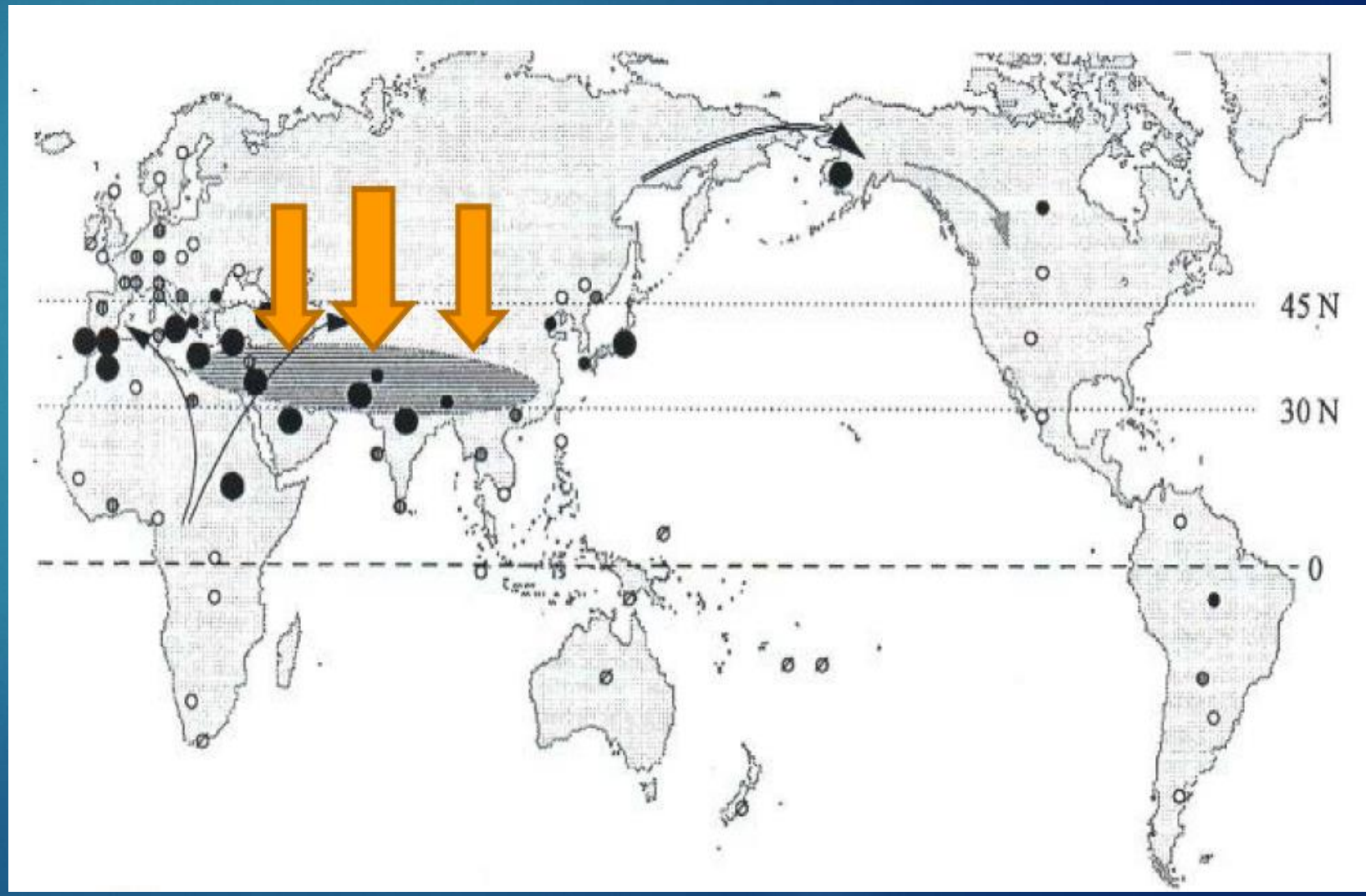
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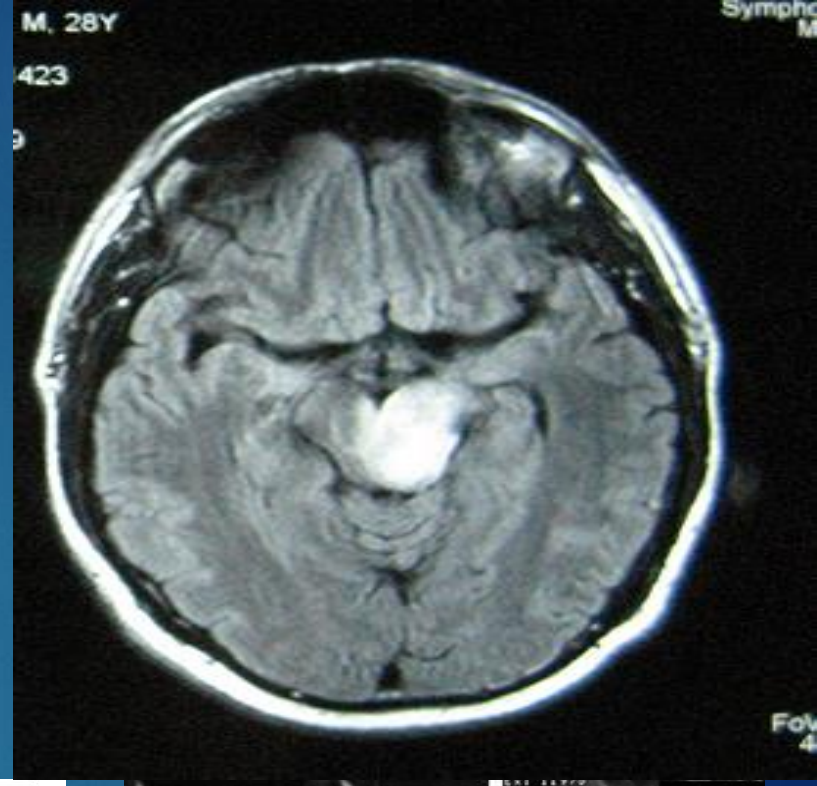
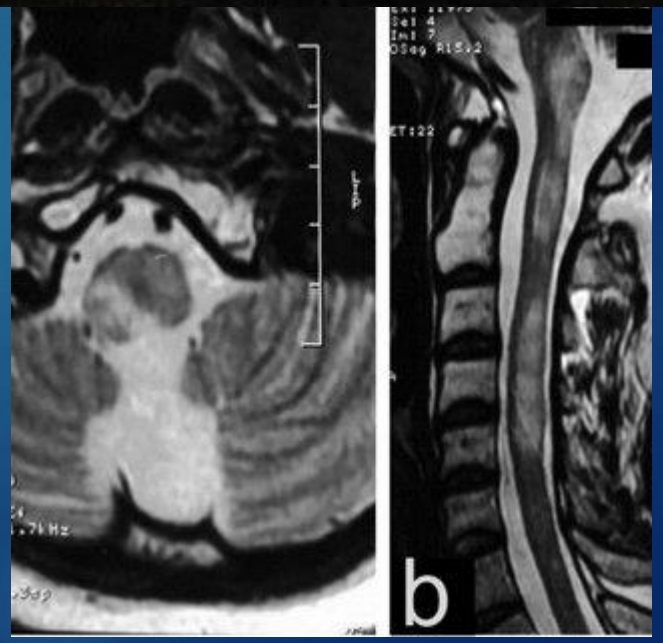
Behcet's Disease

- A multi-system recurrent inflammatory disorder of unknown etiology – strongly associated with HLA-B51 haplotype
- Variable vessel vasculitis (VVV)
- Can affect vessels of any size (small, medium, and large)
- Any type (arteries, veins, and capillaries).

- Also called the "Silk Road Disease"



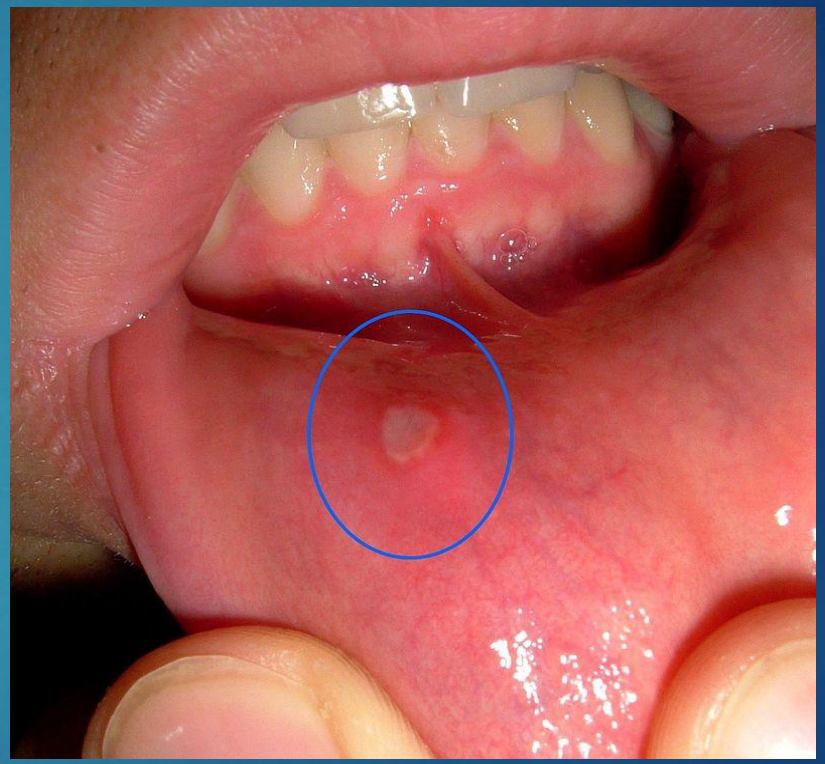
Hulusi Behcet
1889-1948



	Frequency	Comments
Oral ulcers	97–99%	..
Genital ulcers	~85%	..
Genital scar	~50%	More common in men
Papulopustular lesions	~85%	..
Erythema nodosum	~50%	..
Pathergy reaction	~60%	Predominantly in Mediterranean countries and Japan
Uveitis	~50%	..
Arthritis	30–50%	..
Subcutaneous thrombophlebitis	25%	..
Deep vein thrombosis	~5%	..
Arterial occlusion (aneurysm)	~4%	..
Epididymitis	~5%	..
Gastrointestinal lesions	1–30%	More common in Japan

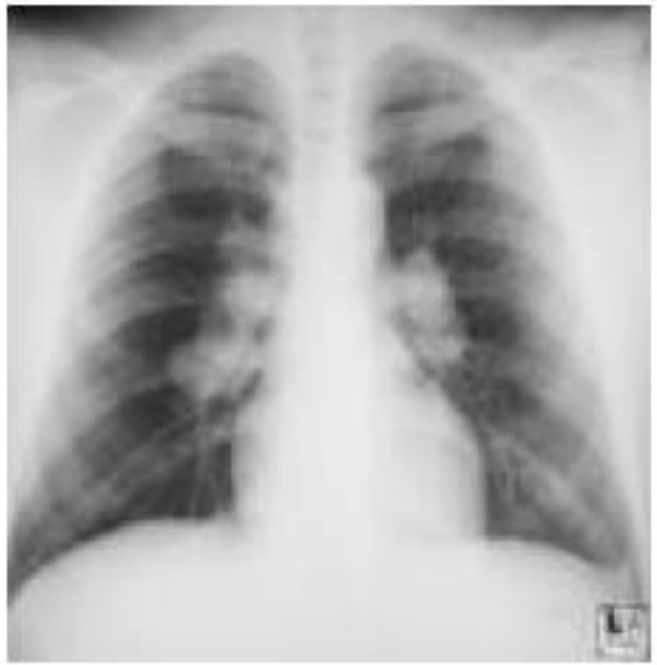
*Adapted from Yazici et al,[4] with permission from Nature Publishing Group.

Table 1: **Clinical manifestations of Behçet's disease***

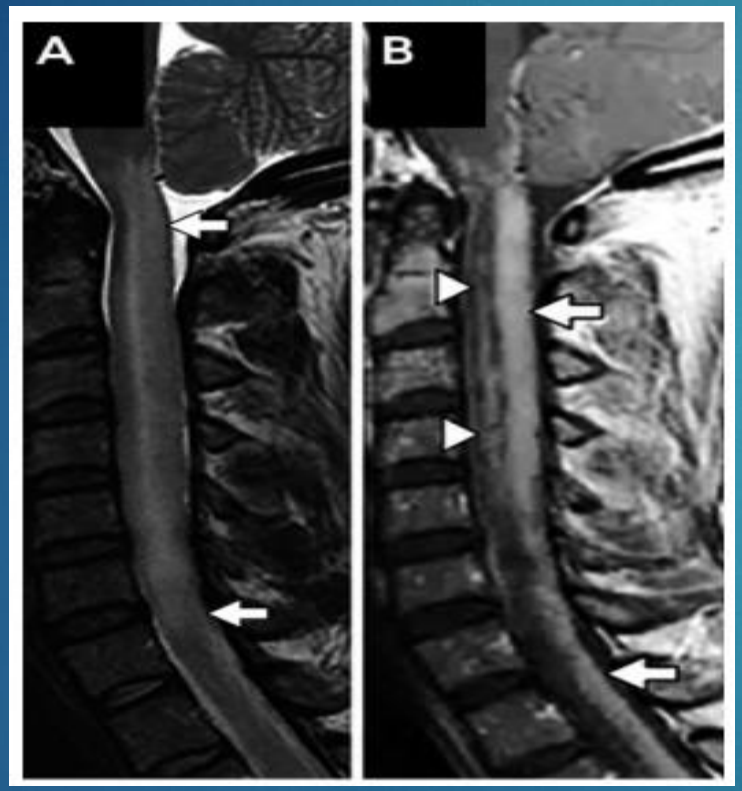


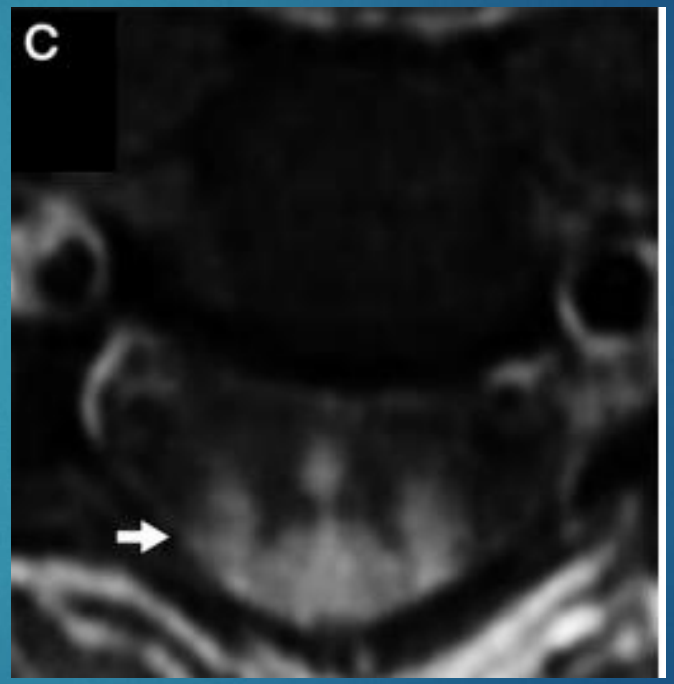
SYSTEMIC SARCOIDOSIS

Aetiology unknown
Auto-inflammatory
Worldwide distribution
European 40 x 10^5
African American 120 x 10^5
Japan 5 x 10^5
China less common
Female > male
30 – 60 years



Neurosarcoidosis





Management

- Life-style modifications
- Treatment of relapses
- Prevention of relapses /disability (Disease-Modifying Therapy)
- Symptomatic treatment.
- Rehabilitation

Life-style modifications

Multiple sclerosis

Original research

Lifestyle factors associated with benign multiple sclerosis

Jie Guo [1], Tomas Olsson,[2] Jan Hillert [2], Lars Alfredsson,[3] Anna Karin Hedström [2]

Multiple sclerosis

Original research

Impact of fish consumption on disability progression in multiple sclerosis

Eva Johansson,[1] Jie Guo,[2] Jing Wu [3], Tomas Olsson,[1] Lars Alfredsson,[3] Anna Karin Hedström [1]

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Relapse treatment

Faster recovery but no evidence of decreasing residual disability

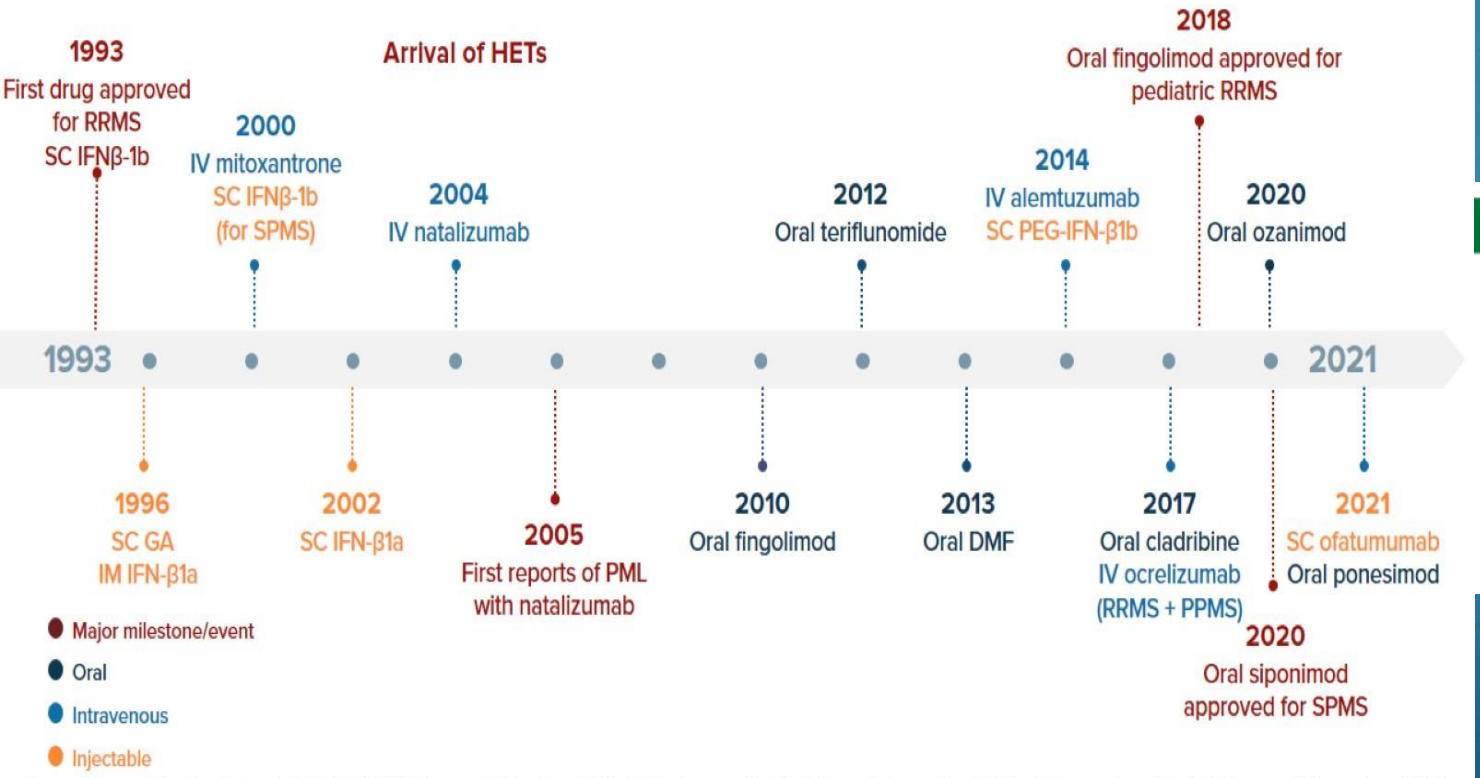
- High-dose steroids
  - IV/oral Methylprednisolone 1 g daily for 3-5 days
  - 30-50 % do not respond adequately
- ACTH gel (IM or SC) 80 u daily for 5-15 days– more potent immunomodulatory effect but expensive and not available.
- Plasma exchange for refractory relapses
- IV Immunoglobulins ?

Management

- Life-style modifications
- Treatment of relapses
- Prevention of relapses /disability (Disease-Modifying Therapy)
- Symptomatic treatment.
- Rehabilitation

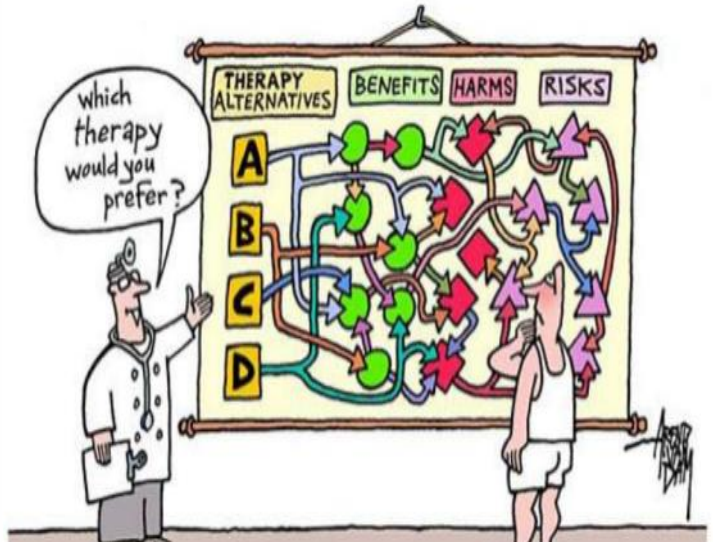
Choosing a Disease-Modifying Drug
Moderate-efficacy vs. High-efficacy Therapies

Decades of MS Drug Development



Tintore M, et al. *Nat Rev Neurol.* 2019;15:53-58; Mayzent® (siponimod) [PI]. EMA. January 14, 2021; Zeposia® (ozanimod) [PI]. EMA. October 26, 2020; Ponvory™ (ponesimod) [PI]. EMA. June 2, 2021; Kesimpta® (ofatumumab) [PI]. EMA. June 24, 2021.

Precision medicine



Multiple sclerosis

Original research

Predictors of early disability accumulation in newly diagnosed multiple sclerosis: clinical, imaging and cerebrospinal fluid measures

Intrathecal IgG synthesis, spinal cord lesion number , age and polysymptomatic manifestation
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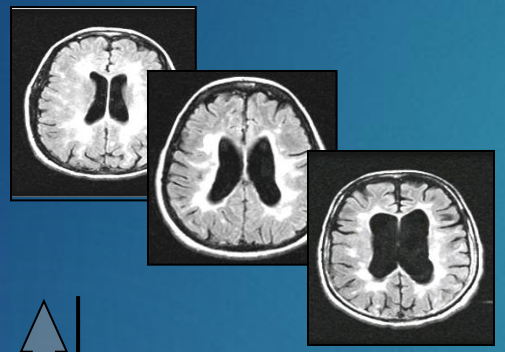
The Burden of MS-without treatment

10 Years*



Progressive MS

15 Years*

Requiring a Cane

25 Years*

Confined to Wheelchair

*mean time for development