Multiple Sclerosis and related disorders

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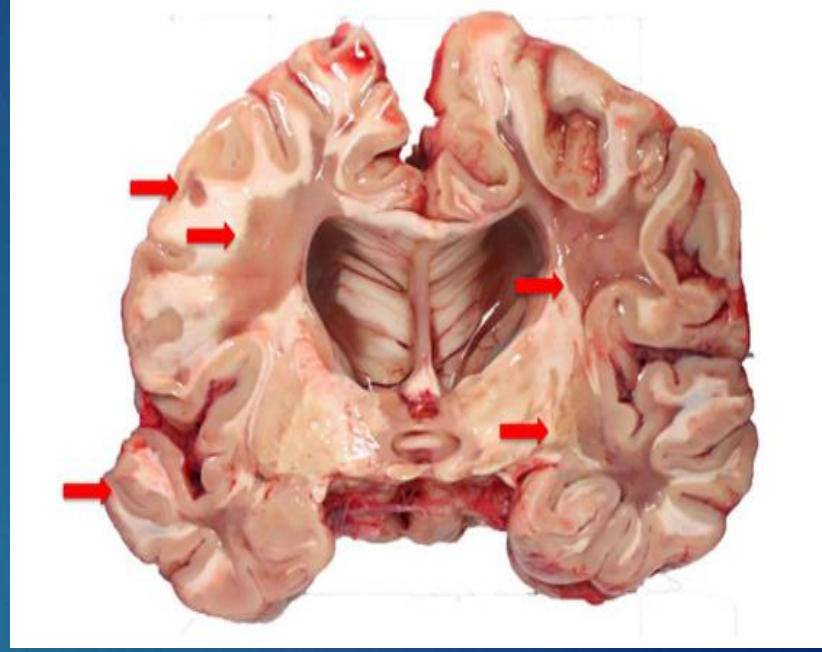
Multiple (Disseminated) Sclerosis

- 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

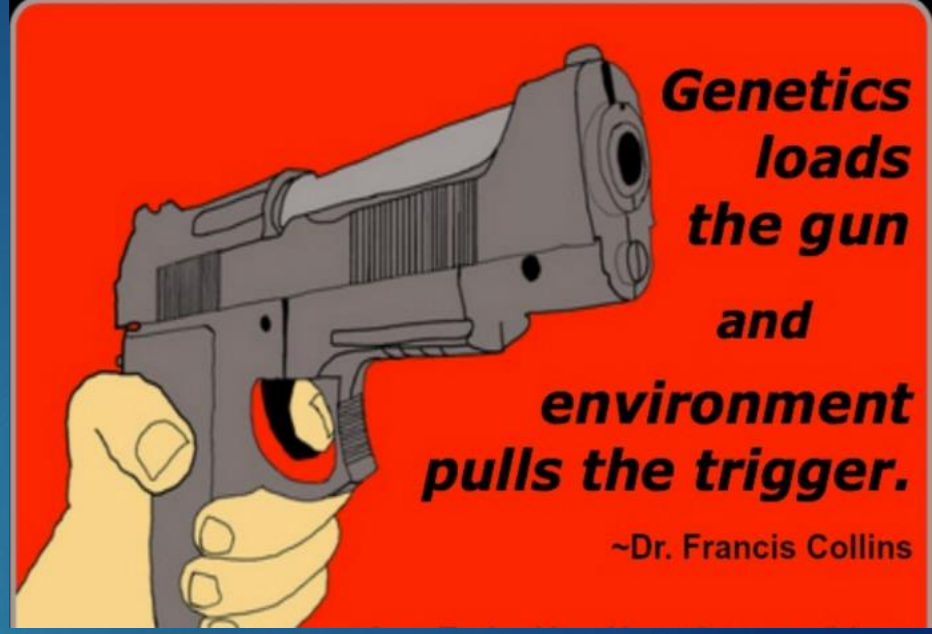
- MS is a chronic inflammatory disease of the **CNS** that leads to focal destruction of myelin , axonal damage and reactive gliosis of astrocytes in the white and grey matter .

- MS is characterised by multifocal demyelinating lesions or ‘plaques’ in both the white matter and in the cortical and subcortical grey matter
- Plaques are most commonly seen in the spinal cord , optic nerves , brainstem/cerebellum and periventricular white matter.
- Plaques are due to focal loss of myelin (oligodendrocytes), with relative preservation of axons and astrocytic gliosis.

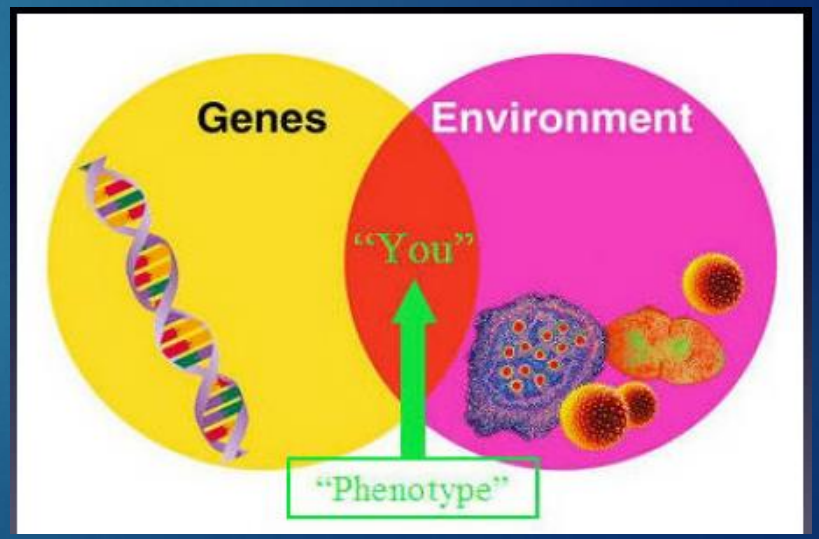
Macroscopic appearance of the brain and spinal cord with MS

- The brain and spinal cord of subjects with MS typically appear smaller than normal, particularly later in the disease.
- The corpus callosum thins and the lateral ventricles dilate due to the loss of brain tissue.
- These observations emphasise the neurodegenerative aspects of the disease.

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

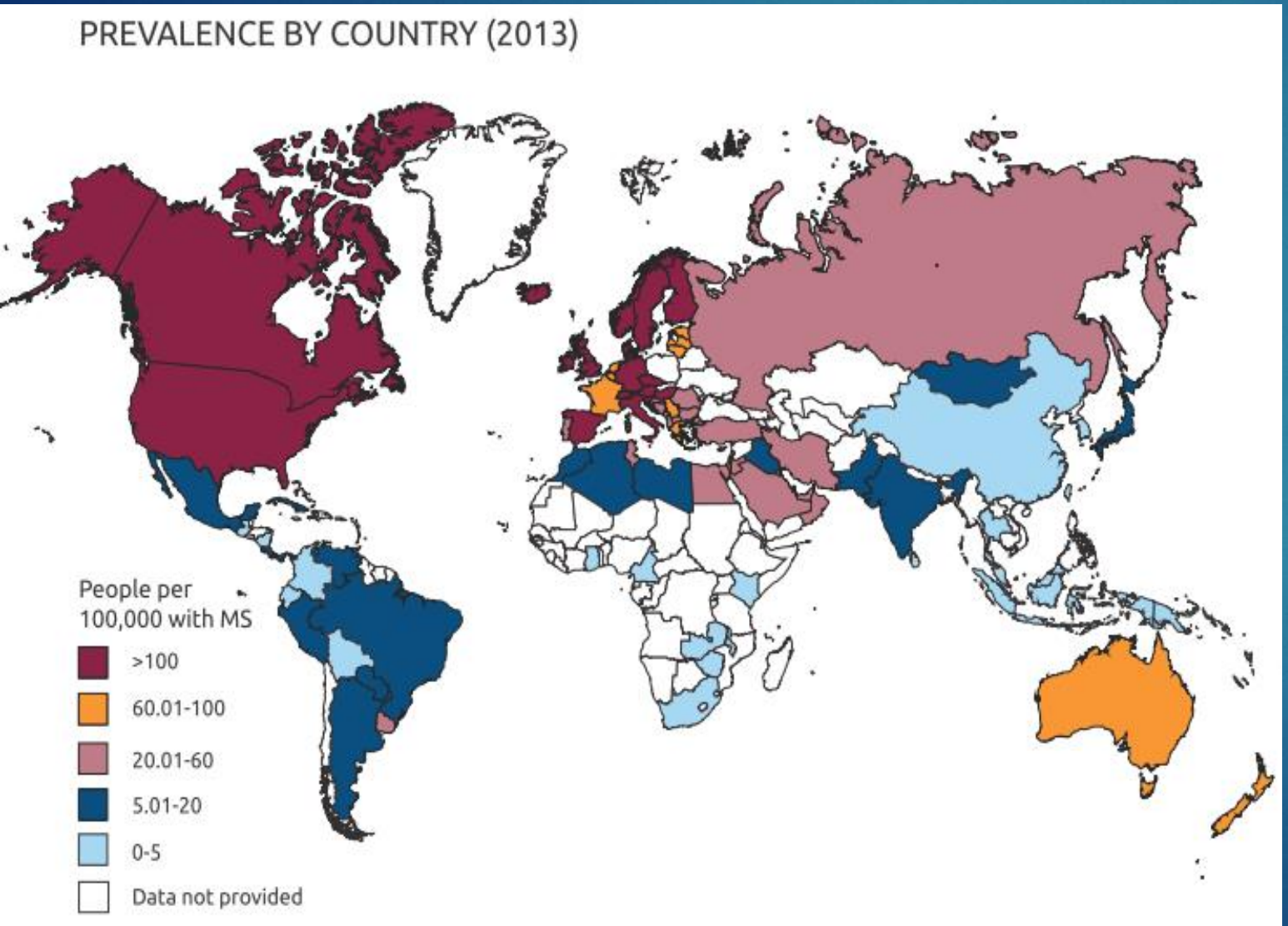


- It is considered an immune-mediated disease in genetically susceptible individuals.
- The immune attack is triggered by an environmental agent that is acquired in childhood (<15 yrs).

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- Geographical distribution



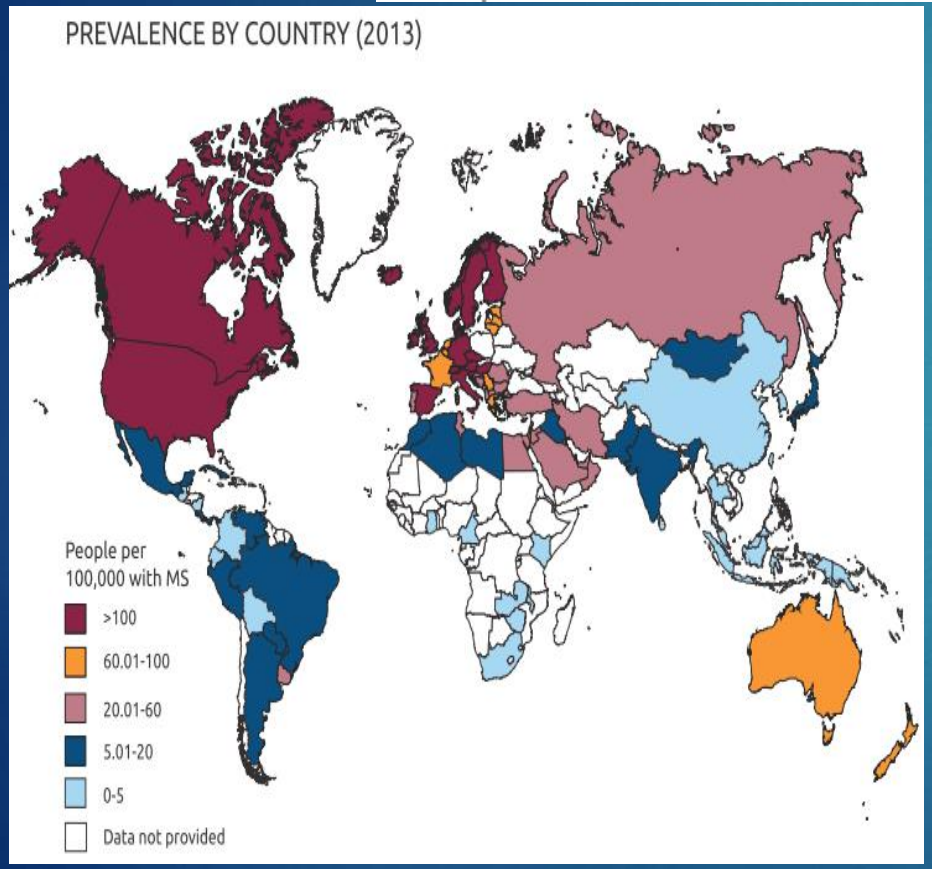
- A very specific geographic distribution around the world – the effect of latitude
- Epidemiology studies in the Middle East show an intermediate prevalence of around 40/100000.
- Data from migration studies shows that if the exposure to a higher risk environment occurs before the age of 15 years, the migrant assumes that risk - white British migrants to South Africa

Viking voyages: the origin of multiple sclerosis?

An essay in medical history

Poser M. Viking voyages: the origin of multiple sclerosis? An essay in medical history.
Acta Neurol Scand 1995: Suppl. 161: 11–22

C. M. Poser
Department of Neurology, Harvard Medical School and Beth Israel Hospital, Boston, USA



- The 'Viking theory' suggests that the distribution is strongly linked to the spread of Scandinavian genes, initially by the Vikings and later by a second wave of Scandinavian migration.

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..

Factors explaining the rise in MS prevalence

- Longer survival
- Better/earlier diagnosis due to improved imaging and more sensitive diagnostic criteria
- But , there is also an actual increase in incidence of the disease

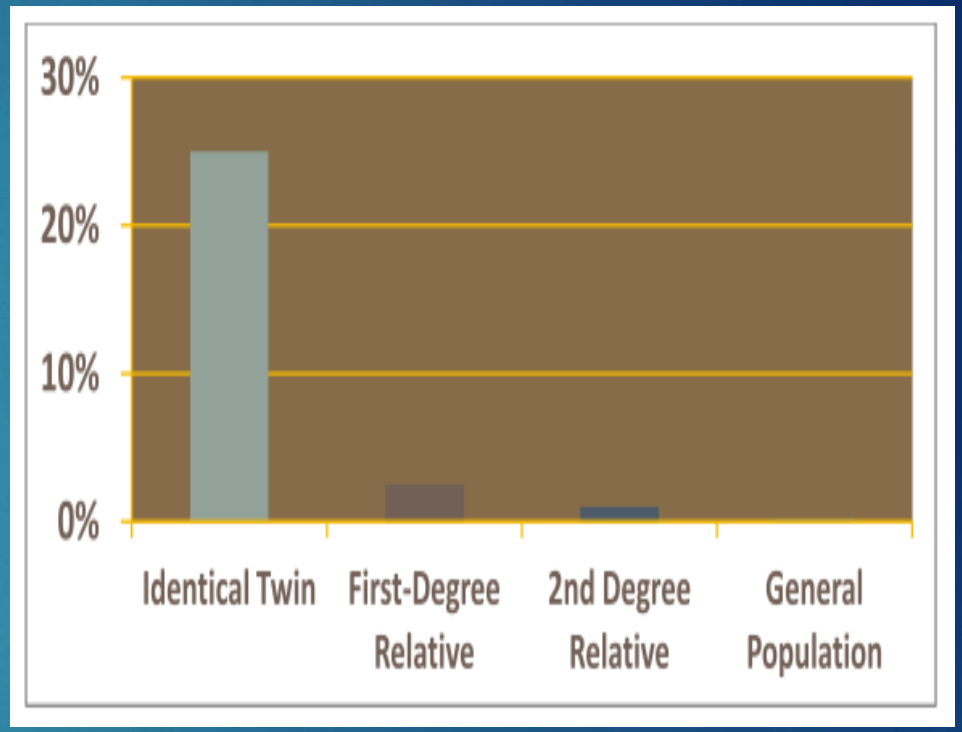
Genetic factors

- The strongest known genetic factor affecting MS susceptibility is the HLA-DRB1*1501 haplotype.
- However, it is not essential for the development of MS, as it only increases the risk by 2- to 4-fold and is present in approximately 20% to 30% of healthy individuals

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: 25% concordance
- Dizygotic twins: 5% concordance
- 1 parent has MS: 2%-4%
- Second degree relative: 1%



Lifetime risk of developing MS: 0.1%-0.2%

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

Vitamin D and exposure to sunlight

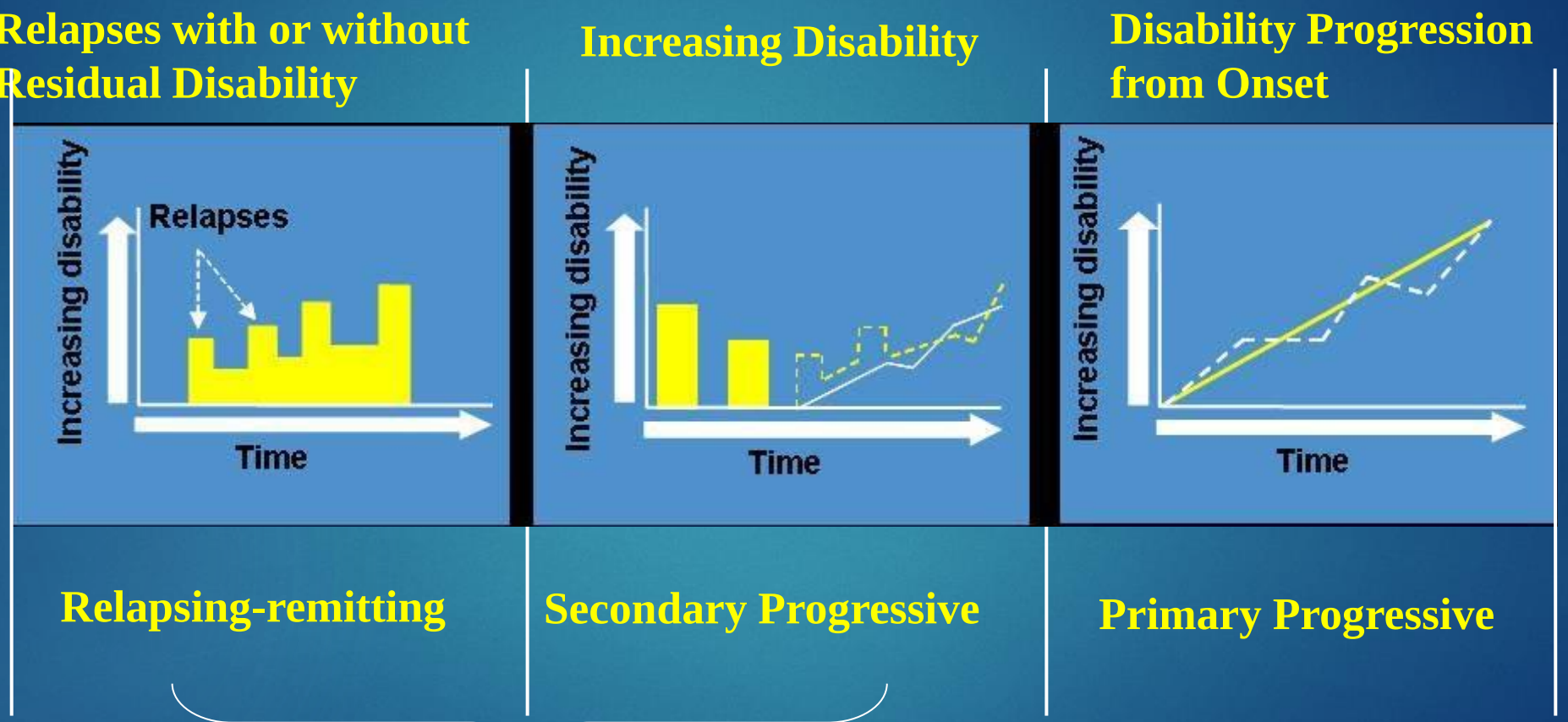
- Another important environmental factor, which has a strong association with the risk of MS is sunlight exposure and vitamin D levels, with a high likelihood of them playing a role in a prenatal period.
- That hypothesis is based on the close relationship between geographical differences in sunlight exposure and the influence of latitude on MS worldwide prevalence, the direct effects of sunlight exposure on serum vitamin D levels and the immunomodulatory effects of vitamin D on cells homeostasis.

Vitamin D

Vitamin D

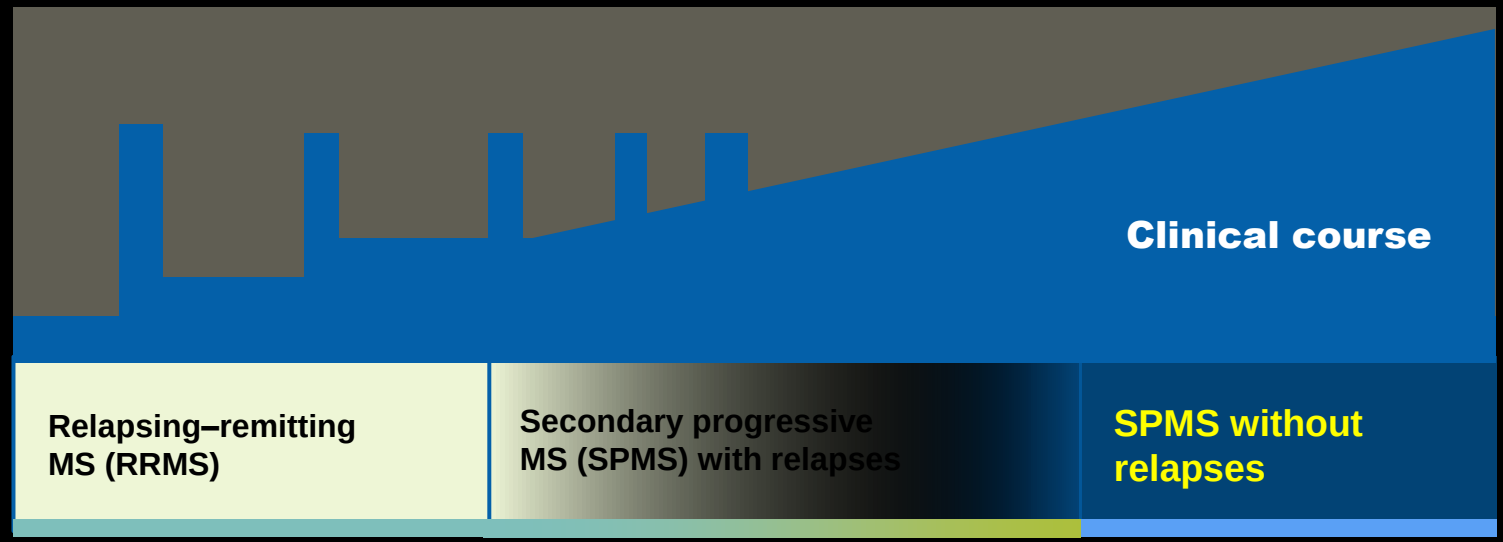
- Vitamin D deficiency associated with increased risk of MS
- Expression of MHC II class allele HLA DRB1*1501 is regulated by vitamin D
- Vitamin D has regulatory effects on T-cells
- Vitamin D and estrogen synergistically suppress autoimmunity

Stages of MS

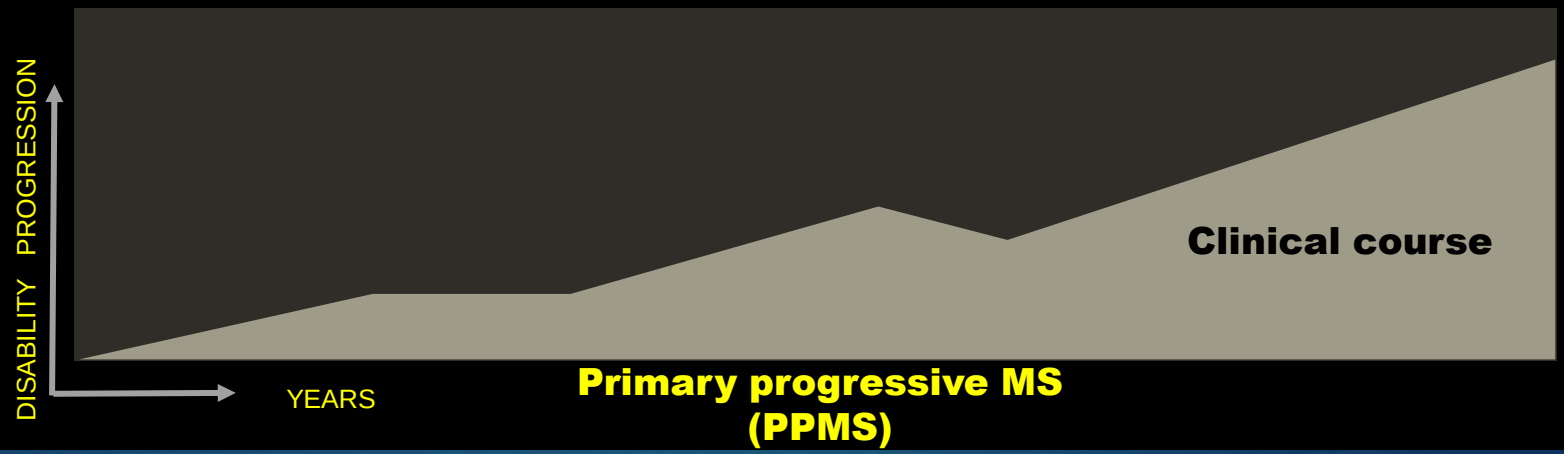

Relapses with or without Residual Disability
Increasing Disability
Disability Progression from Onset
Increasing disability
Relapses
Time
Increasing disability
Time
Increasing disability
Time
Relapsing-remitting
Secondary Progressive
Primary Progressive
90%
10%

MS disease continuum

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



~10%
of patients have primary progressive onset of MS

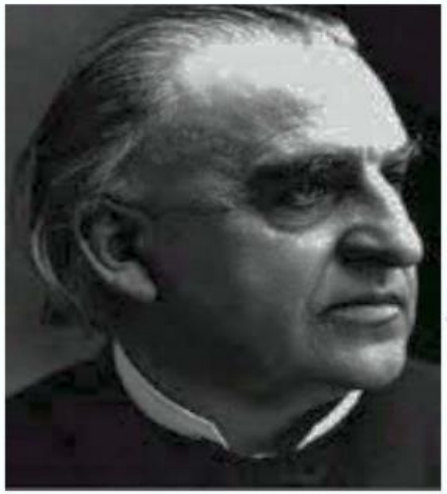


Establishing a diagnosis of Relapsing MS

- 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

Clinically Isolated Syndrome

- **The first clinical presentation of MS. Usually**

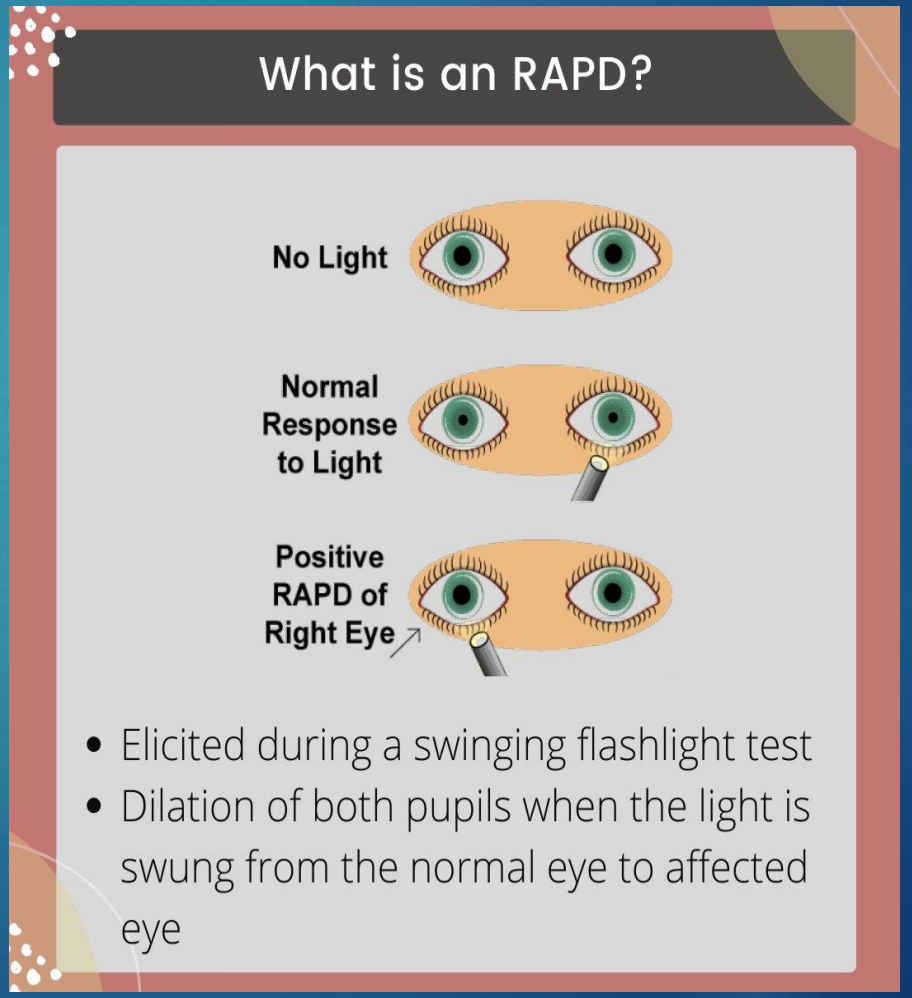
- **optic neuritis ,or**
- **partial myelitis ,or**
- **a brain stem syndrome.**
- **Less commonly a hemispheric presentation or multifocal.**

Common Relapses

Symptoms	Part of CNS Involved
Optic neuritis	Optic nerve
Partial myelitis (numbness & tingling) Hemi or paraparesis Bowel/bladder dysfunction	Spinal cord
Diplopia/ Internuclear ophthalmoplegia Lhermitte's sign Dizziness/vertigo Trigeminal neuralgia	Brain stem

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 loss (scotoma)
- Good recovery >90% starting within 2-3 weeks
- Normal OD in 70%
- Optic atrophy after 4-6weeks



Brainstem/Cerebellar

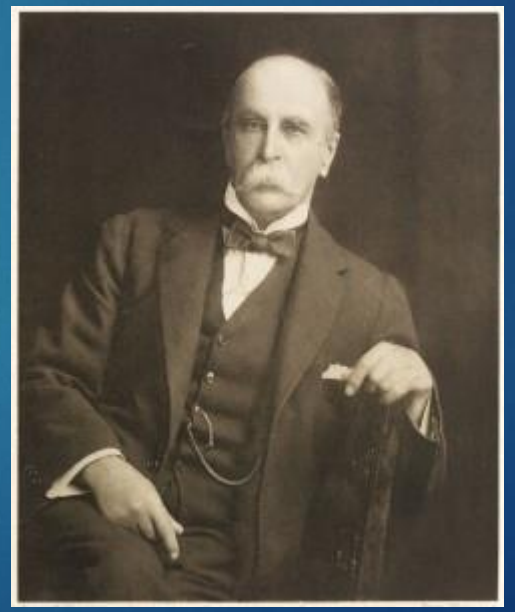
MS	*Less common*	*Atypical*
Internuclear ophthalmoplegia	Facial palsy, facial myokymia	
Ataxia and multidirectional nystagmus	Deafness	Vascular territory syndrome, e.g., lateral medullary
Sixth nerve palsy	One-and-a-half syndrome	Third nerve palsy
Facial numbness	Trigeminal neuralgia	Progressive trigeminal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

William Osler

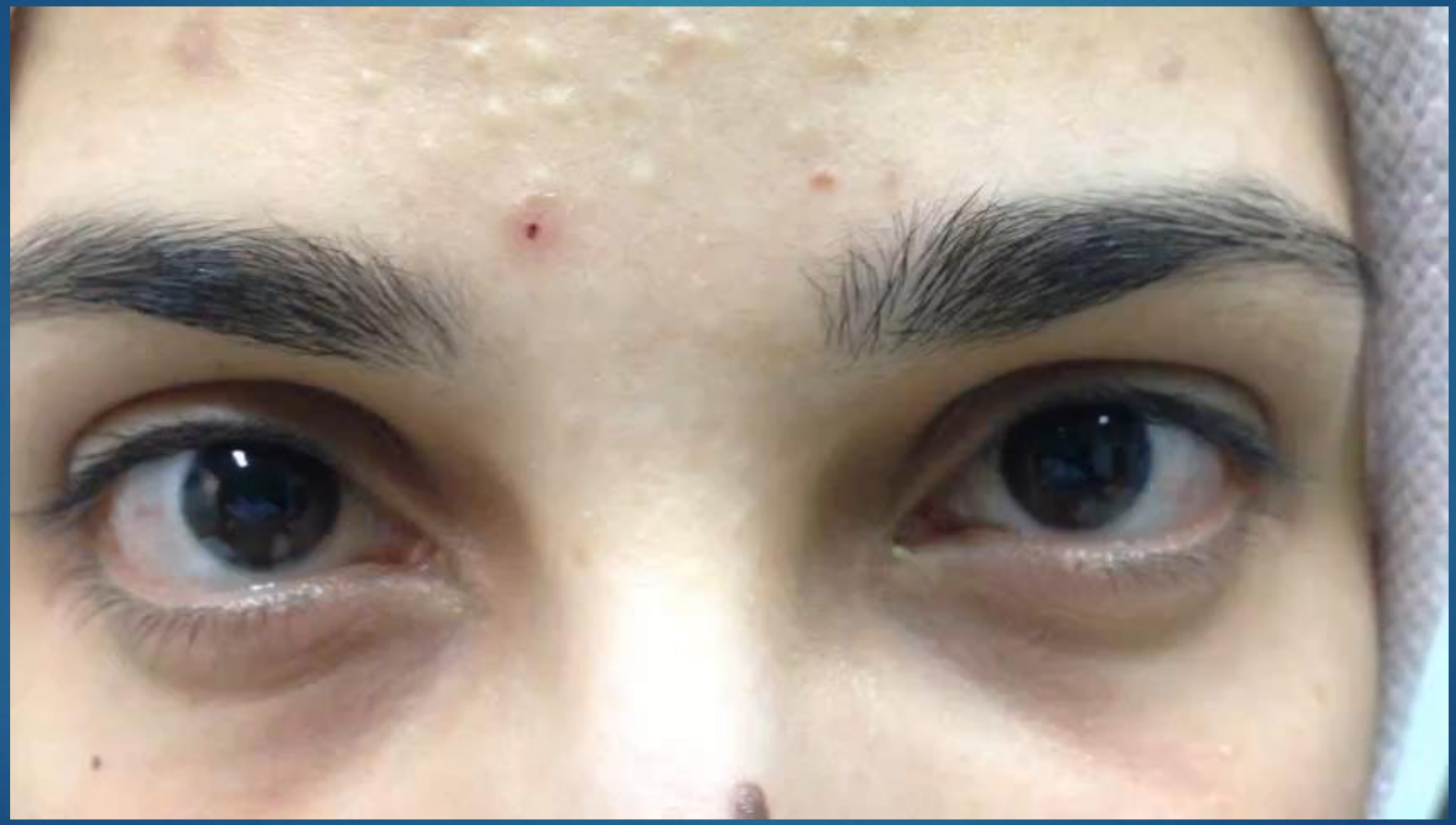
To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all

The value of experience is not in seeing much, but in seeing wisely

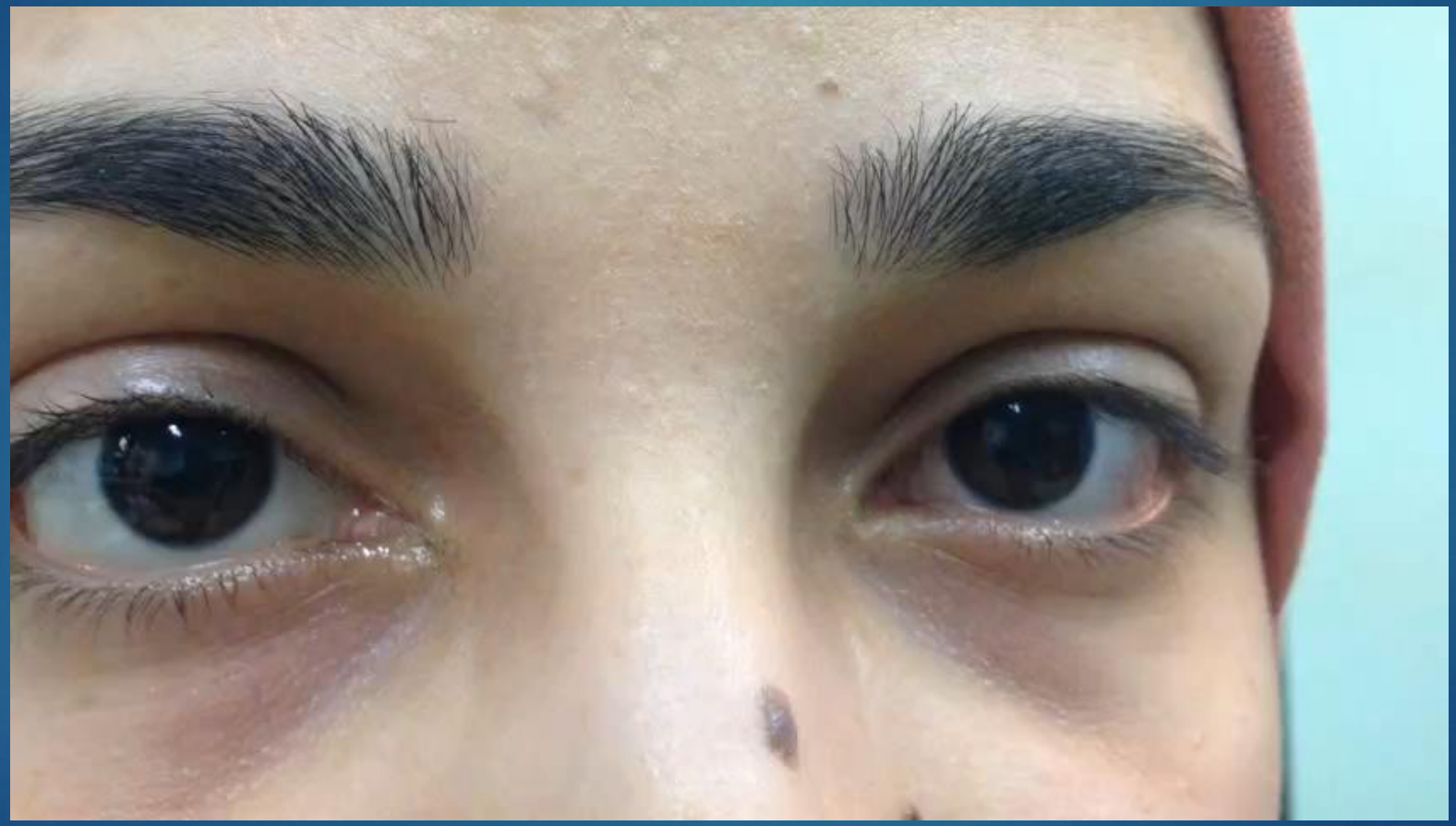
-Osler



Video- 24 year old girl
1 week hx of double vision



3 weeks later after IV Methylprednisolone



MS symptoms (not relapses)

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

- Fatigue
- Pain, spasticity ,spasms, Ataxia
- Uhthoff's phenomenon- Pseudorelapses
- 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

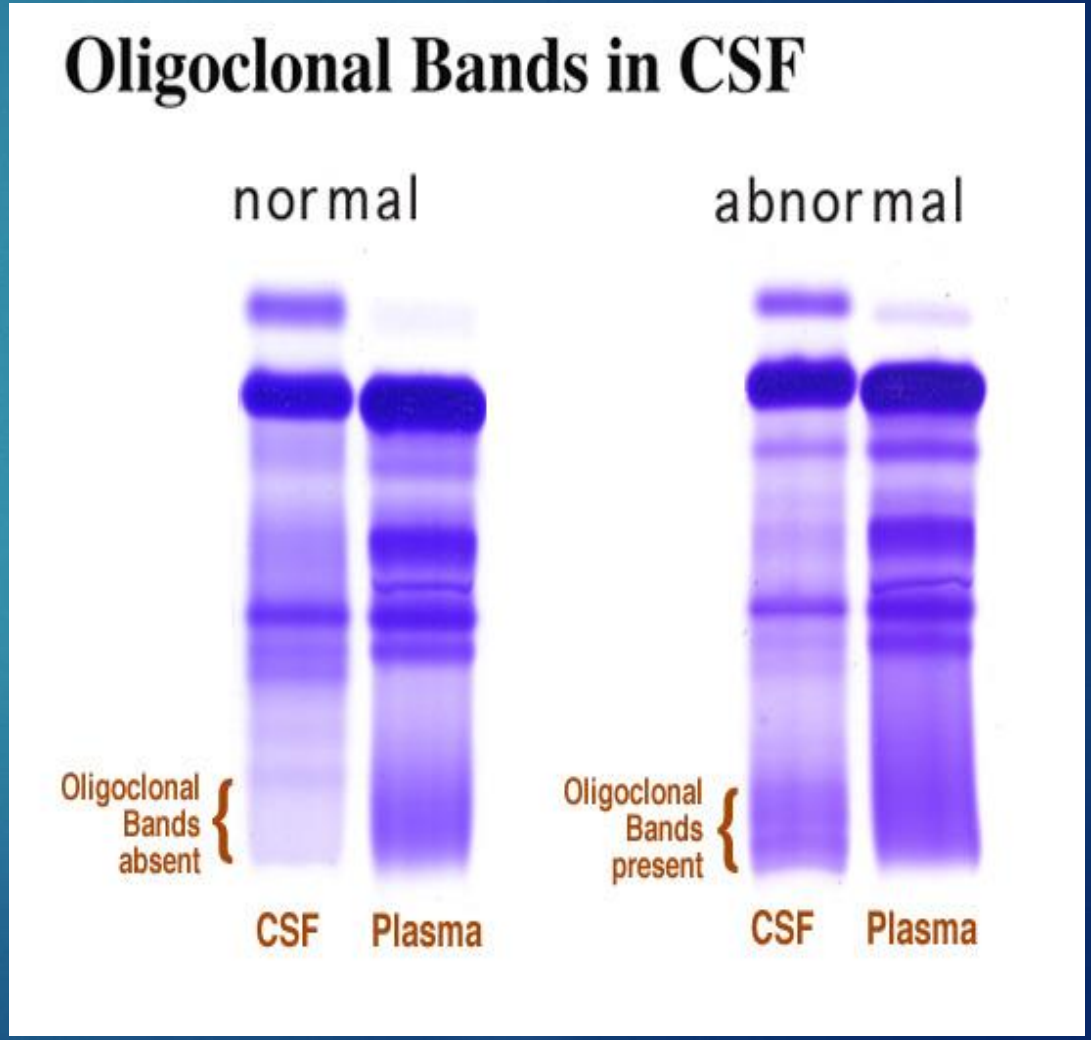
- Normal systemic inflammatory markers (ESR, CRP).

- Autoantibodies (Low-titre ANA may occur)

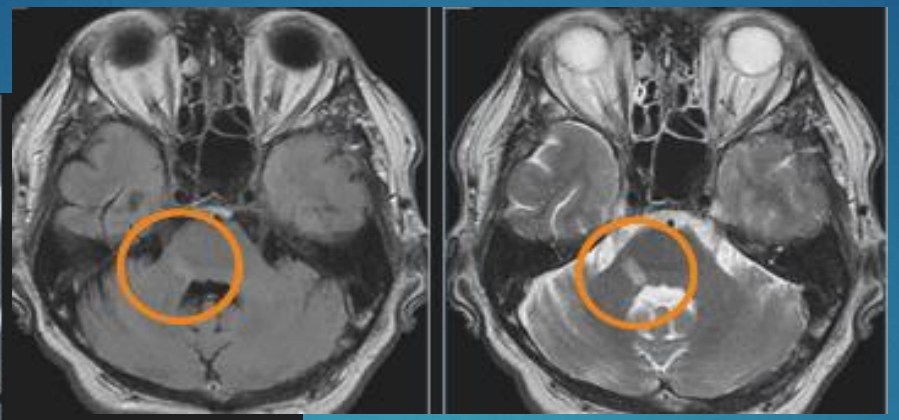
- Vasculitis screen, B12, TFT, LFT, serum ACE/CXR

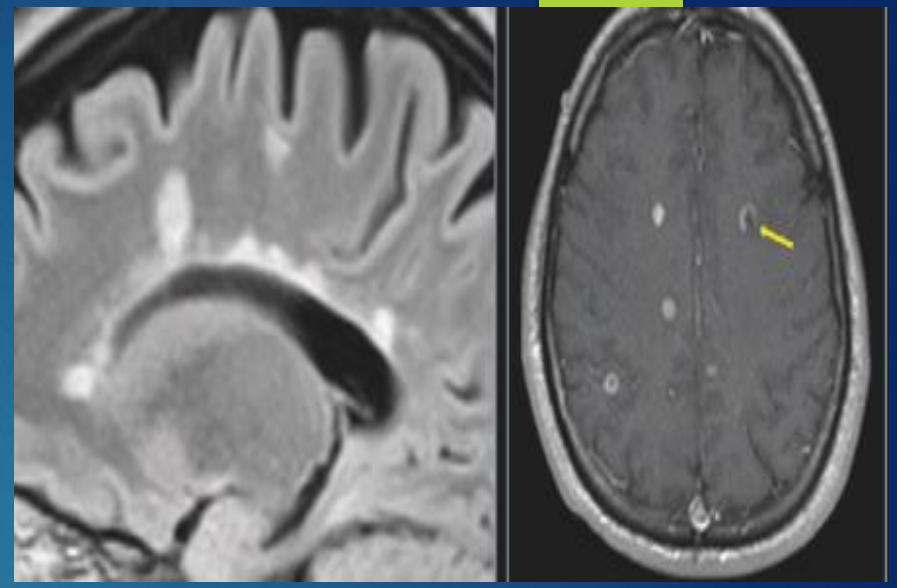
Frequencies of abnormal CSF variables in clinically definite MS

- 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



MRI- Typical MS



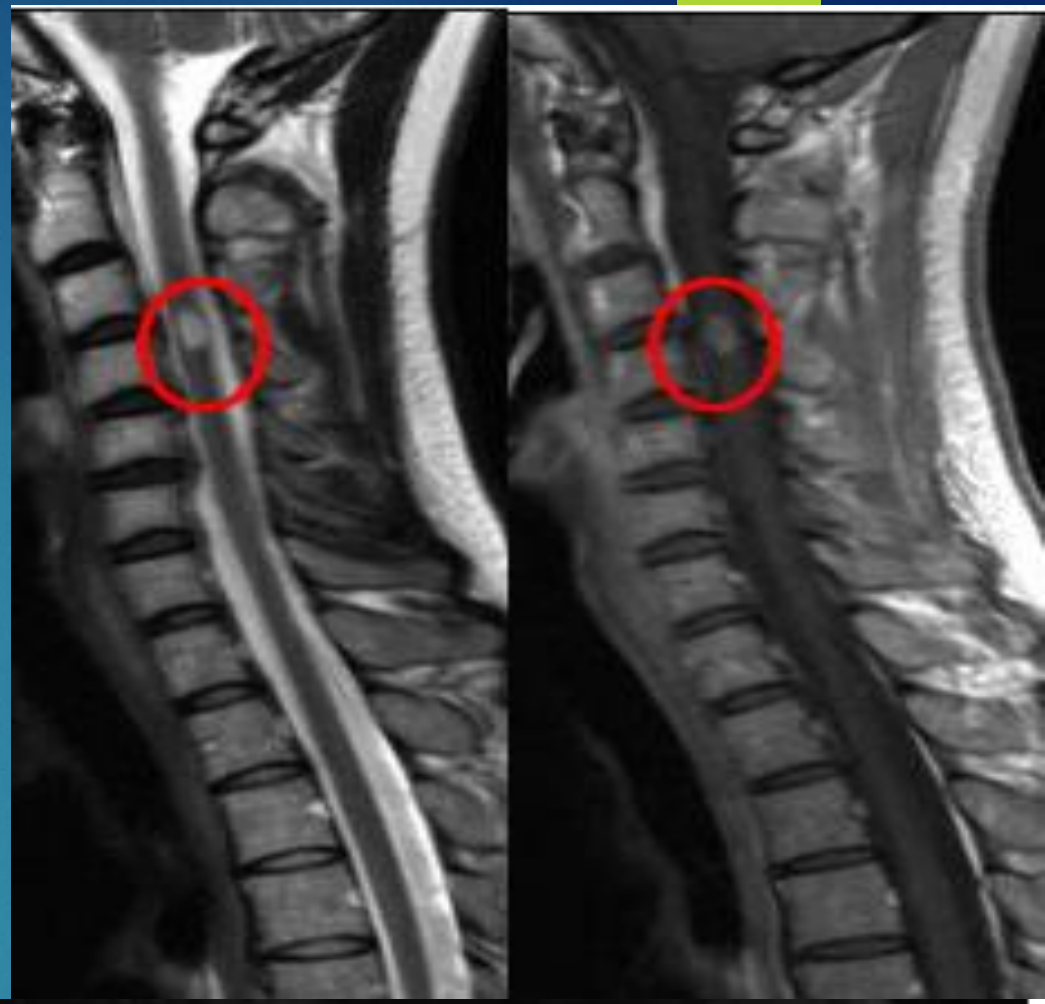


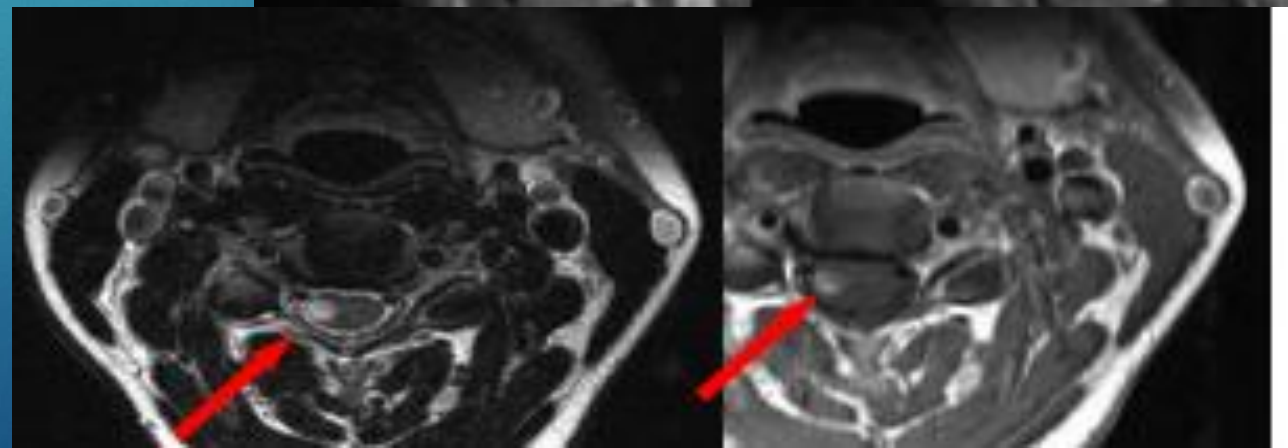
Lesion configuration	ovoid (round shape)
Size of lesions	> punctate
Typical lesion location	periventricular, juxtacortical, infratentorial
Lesion pattern	random, asymmetric
Tissue destruction	variable
Contrast enhancement	frequent

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 radiologically is very important and can be very challenging

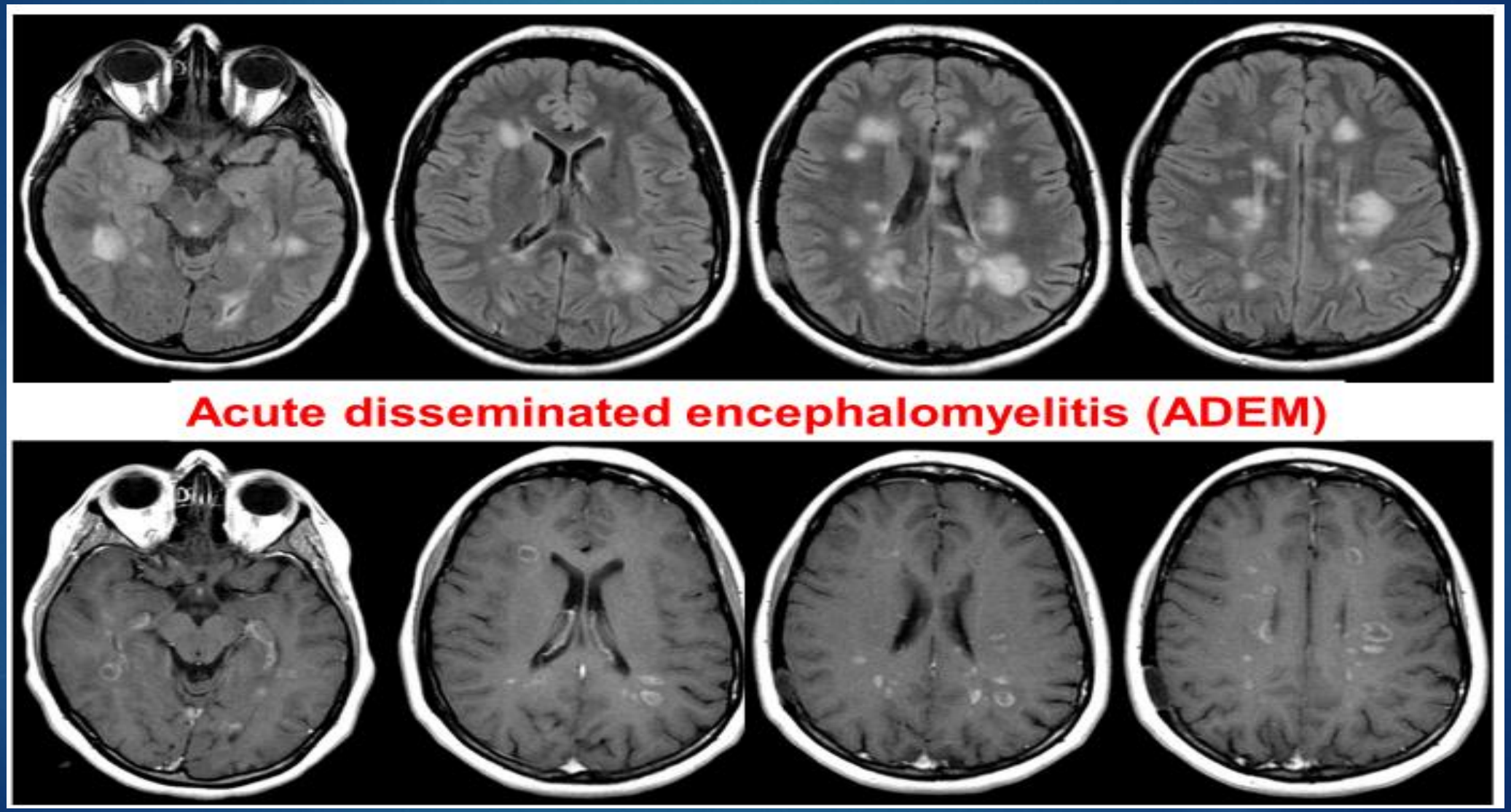
Differential Diagnosis

- 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 (Devic's disease)
- Myelin Oligodendrocyte Glycoprotein-associated Demyelination (MOGAD)

ADEM

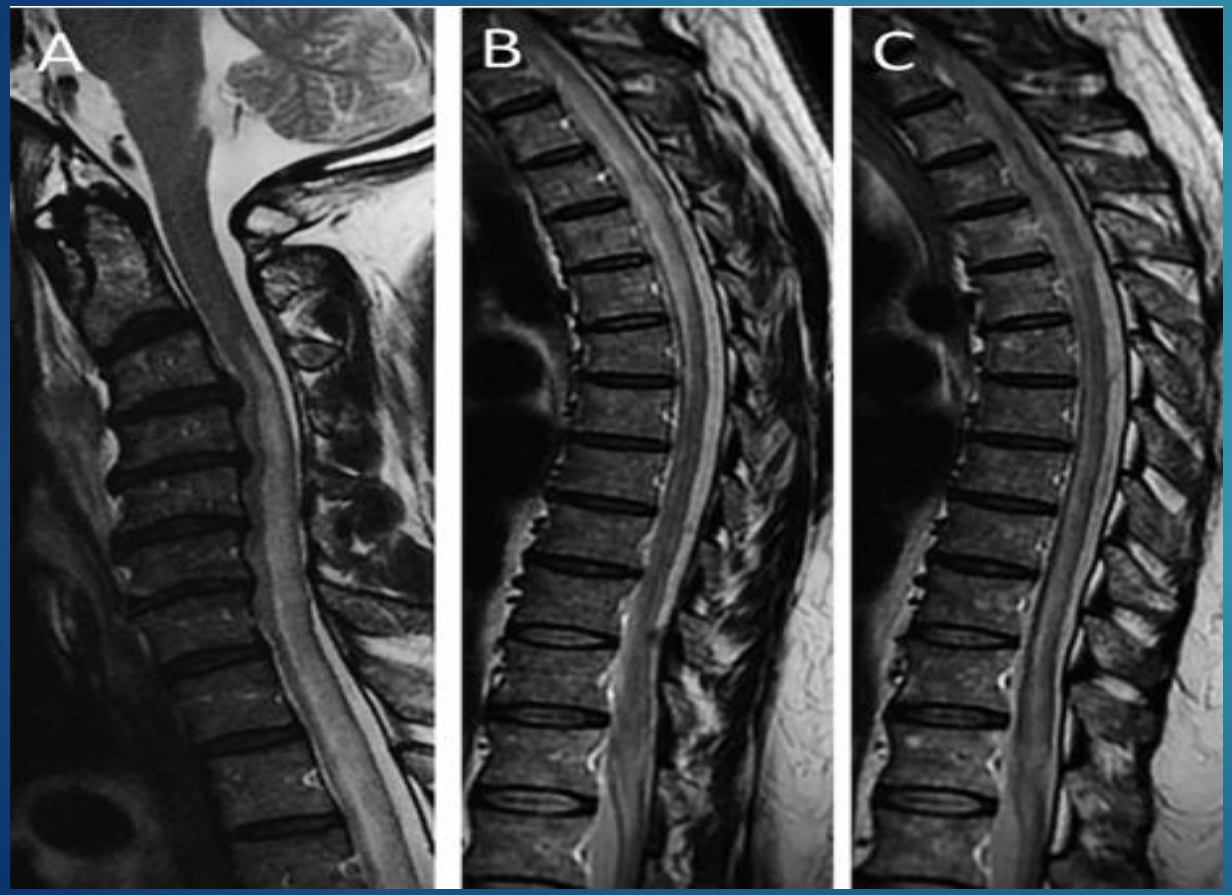


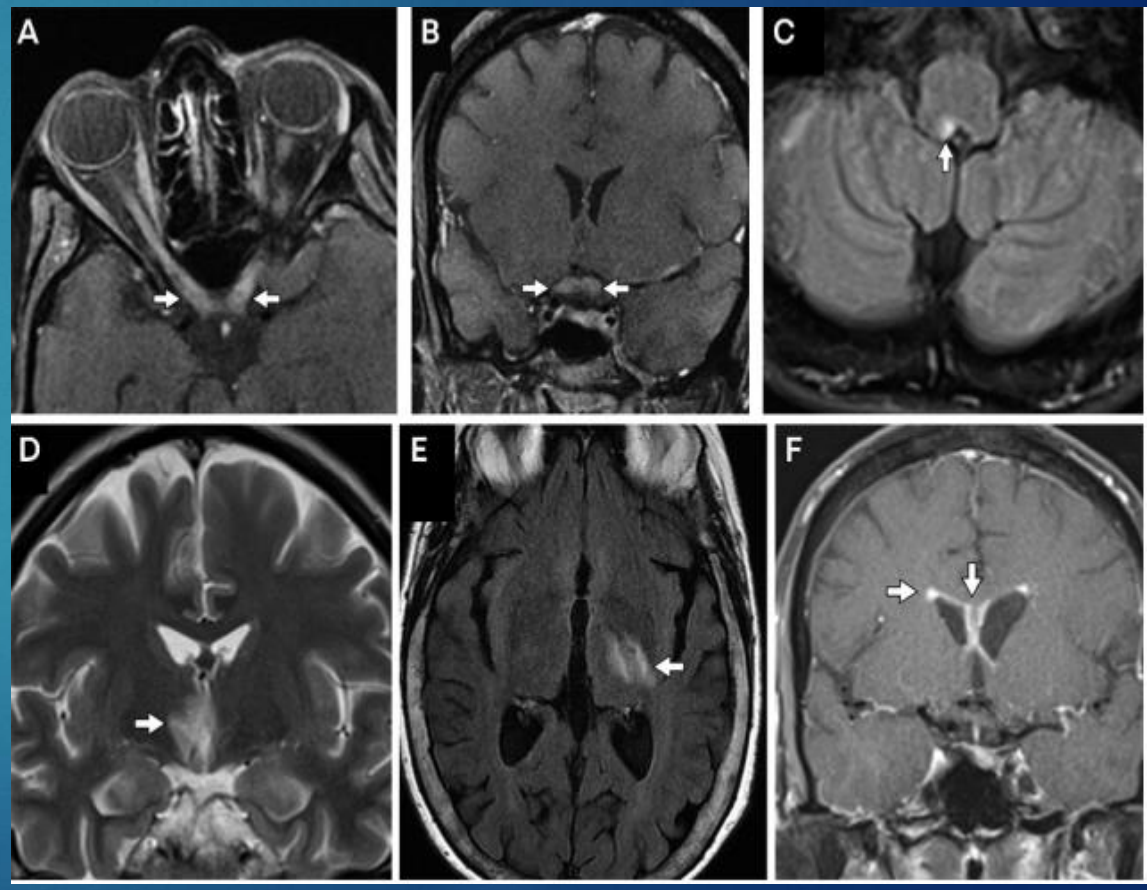
MS vs. NMOSD

- Clinical, imaging, and CSF features of MS and NMOSD can overlap
- Serological testing for AQP4 and for MOG should be done in all patients with features suggesting NMOSD (such as bilateral optic neuritis, severe brainstem involvement, longitudinally extensive spinal cord lesions, large cerebral lesions, or normal brain MRI.

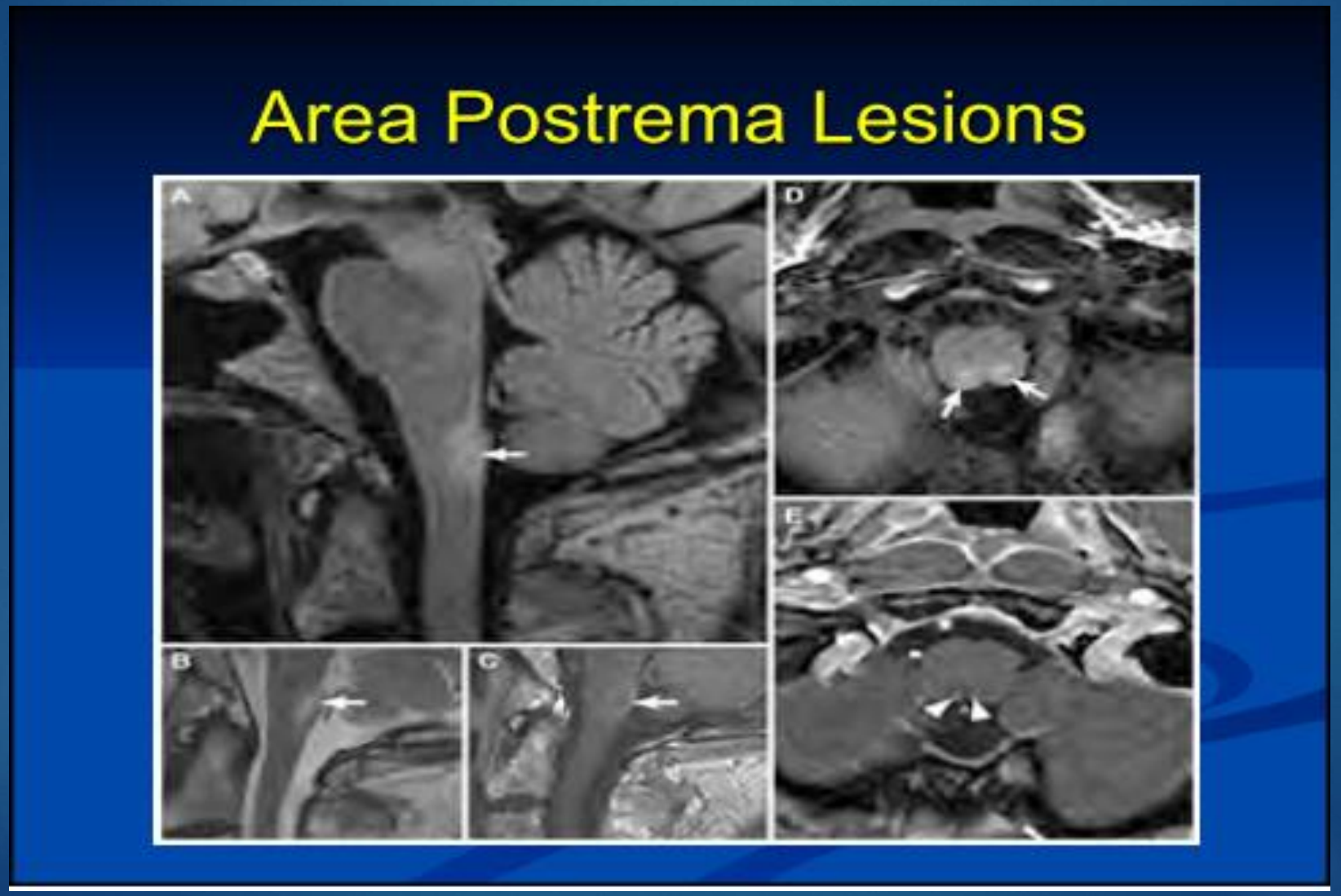
- Should also be considered in groups at higher risk of NMOSD (such as African American, Asian, Latin American, and pediatric populations).
- The treatments for MS and NMOSD are different (some MS treatments can exacerbate NMOSD).

NMOSD

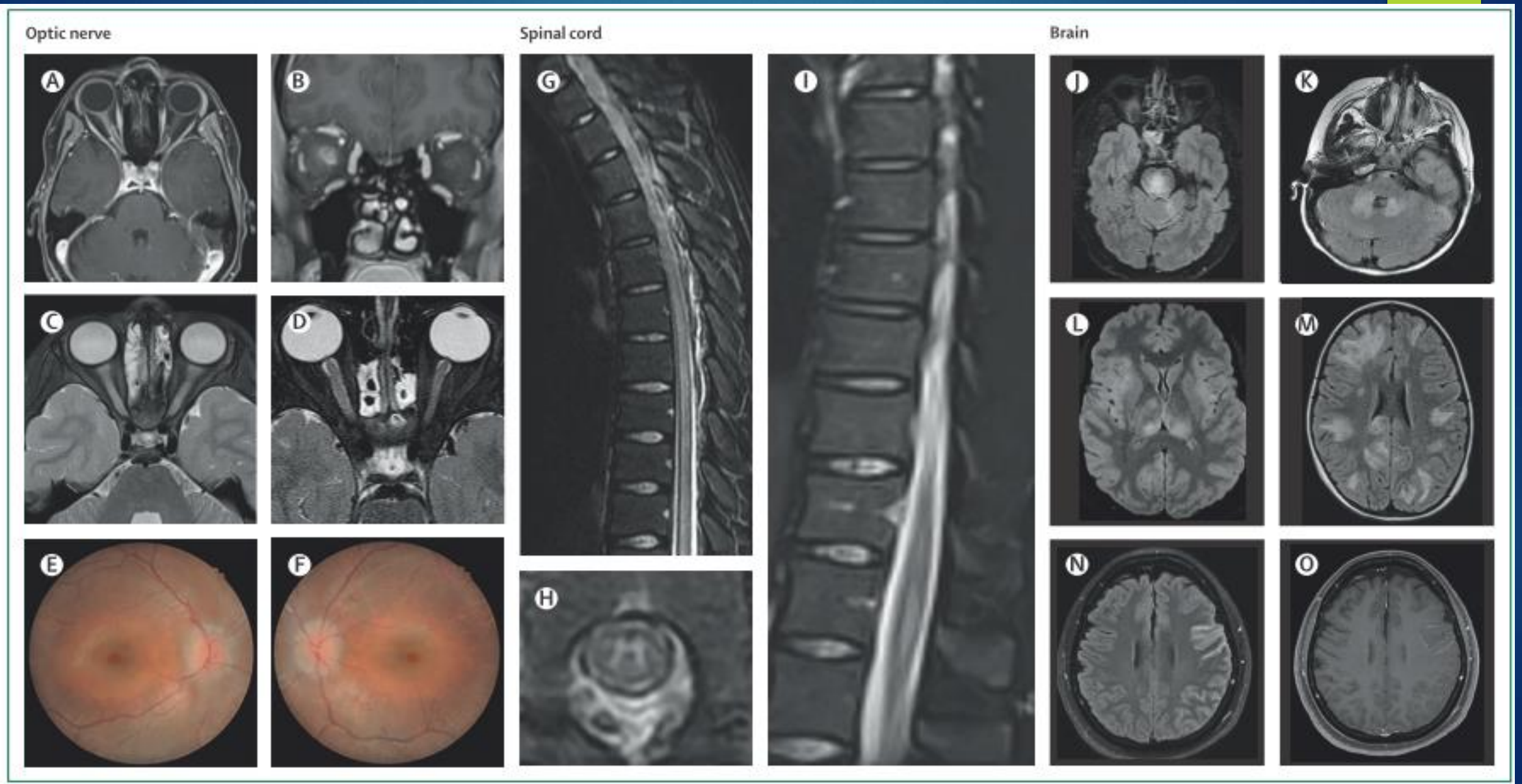




Typical of NMOSD-causes hiccups and vomiting

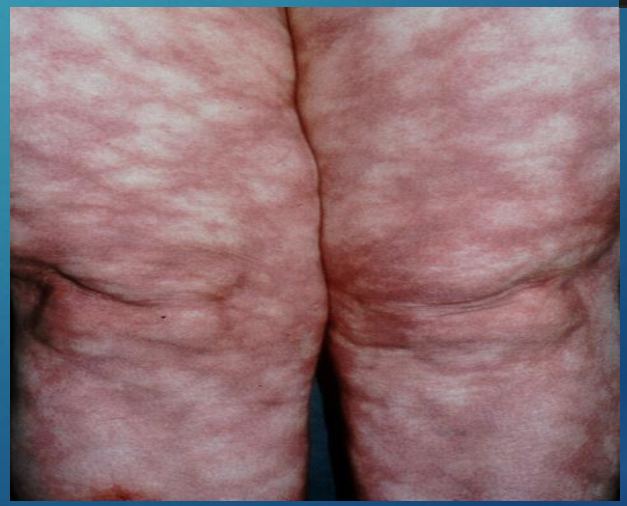


MOGAD



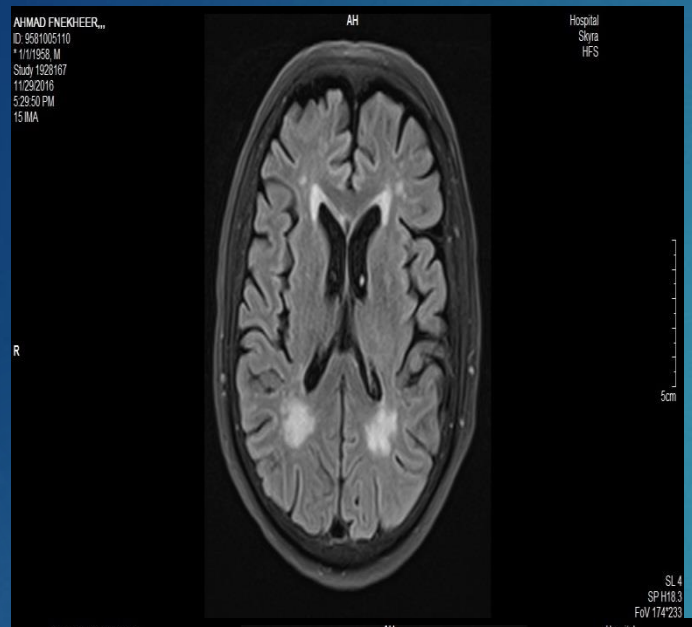
Demyelination Secondary to systemic diseases Ischemic/inflammatory…

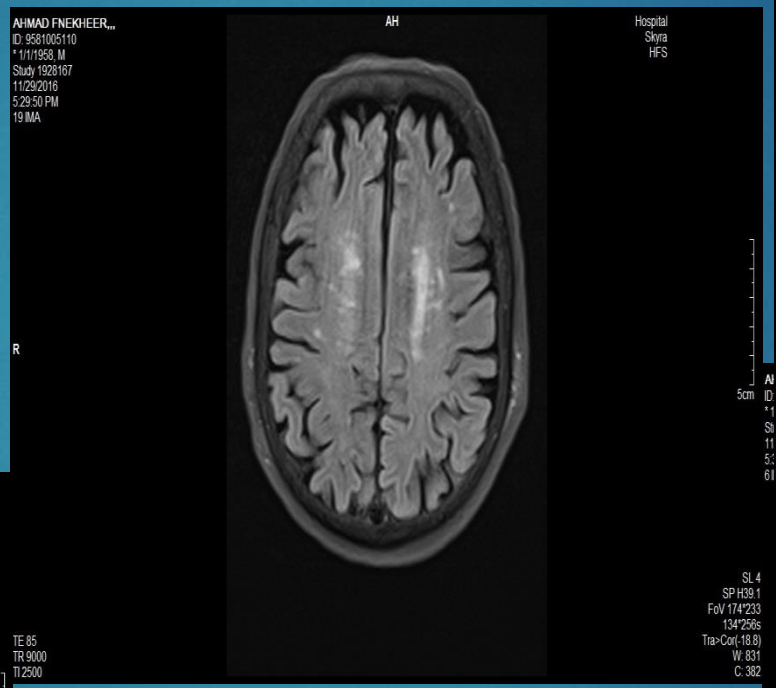
- Non-specific Age-related WM changes- UBO's !
- Small vessel disease
- Migraine,
- Vasculitis (SLE, APLA syndrome*, Sjogren's , Behcet's)
- Infection (Lyme disease)
- Sarcoidosis, Susac's syndrome
- B12 deficiency/ Hyperhomocystinemia

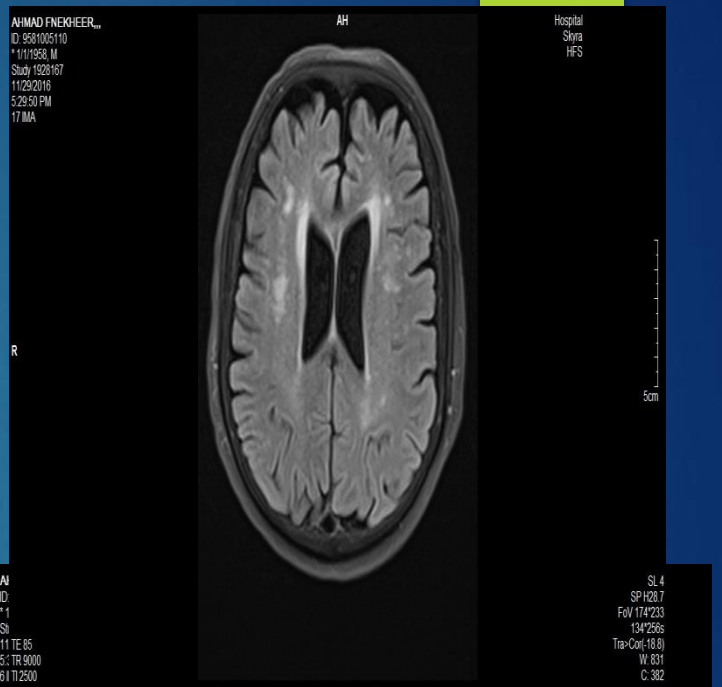


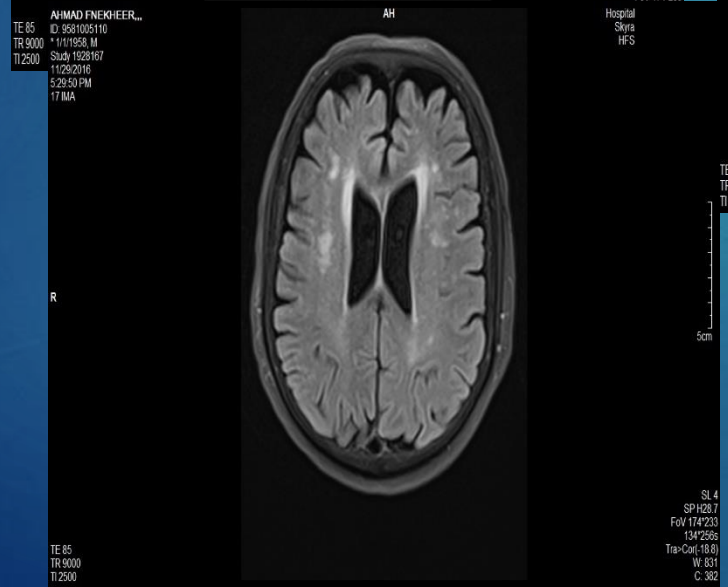
*Livedo reticularis

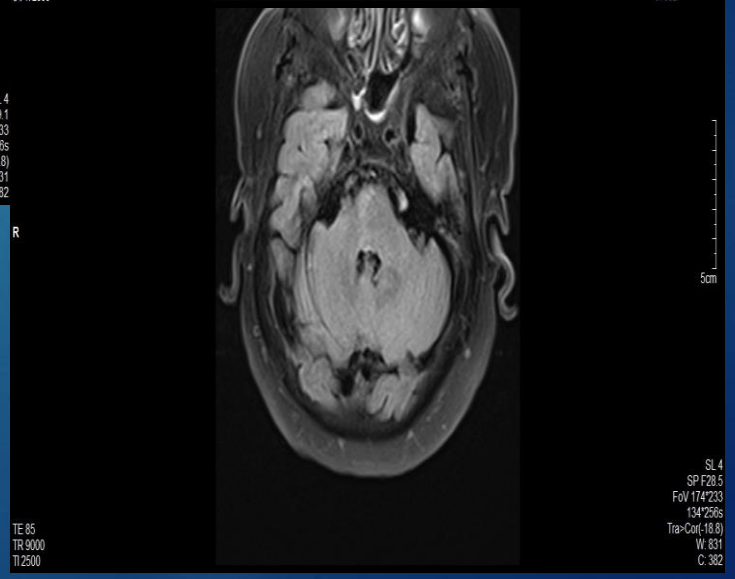
Small vessel disease





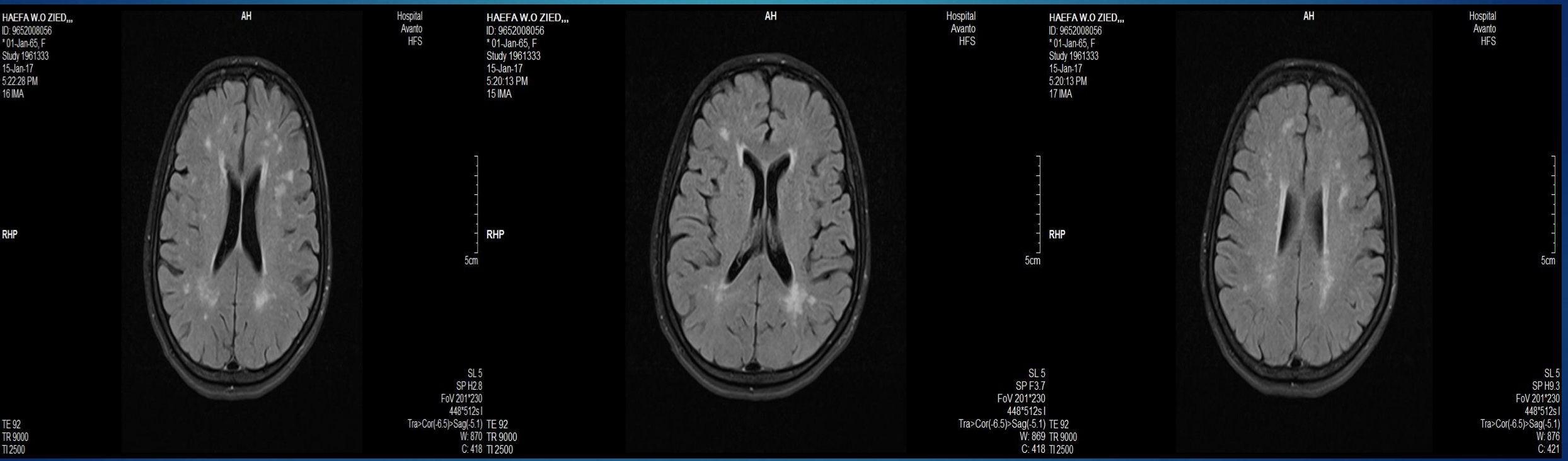






50 yr old lady seen last week with headache -2/12.
Arthralgia, dry mouth, ESR 80 mm/1st hr

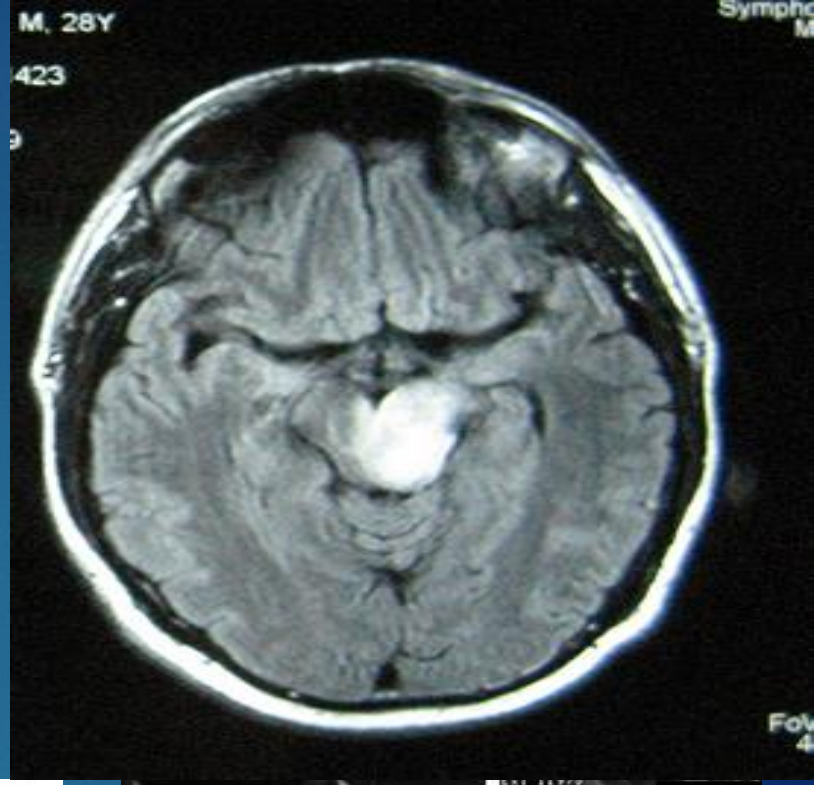
Sjogren's Disease with secondary CNS vasculitis



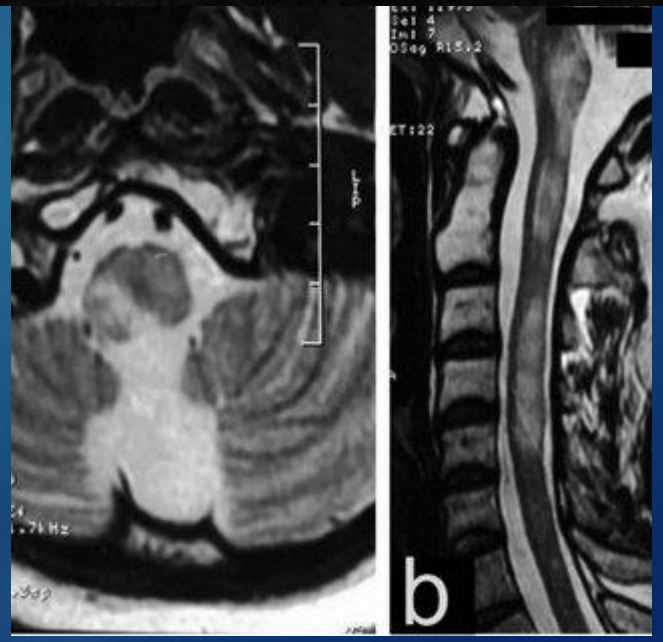
Behcet's Disease

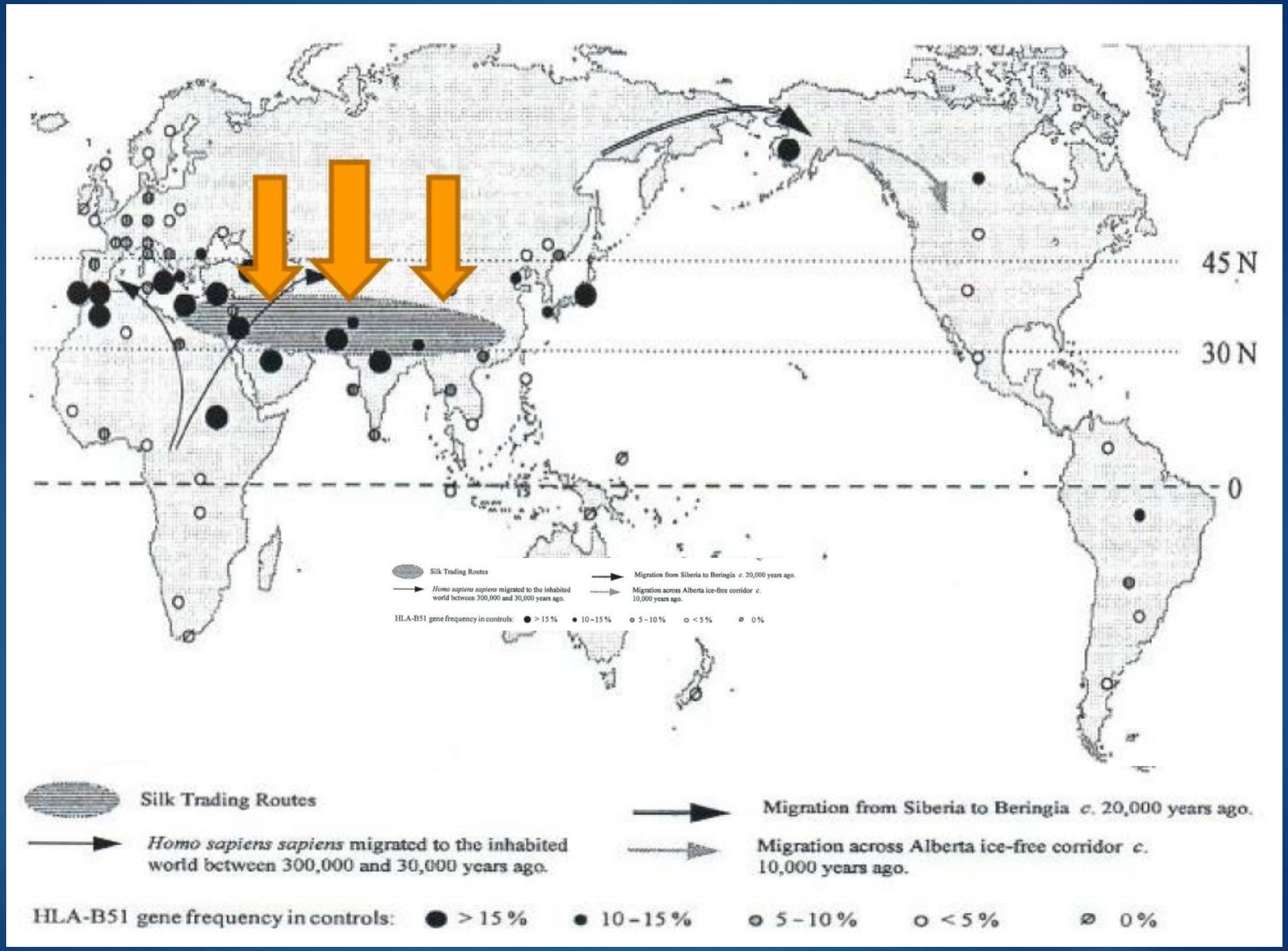
- A multi-system recurrent inflammatory disorder of unknown etiology – strongly associated with HLA-B51 haplotype
- Variable vessel vasculitis (VVV)
- Can affect vessels of any size (small, medium, and large)
- Any type (arteries, veins, and capillaries).

- Also called the "Silk Road Disease"



Hulusi Behcet
1889-1948




45 N
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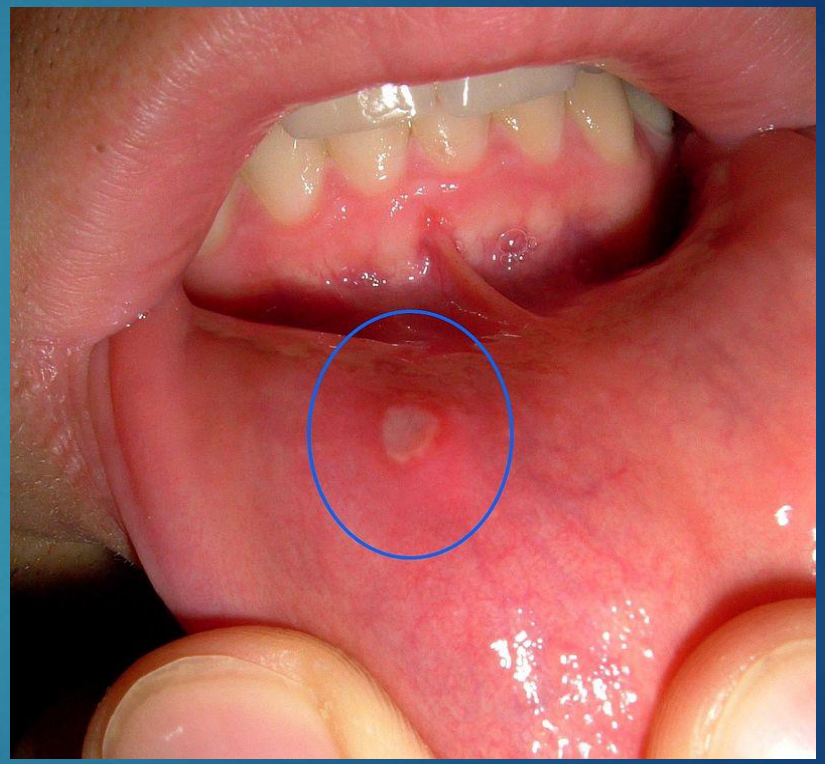
Silk Trading Routes
Homo sapiens sapiens migrated to the inhabited world between 300,000 and 30,000 years ago.
Migration from Siberia to Beringia c. 20,000 years ago.
Migration across Alberta ice-free corridor c. 10,000 years ago.
HLA-B51 gene frequency in controls: > 15 % 10 – 15 % 5 – 10 % < 5 % 0 %

	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

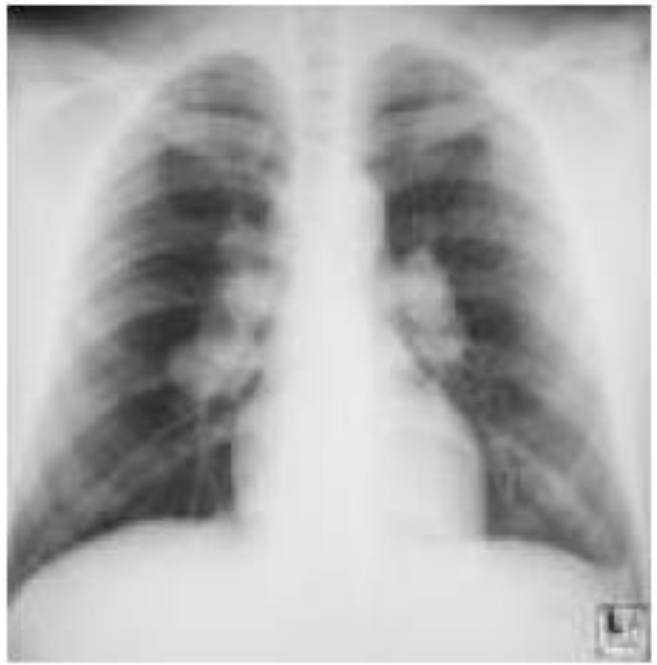
*Adapted from Yazici et al,[4] with permission from Nature Publishing Group.

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

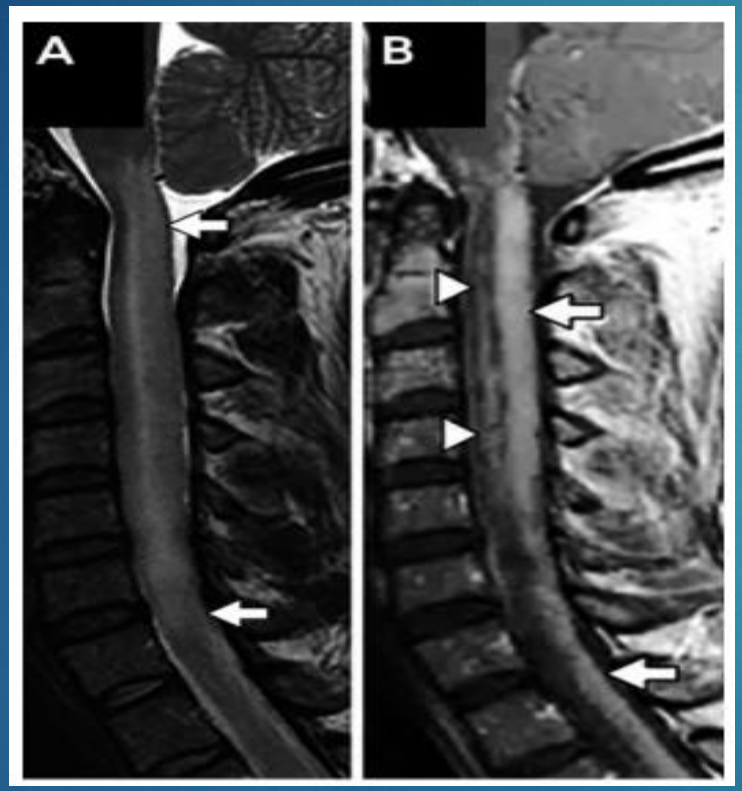


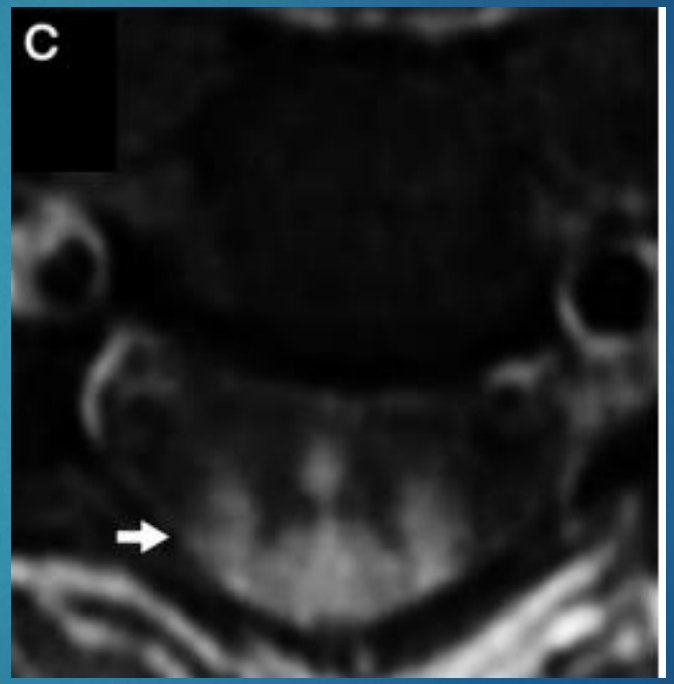
SYSTEMIC SARCOIDOSIS

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



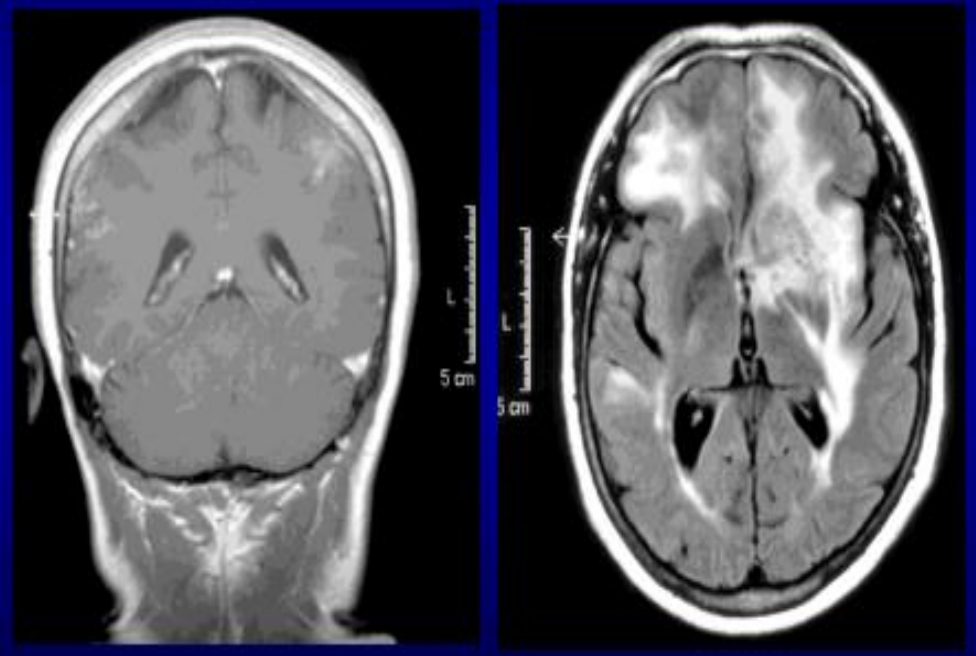
Neurosarcoidosis



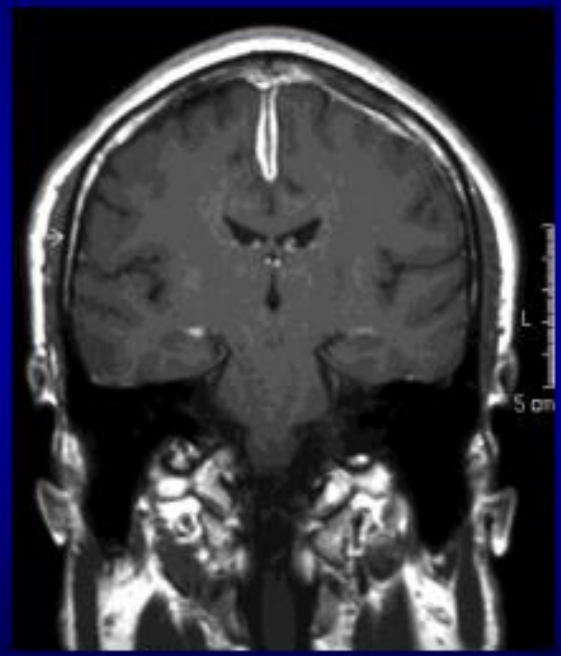


Neurosarcoidosis

Meningoencephalitis



Pachymeningitis



Summary of How to diagnose MS

- **Clinical:** symptoms and signs suggestive of MS
- **MRI brain/ Spine:** lesions suggestive of MS
- **CSF studies:** supportive of MS / exclude mimics
- **Visual Evoked Potentials :** supportive of MS
- **Laboratory investigations:** to exclude other diseases

Management

Life-style modifications

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

Relapses

- New focal neurological symptoms/signs lasting >24 hrs after at least 1 month of neurological stability

- Consider “pseudo-relapses” due to fever, infection, hot weather, emotional stress? (But stress may also trigger true relapses)

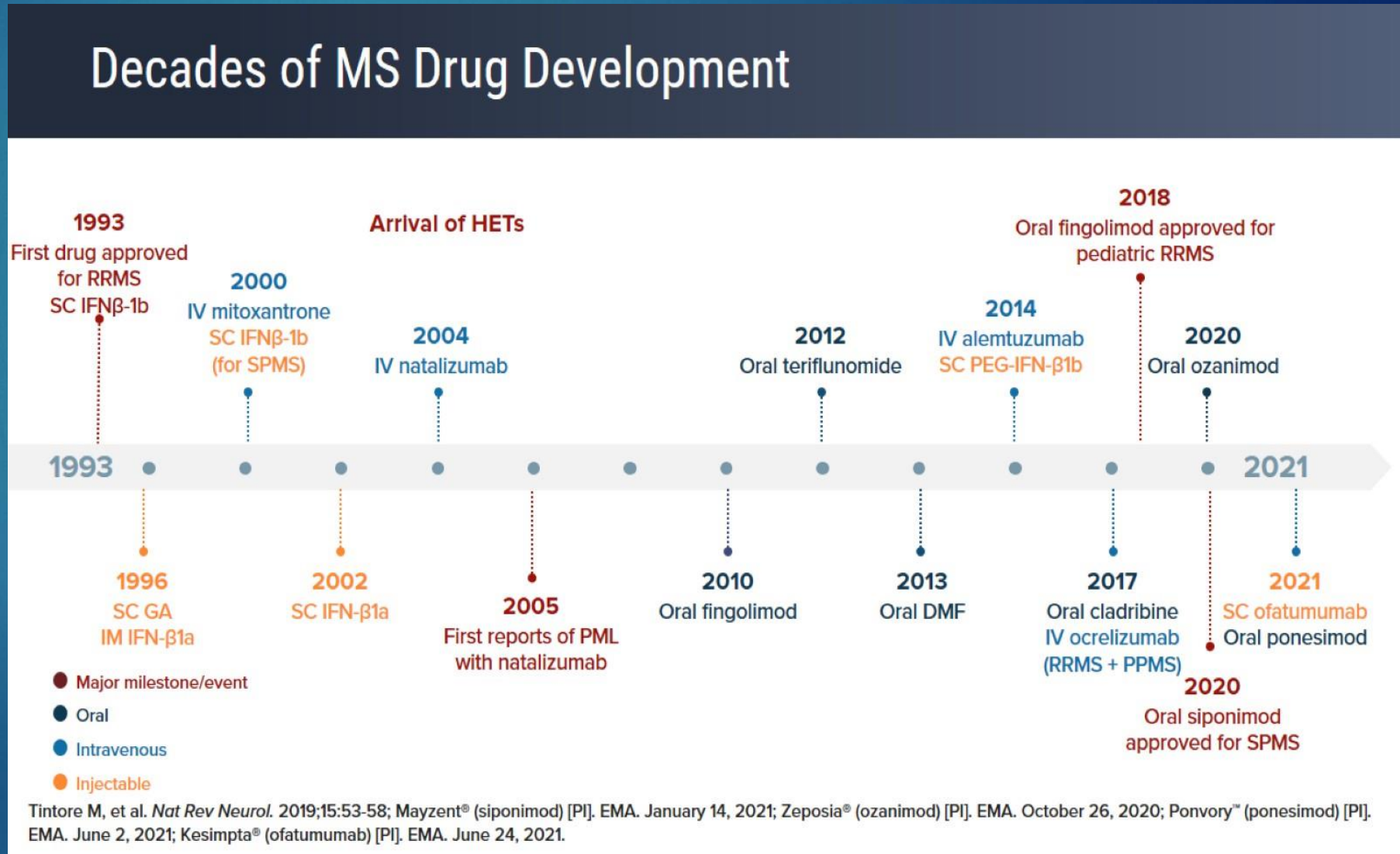
Relapse treatment

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 ?

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

- The available treatment arsenal now contains up to 18 drugs



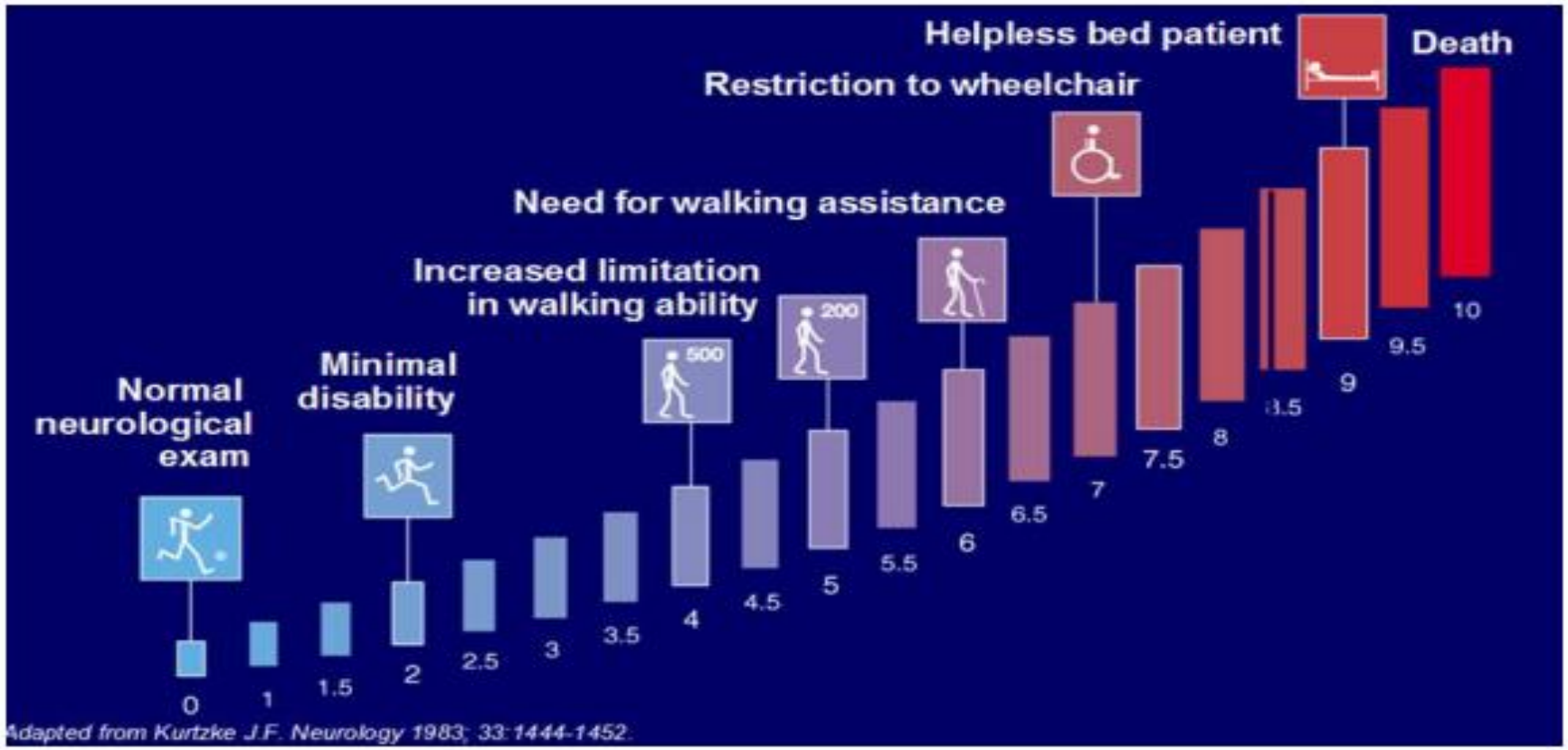
How can I predict who will do better or worse?

Prognostic features in early MS

Better prognosis	Poorer prognosis
• Caucasian	• Afro-American or non-white
• Monofocal onset	• Multifocal onset
• Onset with optic neuritis or isolated sensory symptoms	• Onset with motor, cerebellar, or bladder/bowel symptoms
• Low relapse rate first 2–5 years	• High relapse rate first 2–5 years
• Good recovery after 1st relapse	• Short inter-attack latency
• Long interval to second relapse	• Disability at 5 years
• No or low disability at 5 years	• Abnormal MRI ≥2 contrast lesions ≥9 T_2 lesions Black holes
• Low lesion load on MRI	
• NEDA at 2 years	

Goals of Treatment in MS

Expanded Disability Status Scale (EDSS)

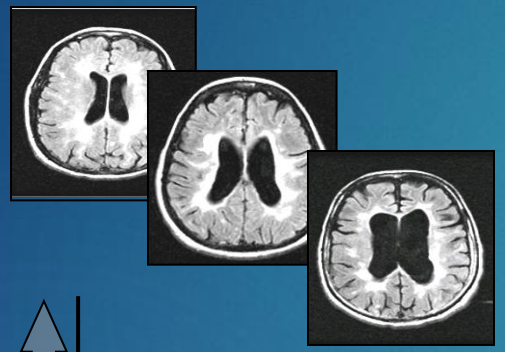


Progression from EDSS 0-4 (inflammatory phase): 1-32 years

Progression from EDSS 4-7 (degenerative phase): 7-11 years

The Burden of MS-without treatment

10 Years*



Progressive MS

15 Years*

Requiring a Cane

25 Years*

C

Confined to Wheelchair

*mean time for development

DMT Side Effects - Injectables (SC/IM)

Glatiramer Acetate

- Injection Site Reactions

Interferons

- Injection Site Reactions
- Flu-like symptoms
- Liver dysfunction
- Bone marrow suppression
- Endocrine abnormalities
- Other:
  - Depression
  - Spasticity
  - Headaches

Other moderate-efficacy therapies - AE's and risks

- Dimethyl fumarate
  - – GI upset
  - - flushing
  - - Lymphopenia
  - - Progressive Multifocal Leukoencephalopathy- rarely

- Teriflunomide
  - - Hair loss
  - - Diarrhea
  - - Teratogenicity

DMT and infections

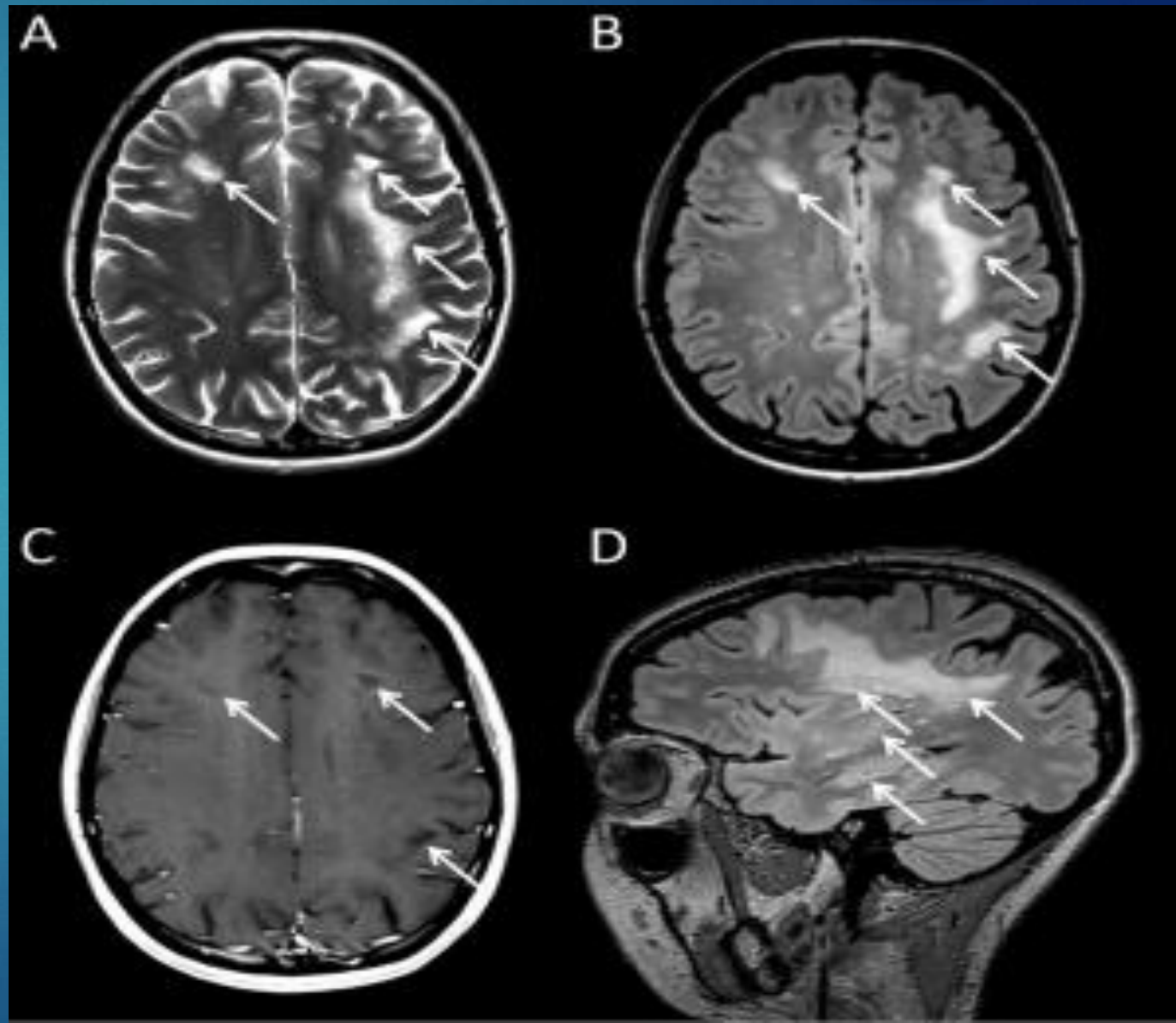
DMT	VZV/HSV	TB	PML	Hepatitis B reactivation risk	Rates of serious infections versus comparator in phase 3 trials*
Teriflunomide	Low	Moderate†	Low	Low	No excess
Dimethyl Fumarate	Low	Low	Moderate	Low	No excess
Fingolimod	Moderate	Low	Moderate	Low	No excess
Cladribine	Moderate	Moderate†	Low‡	High	Small excess
Alemtuzumab	Moderate(Low with prophylaxis)	Moderate†	Low‡	High	Small excess[39 48 49 212]
Natalizumab	Low	Low	High	Moderate	No excess
Ocrelizumab	Moderate	Low	Low	Very high	No excess
Ofatumumab	Low	Low	Low	High	No excess

Progressive Multifocal Leukoencephalopathy

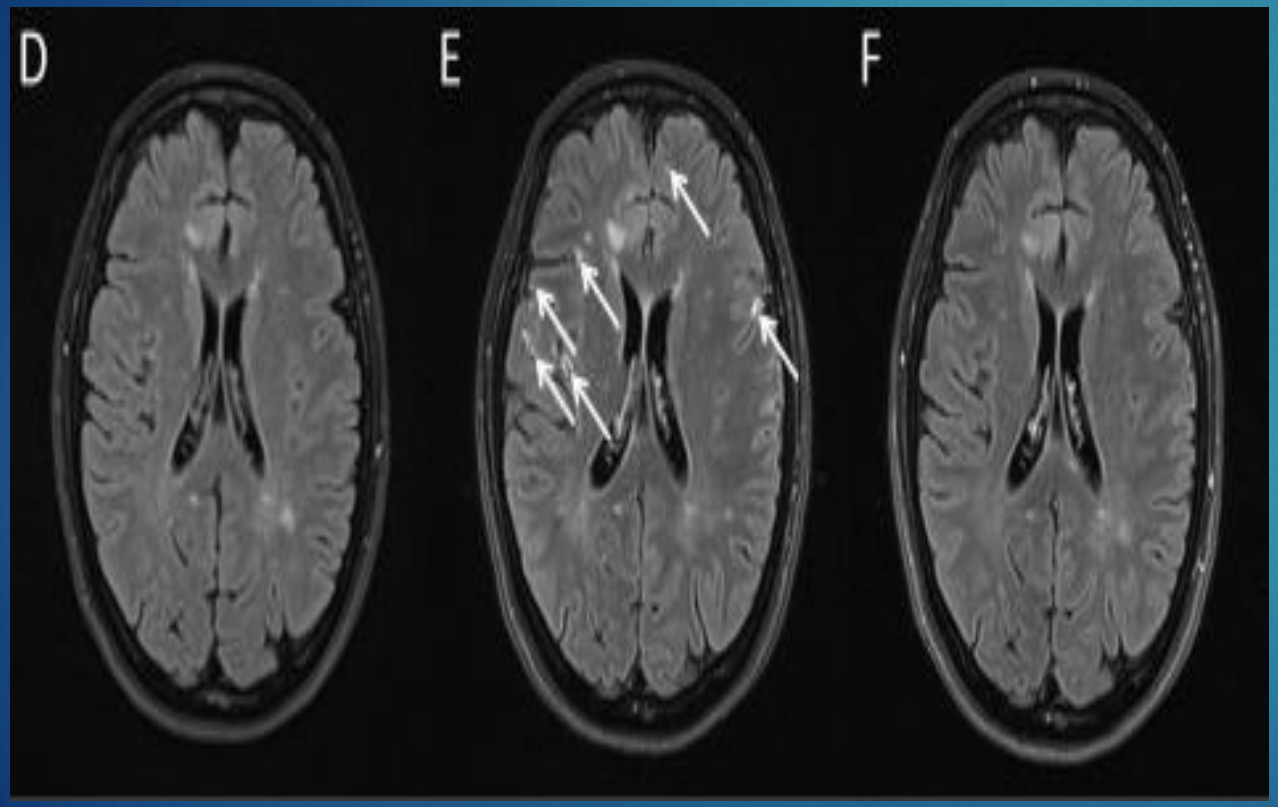
- Reactivation of latent a Polyomavirus (JC virus) -present in around 50% of normal people)
- AIDS patients

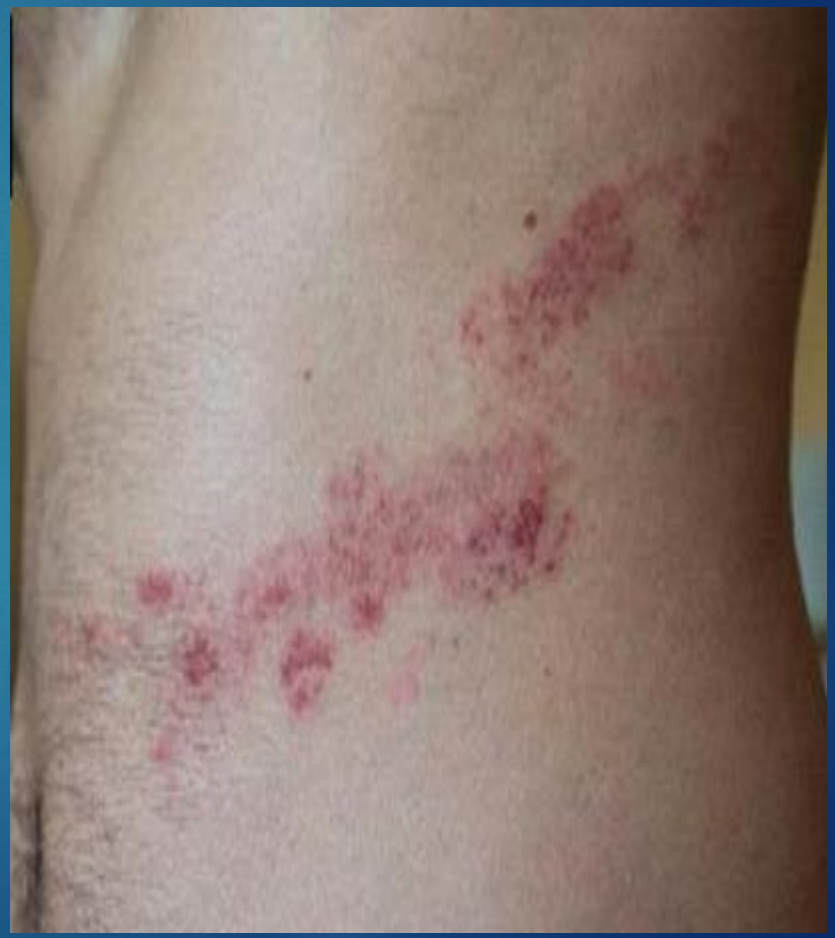
- Natalizumab > Fingolimod.
- Rarely Dimethyl Fumarate

- Multifocal presentation – cognitive, pyramidal, ataxia
- Usually leads to death or severe disability



VZV





MS and Pregnancy

- Register your attendance with your university number
- Make sure that the settings of your phone allow tracking location

Go to settings > privacy> location> services> make sure that location services is ON