Multiple Sclerosis and related disorders

Dr Majed Habahbeh MBBS FRCP

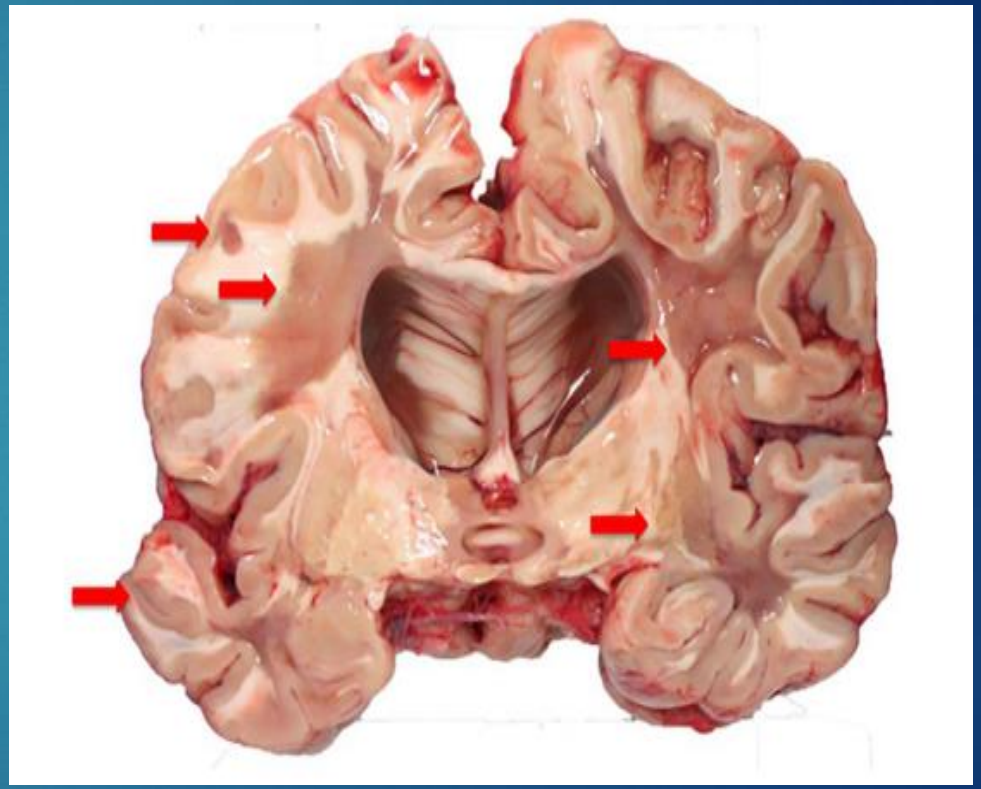
Multiple (Disseminated) Sclerosis

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

Pathology

- 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



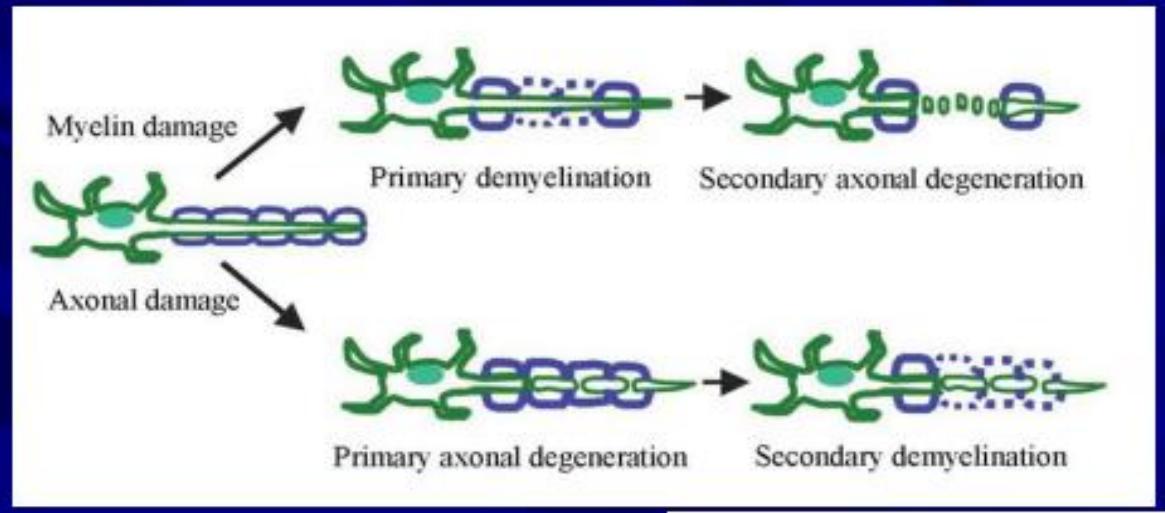
Pathology

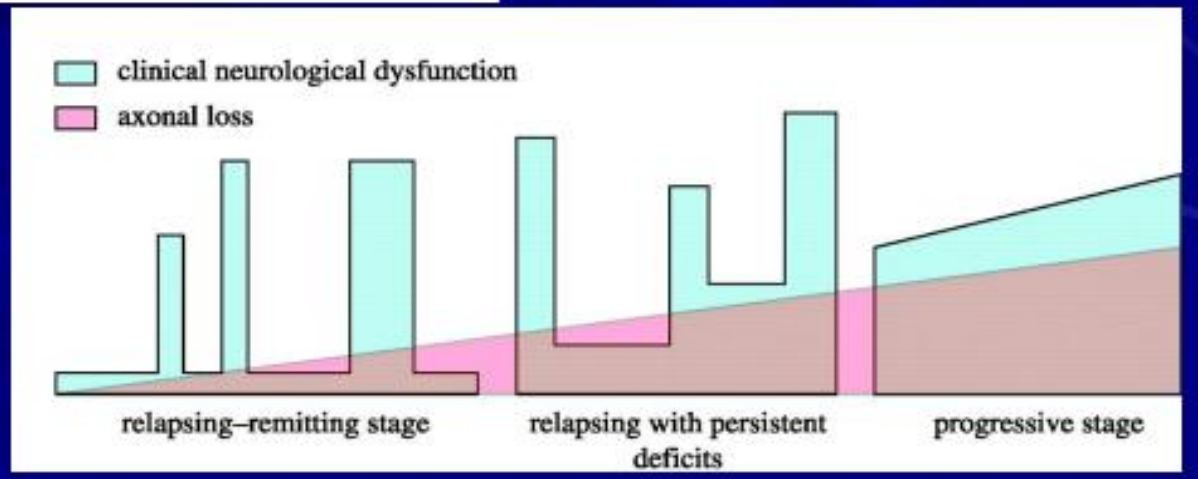
- Plaques are most commonly seen in the spinal cord , optic nerves , brainstem/cerebellum and periventricular white matter.
- Plaques are due to focal loss of myelin (oligodendrocytes), with relative preservation of axons and astrocytic gliosis.
- The pathological features of individual lesions vary and depend on location, age and whether or not there has been any regeneration.
- MS lesions are typically divided into three pathological categories: active (acute), chronic active and chronic inactive.
- More recently active lesions have been further classified into different pathological subtypes

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.
- Atrophy can be prominent particularly in the optic nerves and chiasm, pons, medulla and spinal cord.
- 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.

Neuro-inflammation & Neuro-degeneration





Pathophysiology

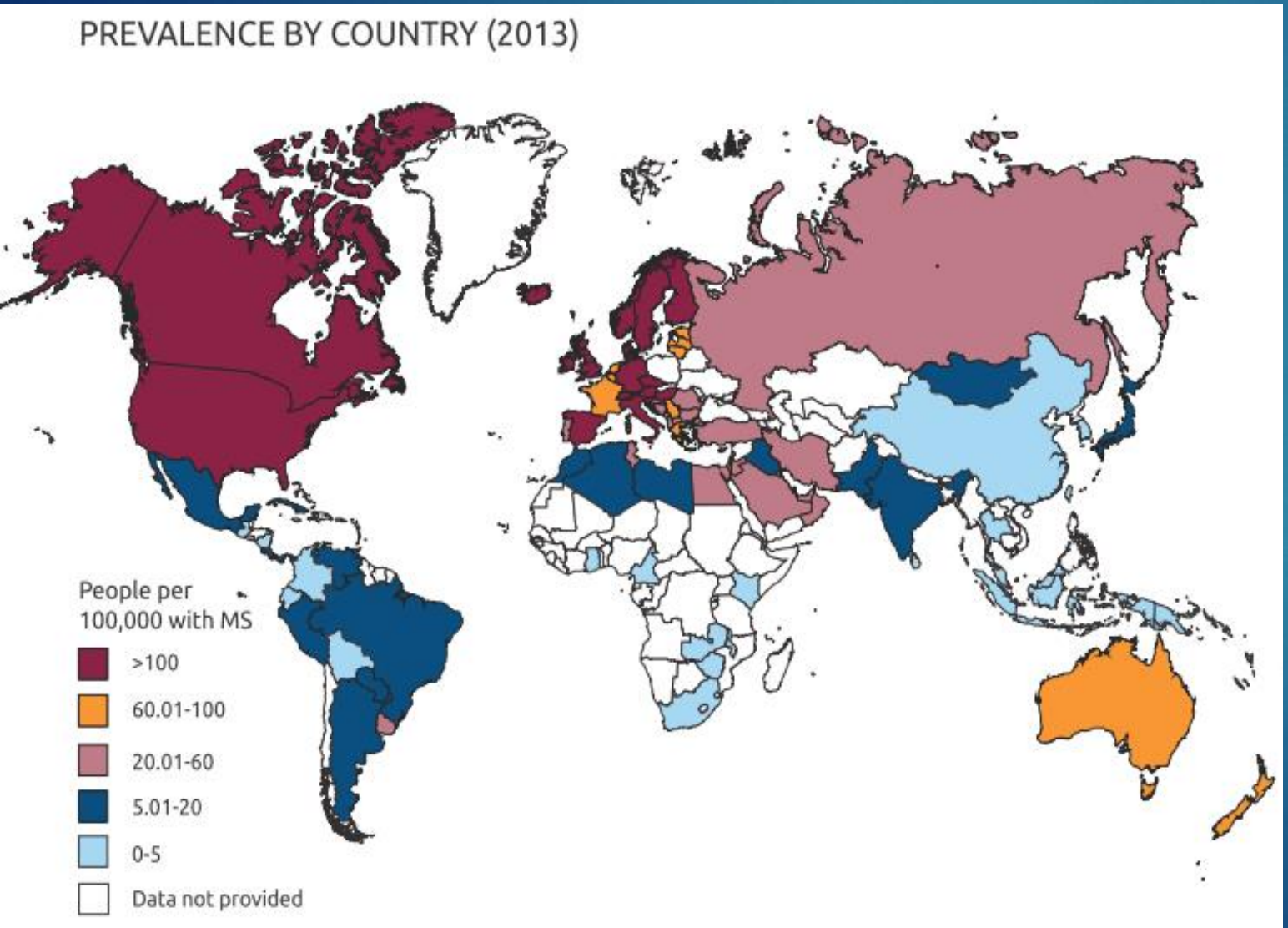
Multiple sclerosis is an autoimmune disease in which lymphocytes migrate out of lymph nodes into the circulation, cross the blood–brain barrier, and aggressively target putative myelin antigens in the CNS , causing inflammation, demyelination , neuroaxonal injury, astrogliosis, and ultimately neurodegeneration

- 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

Genetic factors

- The strongest known genetic factor affecting MS susceptibility is the HLA-DRB1*1501 haplotype.

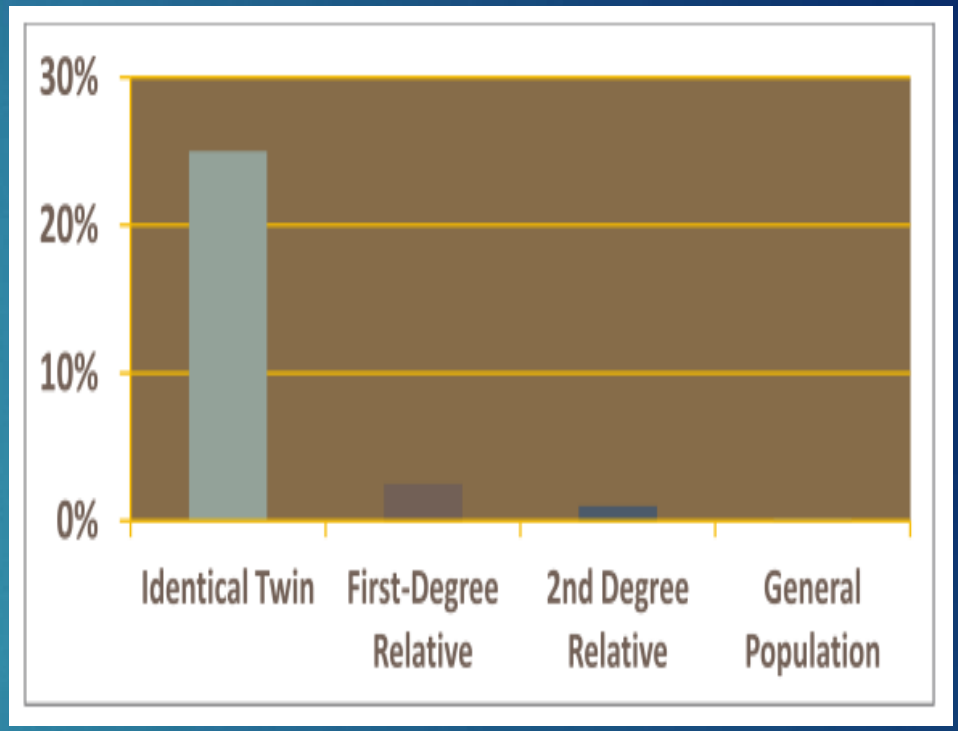
- However, it is not essential for the development of MS, as it only increases the risk by 2- to 4-fold and is present in approximately 20% to 30% of healthy individuals

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%



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

Putative causes 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

EBV theory

- Many observations implicate EBV in the pathogenesis of MS :

- universal EBV seropositivity,
- high anti-EBV antibody levels,
- alterations in EBV-specific CD8+ T-cell immunity,
- increased shedding of EBV from saliva and accumulation of EBV-infected B cells and plasma cells in the brain.

EBV theory

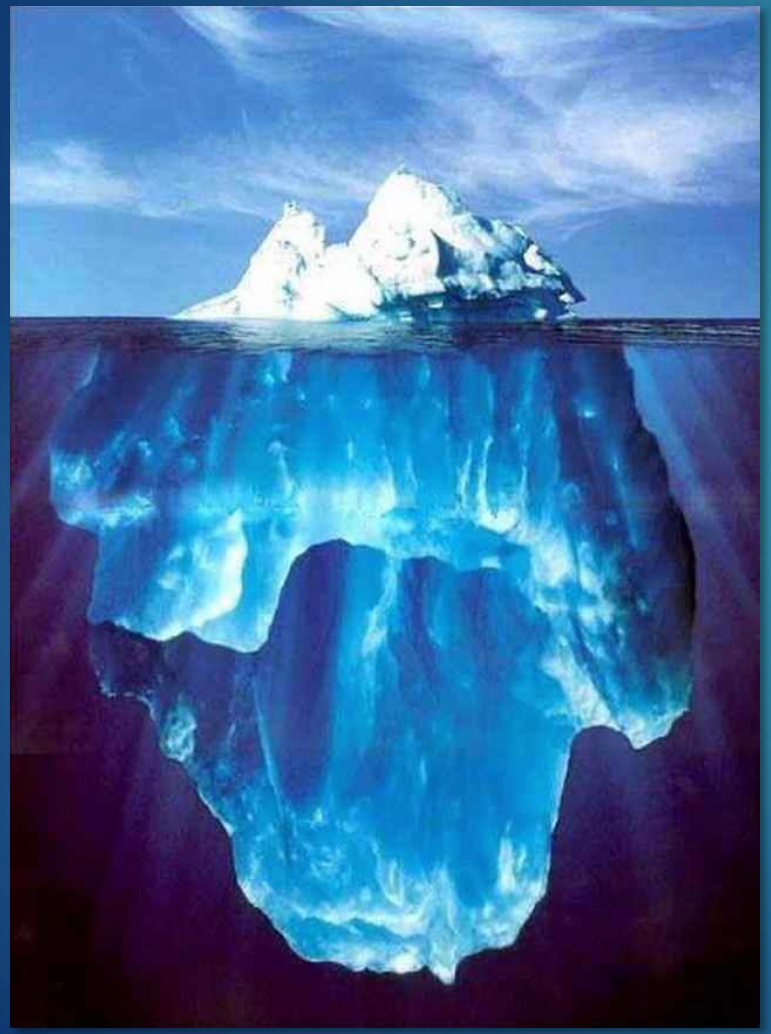
- Rapidly accumulating evidence for a pathogenic role of EBV in MS provides ground for optimism that it might be possible to prevent and cure MS by effectively controlling EBV infection through vaccination, antiviral drugs or treatment with EBV-specific cytotoxic CD8+ T cells.

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

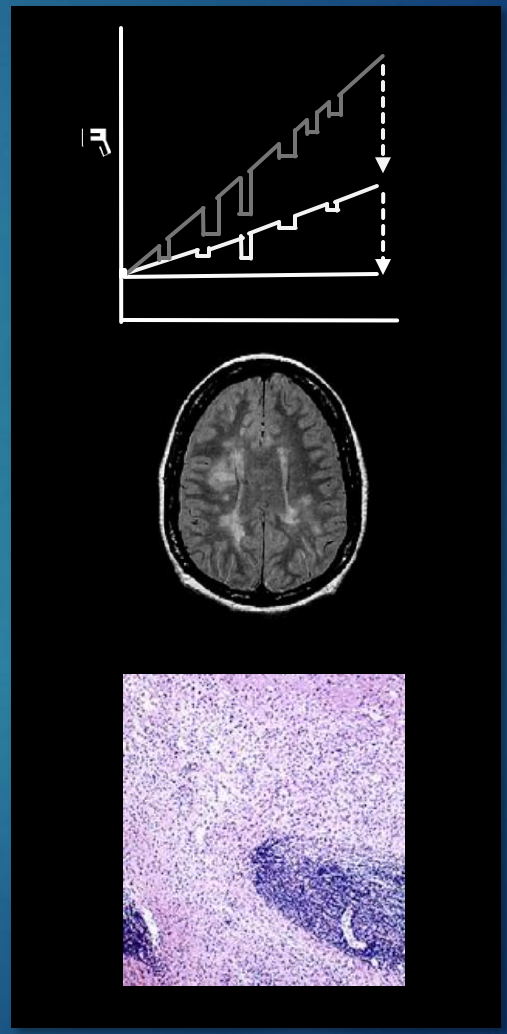
The Iceberg Model of MS



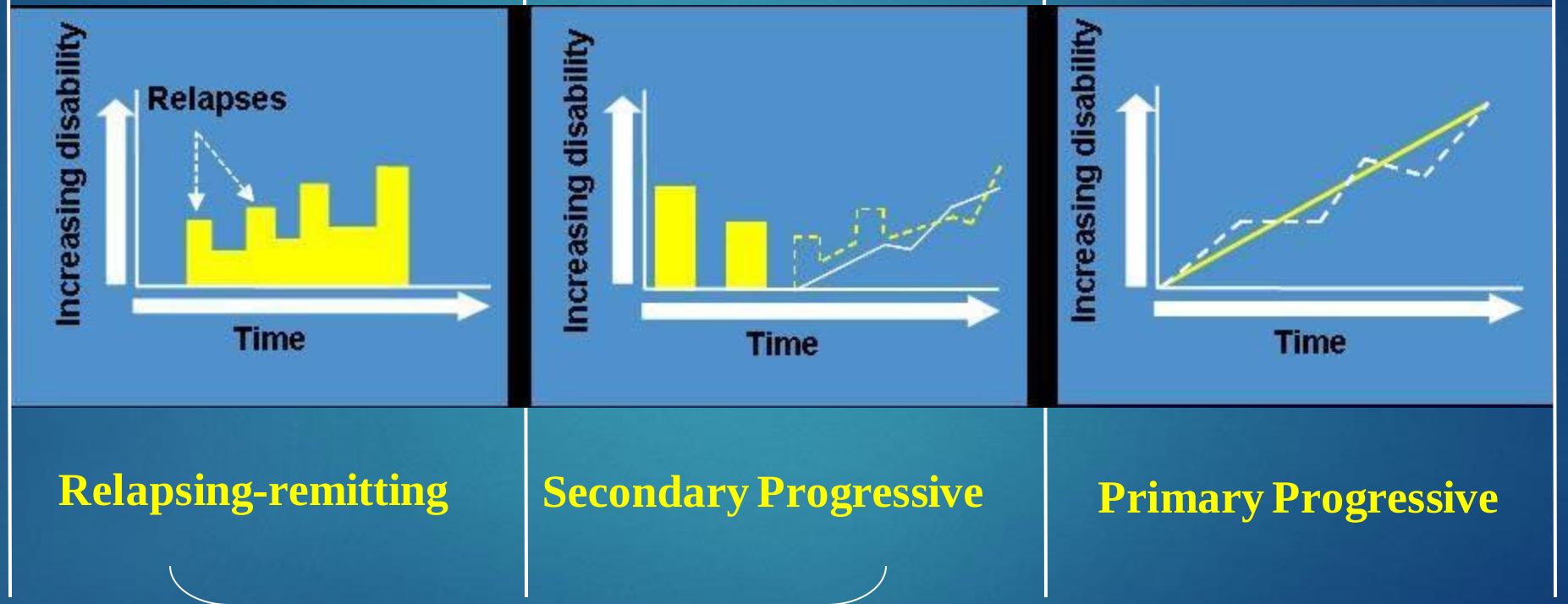
Clinical

MRI

Pathology



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%

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.

Clinically Isolated Syndrome

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

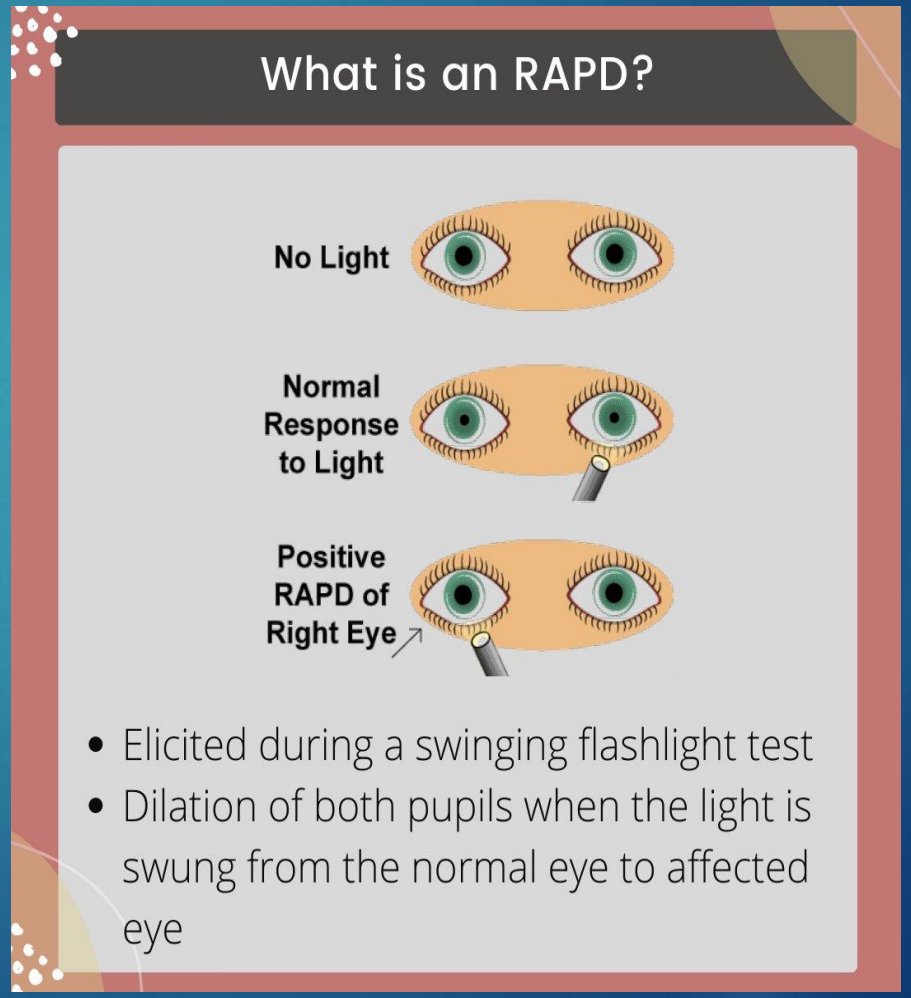
- **optic neuritis ,or**
- **partial myelitis ,or**
- **a brain stem syndrome.**
- **Less commonly a hemispheric presentation or multifocal.**

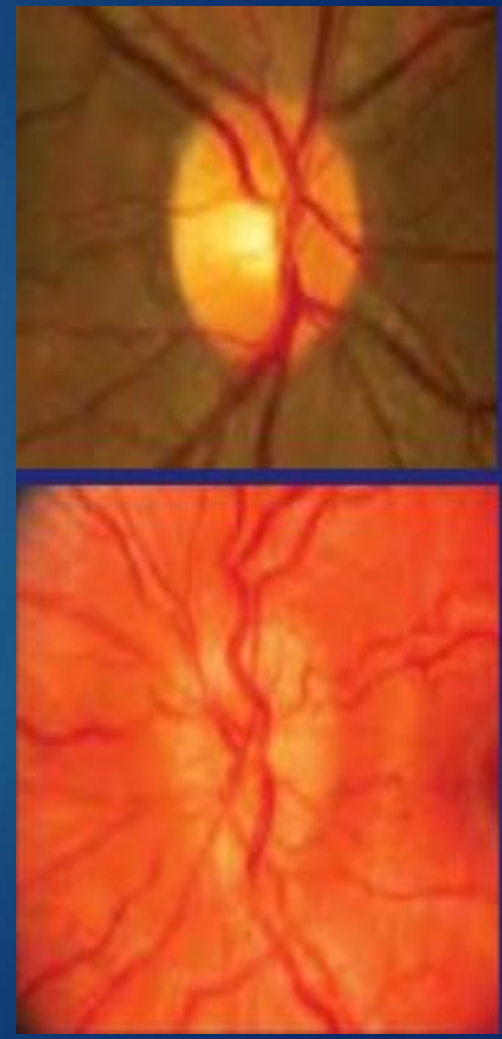
Common Relapses

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





Differential diagnosis of optic neuritis

Compressive optic neuropathies
Primary tumours, gliomas, meningioma, pituitary tumours – particularly craniopharyngioma in children, metastases, sinus mucocoeles, arterial aneurysms

Ischaemic optic neuropathies
Anterior and posterior ischaemic optic neuropathy, giant cell arteritis, diabetic papillopathy

Infective conditions
Tuberculosis, syphilis, Lyme disease, viral ON, toxocariasis or helminthitis (usually visible retinal/optic head lesion)

Toxic and nutritional optic neuropathy
Vitamin B12 deficiency, tobacco-ethanol amblyopia, methanol intoxication, ethambutol toxicity

Inherited conditions
Leber hereditary optic neuropathy

Ocular causes
Posterior scleritis, maculopathy, retinopathy, big blind spot syndrome

Periorbital infection
Cellulitis, severe suppurative sinusitis

Differential diagnosis

- SLE – AION / optic neuritis
- Sarcoidosis – acute/chronic, delayed VEP
- Sjogren's – subclinical, bilateral
- Behcet's – bilateral atrophy / + uveitis
- Orbital Wegener's – proptosis
- Vogt-Koyanagi-Harada - uveitis/pigment loss
- Central serous retinopathy
- Viral neuro-retinitis

MS symptoms (not relapses)

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

- fatigue
- Pain, spasticity ,spasms, Ataxia
- Uthoff's phenomenon
- 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

Blood tests to exlude other diseases

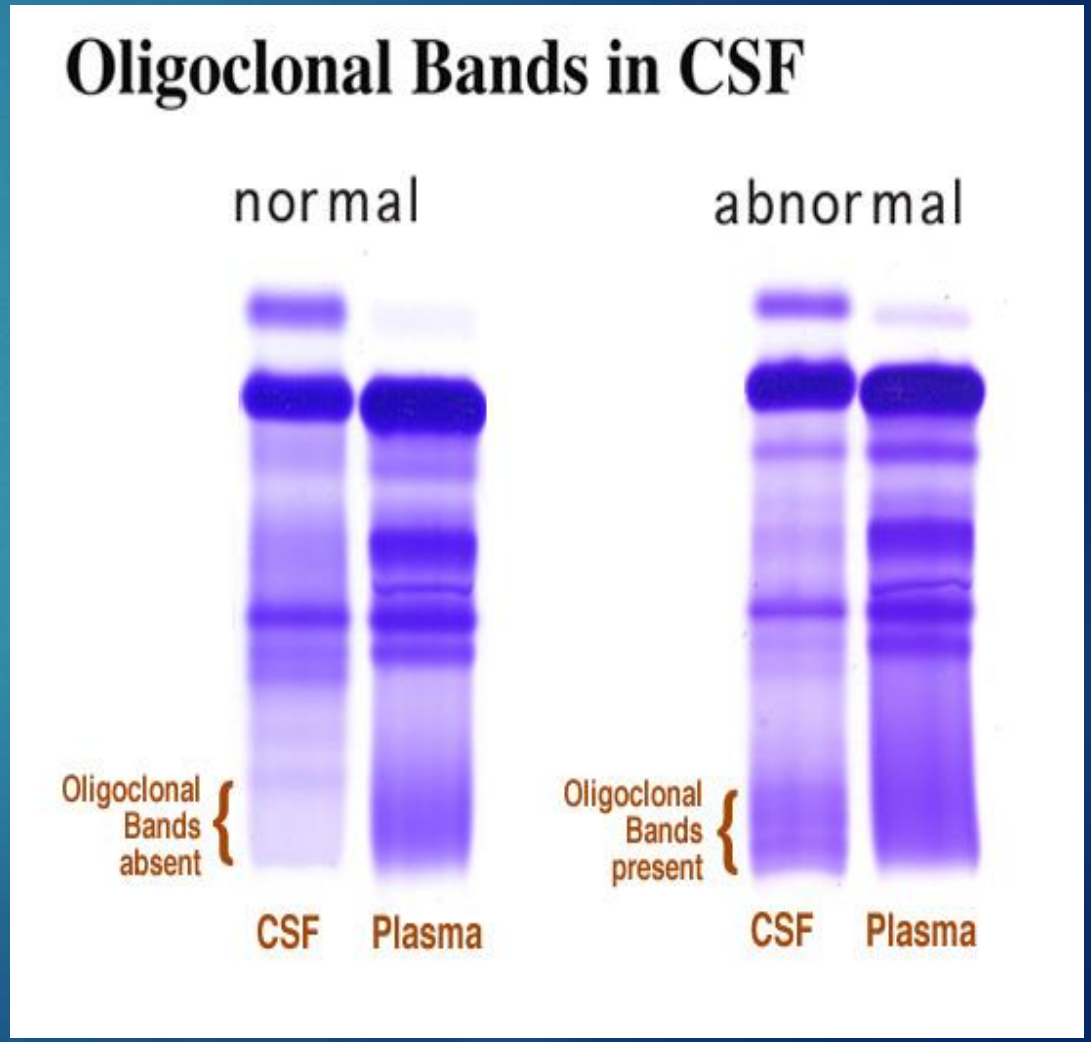
- Normal systemic inflammatory markers (ESR, CRP).

- Autoantibodies (Low-titre ANA may occur)

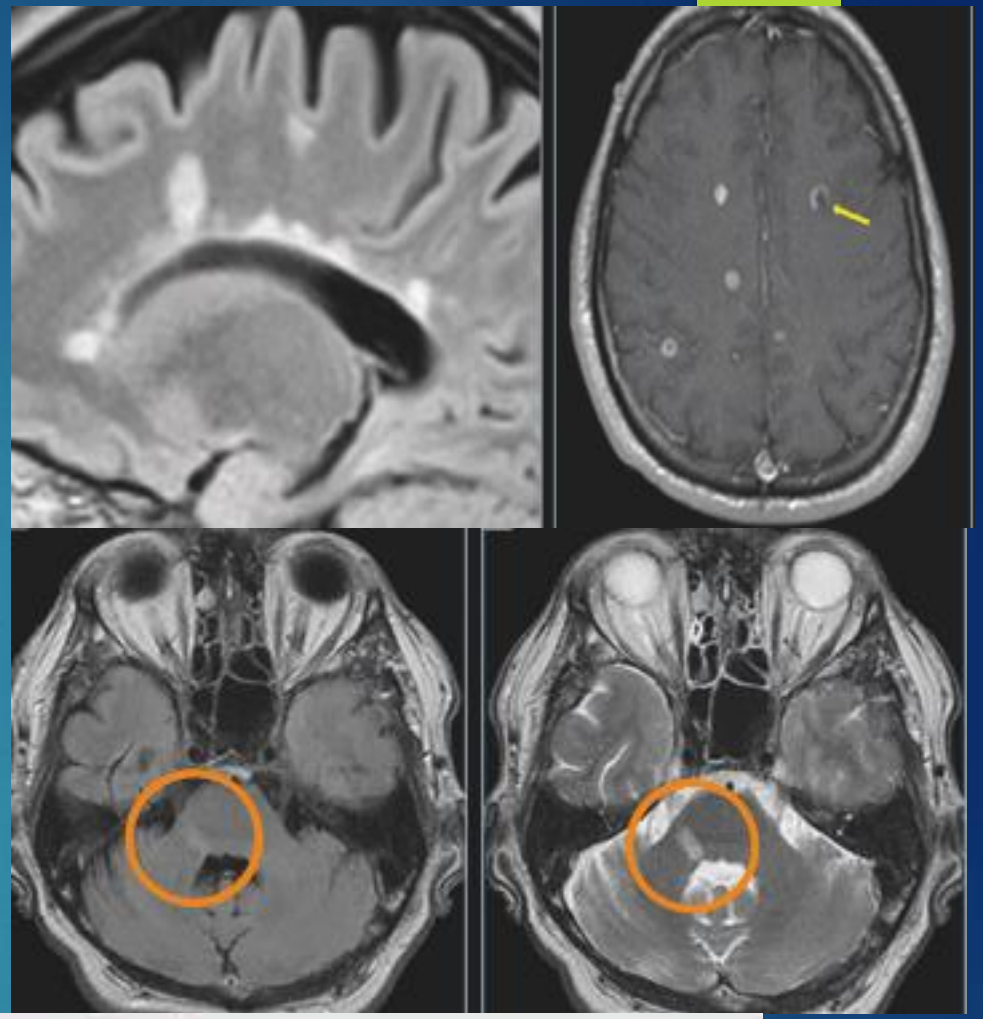
- Vasculitis screen, B12, TFT, LFT, serum ACE/CXR

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

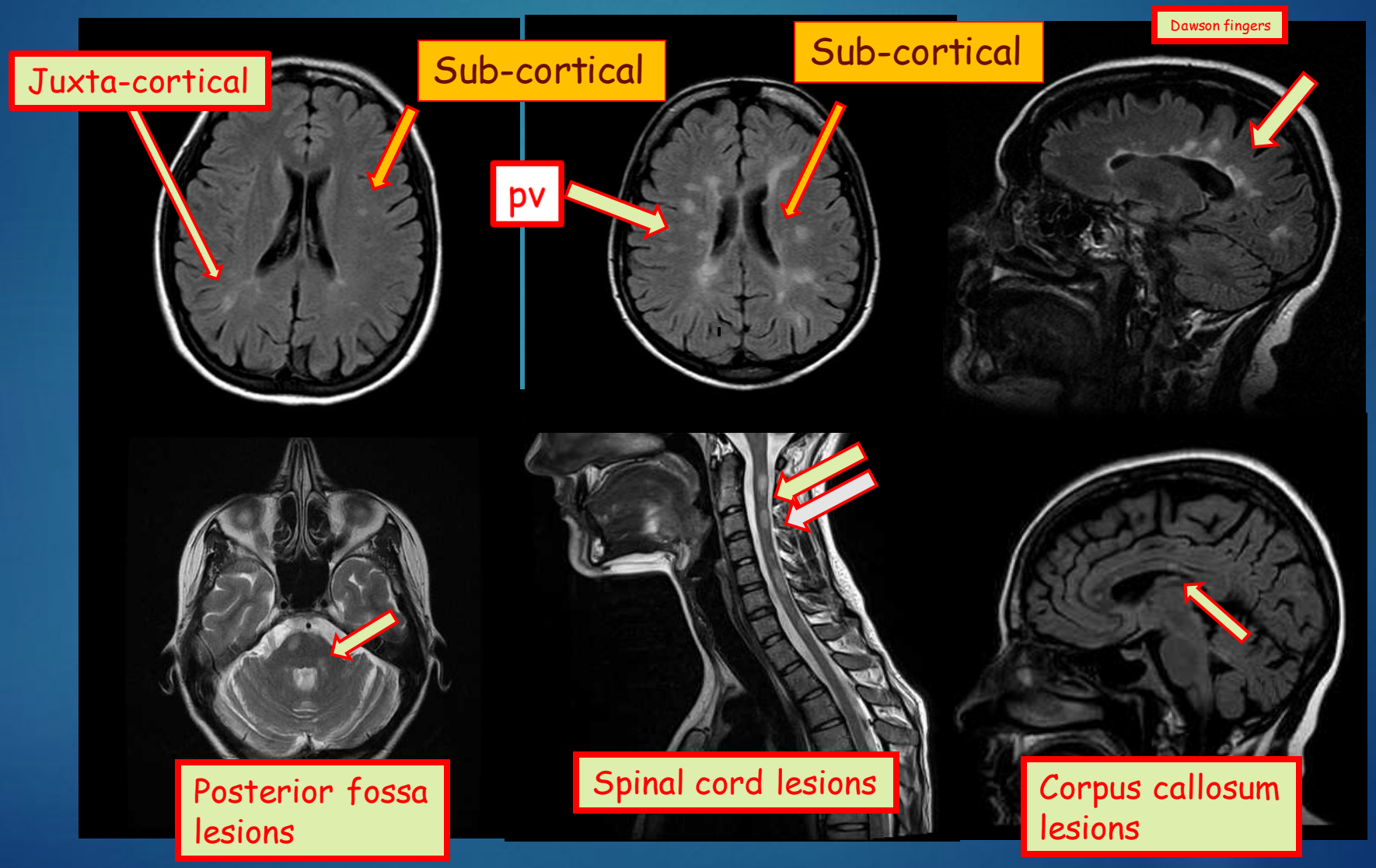


MRI- Typical MS



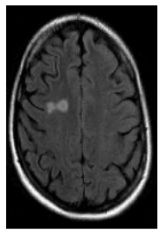
DIS by MRI Demonstrated by ≥ 1 T2 hyperintense lesions in ≥2 of the following CNS areas:	DIT by MRI Demonstrated by:
Periventricular	A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan
Juxtacortical or Cortical	Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time
Infratentorial	
Spinal cord	

Dissemination in Space

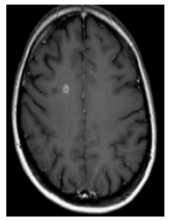


MS brain lesion characteristics

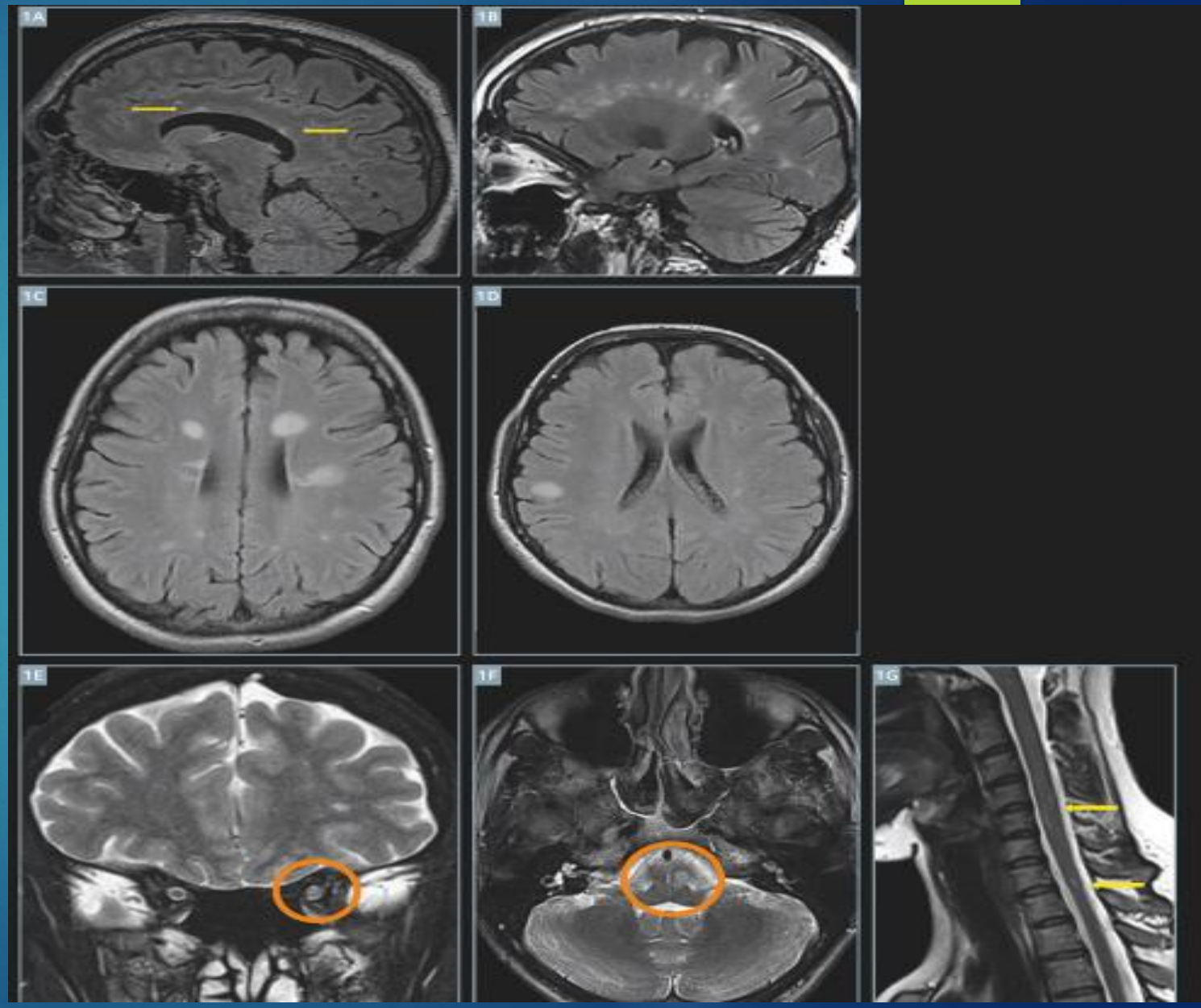
Lesion configuration	ovoid (round shape)
Size of lesions	> punctate
Typical lesion location	periventricular, juxtacortical, infratentorial
Lesion pattern	random, asymmetric
Tissue destruction	variable
Contrast enhancement	frequent



Inflammation / Active lesion



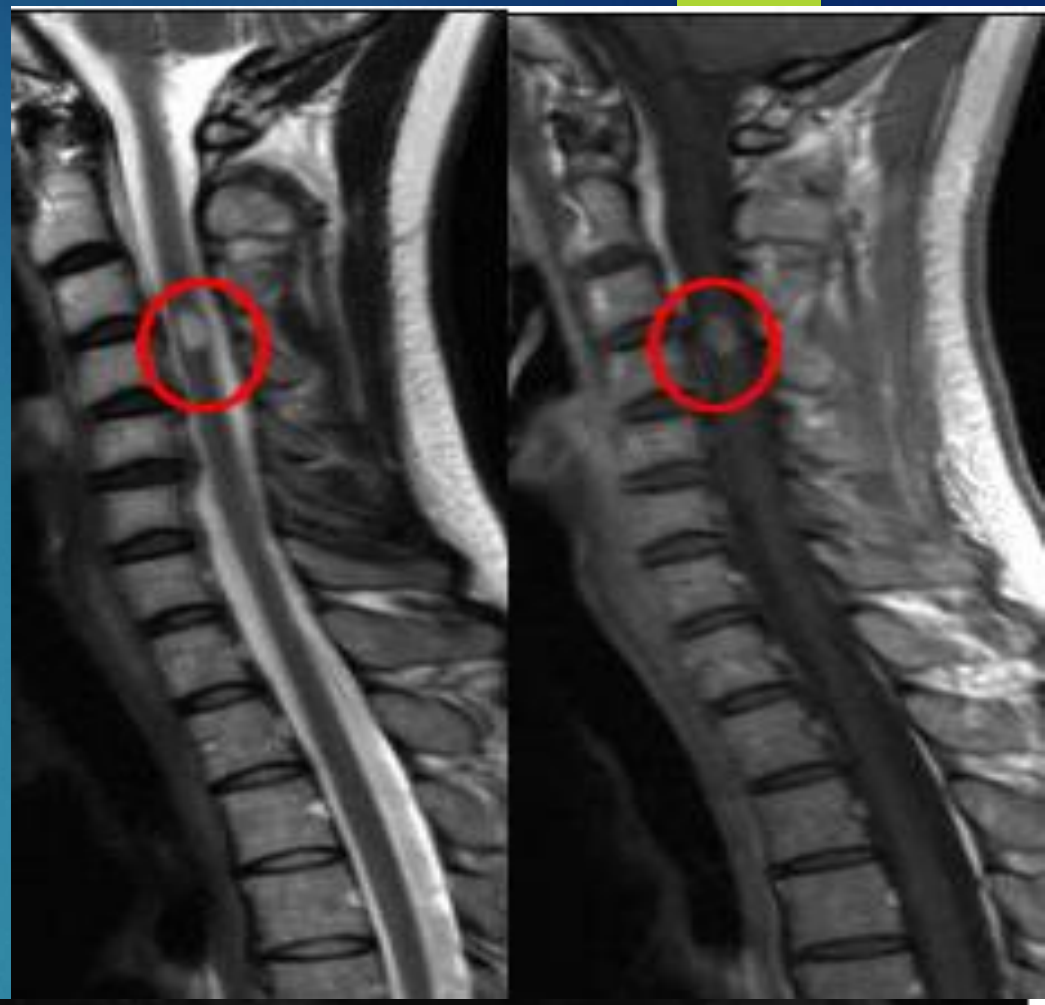
- Gadolinium enhancement indicates break down of blood brain barrier
- Active lesions enhance for 2 – 6 weeks
- Modification of enhancement by
  - Dosage of and delay after contrast material application
  - Imaging parameters
  - Steroid treatment

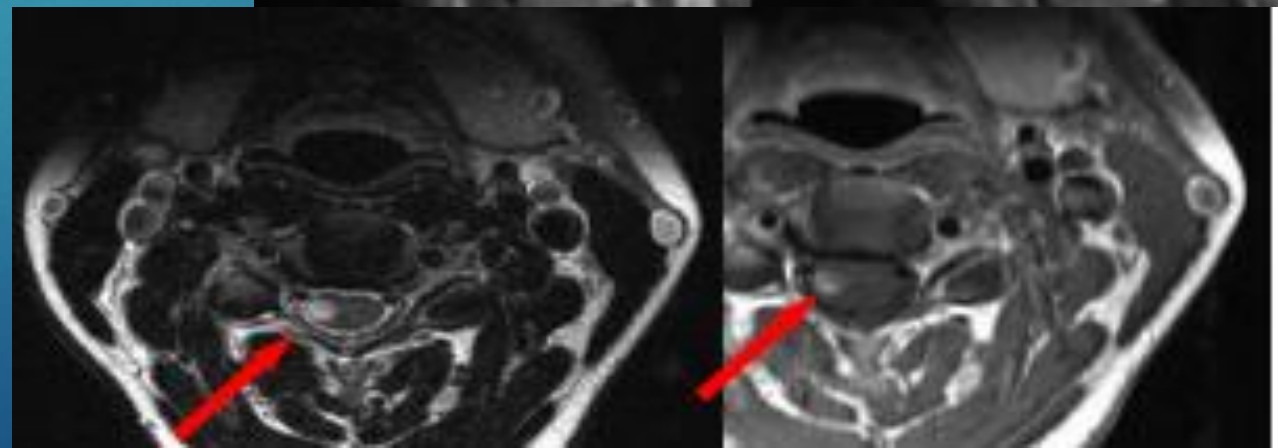


MS spinal cord lesion characteristics

- 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 of relapsing MS

- Systemic diseases complicated by CNS involvement that follow a relapsing-remitting course (eg, systemic vasculitis)
- Diseases of the brain and spinal cord confined to selected physiological systems and usually following a progressive course (eg, the hereditary cerebellar ataxias)
- Disorders affecting one anatomical site and with either a relapsing-remitting or progressive course (especially, tumours and other structural lesions)
- Monophasic disorders affecting many neuroantaomical sites (eg, acute disseminated encephalomyelitis)
- Non-organic symptoms that, intentionally or otherwise, mimic the clinical features of multiple sclerosis (so-called functional or somatisation disorders)

MS like MRI findings / disorder of non idiopathic inflammatory demyelinating etiology

- Age-related white matter changes
- Behcet disease
- Bacterial infections (syphilis, Lyme disease)
- Cerebral autosomal dominant arteriopathy, subcortical infarcts and leukoencephalopathy
- Cervical spondylosis or stenosis
- HIV infection
- Human T-lymphotrophic virus I/II
- Ischemic optic neuropathy (arteriitic and nonarteriitic)
- Leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
- Neoplasms (e.g., lymphoma, glioma, meningioma)
- Migraine
- Sarcoidosis
- Sjögren syndrome
- Stroke and ischemic cerebrovascular disease
- Systemic lupus erythematosus, antiphospholipid antibody syndromes and related collagen / vascular disorders
- Unidentified bright objects
- Vascular malformations
- Vasculitis (primary CNS or other)
- Vitamin B 12 deficiency

Frohman EM et al., Neurology 2004

2015 survey by the MS society in the UK of 1,500 people with MS

- Revealed many people are misdiagnosed and live in uncertainty for years before MS diagnosis.

  - 1 in 4 people with MS misdiagnosed with a "trapped" nerve

  - 1 in 10 people with MS told they'd had a stroke

  - 39% of people with MS waited over a year for diagnosis

  - 25% visit GP four or more times before referral to a neurologist

President of the Royal College of General Practitioners, said:

"MS is incredibly difficult to diagnose in primary care as many of the symptoms are similar to those of other, more common conditions – and some less obvious symptoms may not be disclosed by patients during consultation.

"It is also a relatively rare condition – 5,000 new cases diagnosed every year"

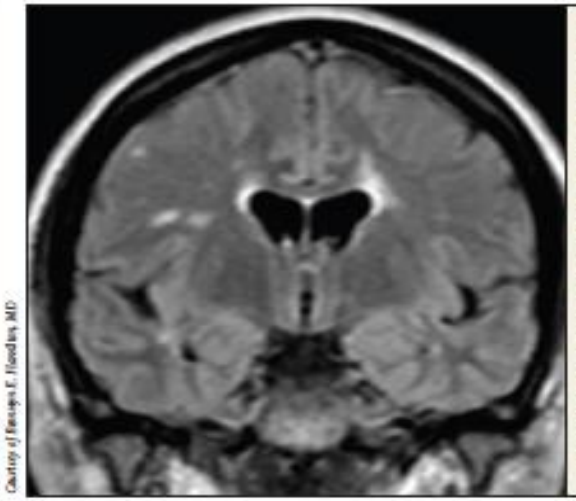
Migraine Patients Often Misdiagnosed with MS Based on Evidence of White Matter Hyperintensities

Study Points to Need for Multiple Criteria for Diagnosis

BY TOM VALEO

ARTICLE IN BRIEF

Investigators reported that 2.4-7.1 percent of 168 headache patients between the ages of 10 and 55 who displayed T2 white matter hyperintensities on a brain MRI met the inclusion criteria for the Barkhof criteria for multiple sclerosis, while 24.4-34.5 percent met the more liberal McDonald criteria.



Courtesy of Bronwyn E. Hamilton, MD

CORONAL FLAIR image in this 54-year-old female imaged for headaches shows many white matter hyperintensites that met that Barkhof and 2010 McDonald criteria for multiple sclerosis. However, her medical history revealed an extensive history of cerebrovascular disease risk factors included hypertension, tobacco abuse, hypercholesterolemia, and coronary artery disease, prior methamphetamine abuse, and a family history of migraines. Formal neurologic evaluation was not concerning for demyelinating disease.

Neurologists called upon to determine the significance of white matter hyperintensities (WMHs) found on a brain scan may over-diagnose multiple sclerosis (MS) if they rely excessively on two common references — the Barkhof and the 2010 McDonald criteria, which consider the "dissemination in space" of the lesions.

According to a new study in the July issue of the journal *Multiple Sclerosis*, 2.4-7.1 percent of 168 headache patients between the ages of 10 and 55 who displayed T2 WMHs on a brain MRI met the inclusion criteria for the Barkhof criteria, while 24.4-34.5 percent met the more liberal McDonald criteria. [See sidebar: "Age-modified Barkhof and McDonald Classification Scheme based on Definitions of Juxtacortical and Periventricular Lesions" for descriptions of the two criteria.]

Even after taking into account the fact that MS is found more often in headache patients, this rate of diagnosis was far above the .09 percent incidence of MS found in the general population, according to lead author Bronwyn E. Hamilton, MD, an assistant professor of neuroradiology at the Oregon Health and Sciences University in Portland.

Continued on page 29

Differential Diagnosis

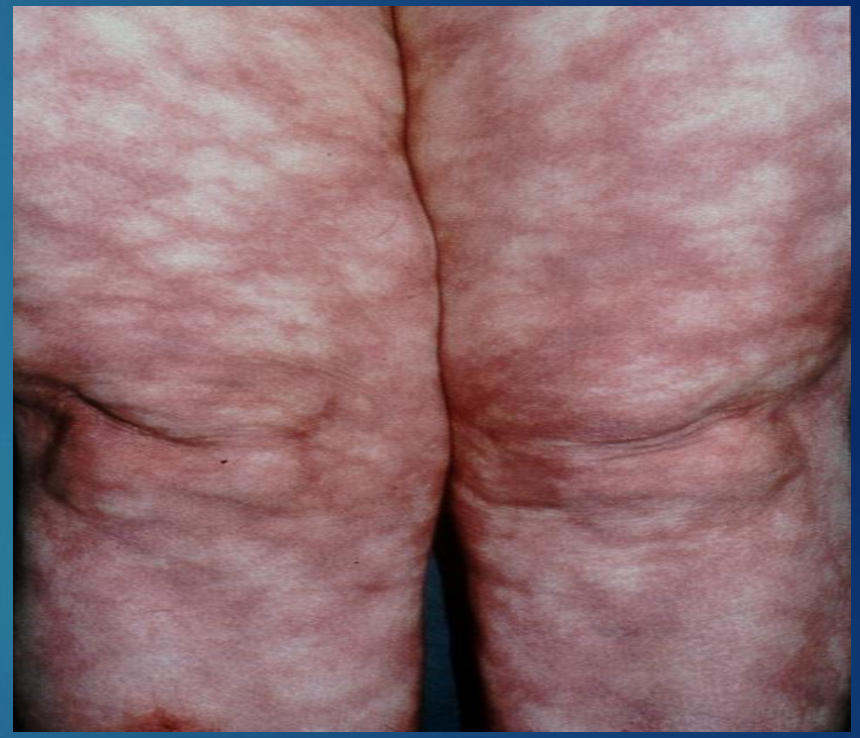
- MS is the most common primary demyelinating disease of the CNS, but other other primary demyelinating disorders should be considered

- Acute Disseminated Encephalomyelitis (ADEM)

- Neuromyelitis Optica /NMO spectrum disorder (Devic's disease)
- Myelin Oligodendrocyte Glycoprotein-associated Demyelination (MOGAD)

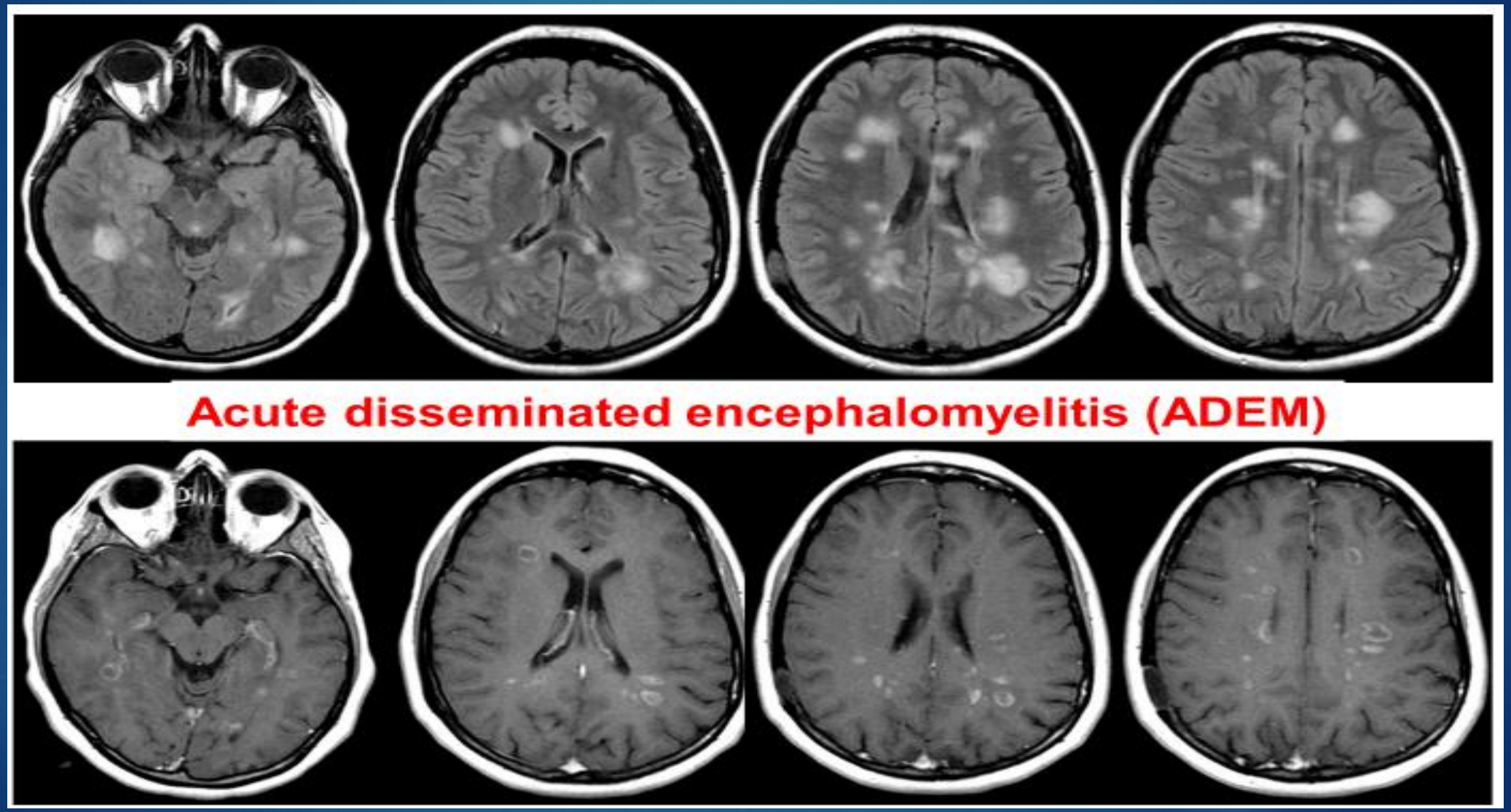
Demyelination Secondary to systemic diseases Ischemic/inflammatory…

- 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

ADEM

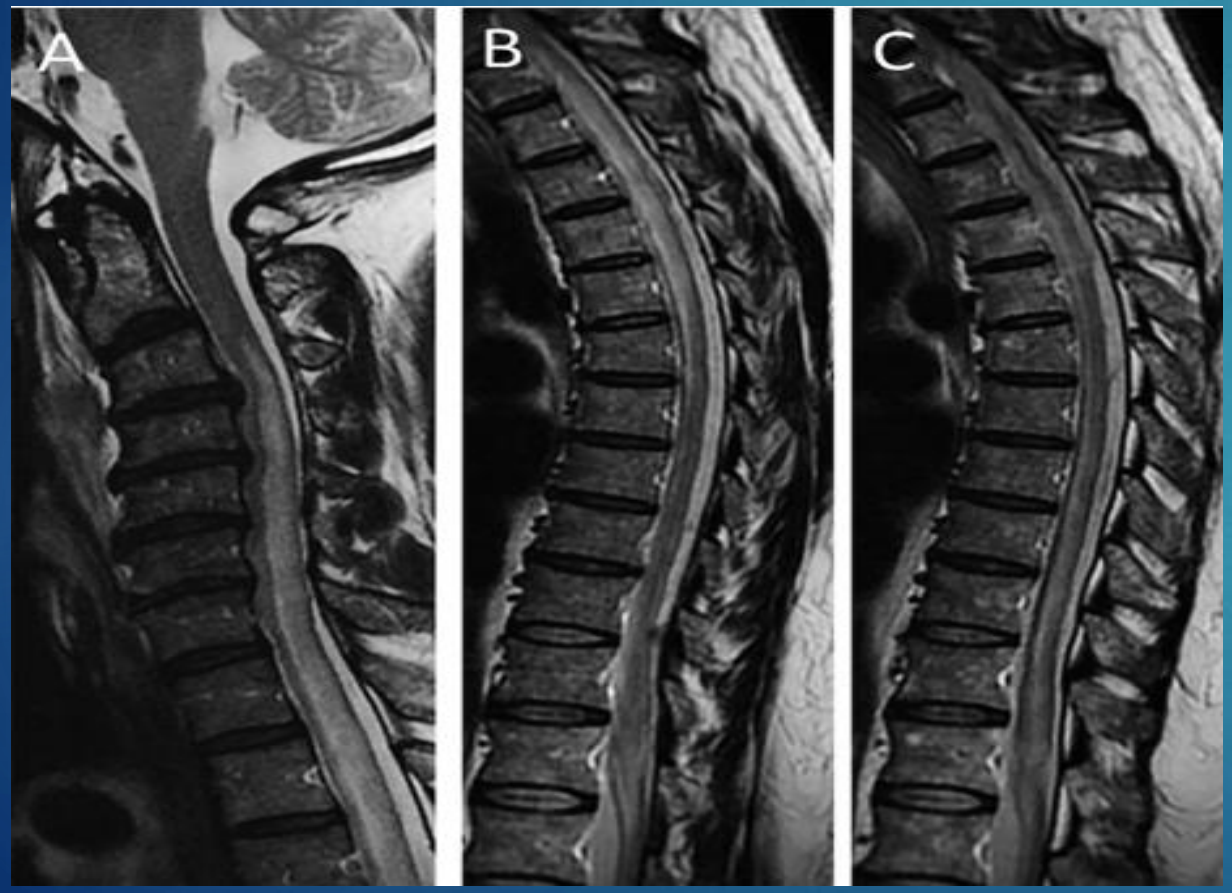


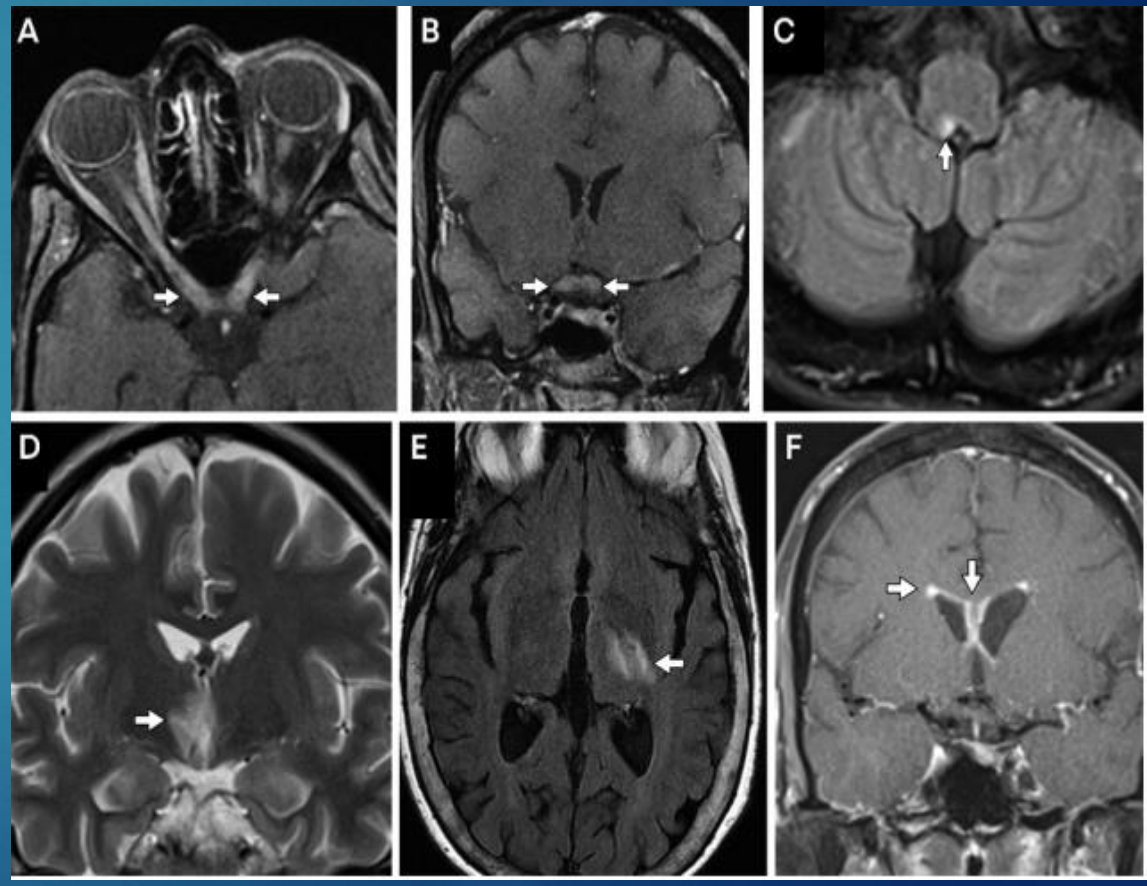
MS vs. NMOSD

- 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.

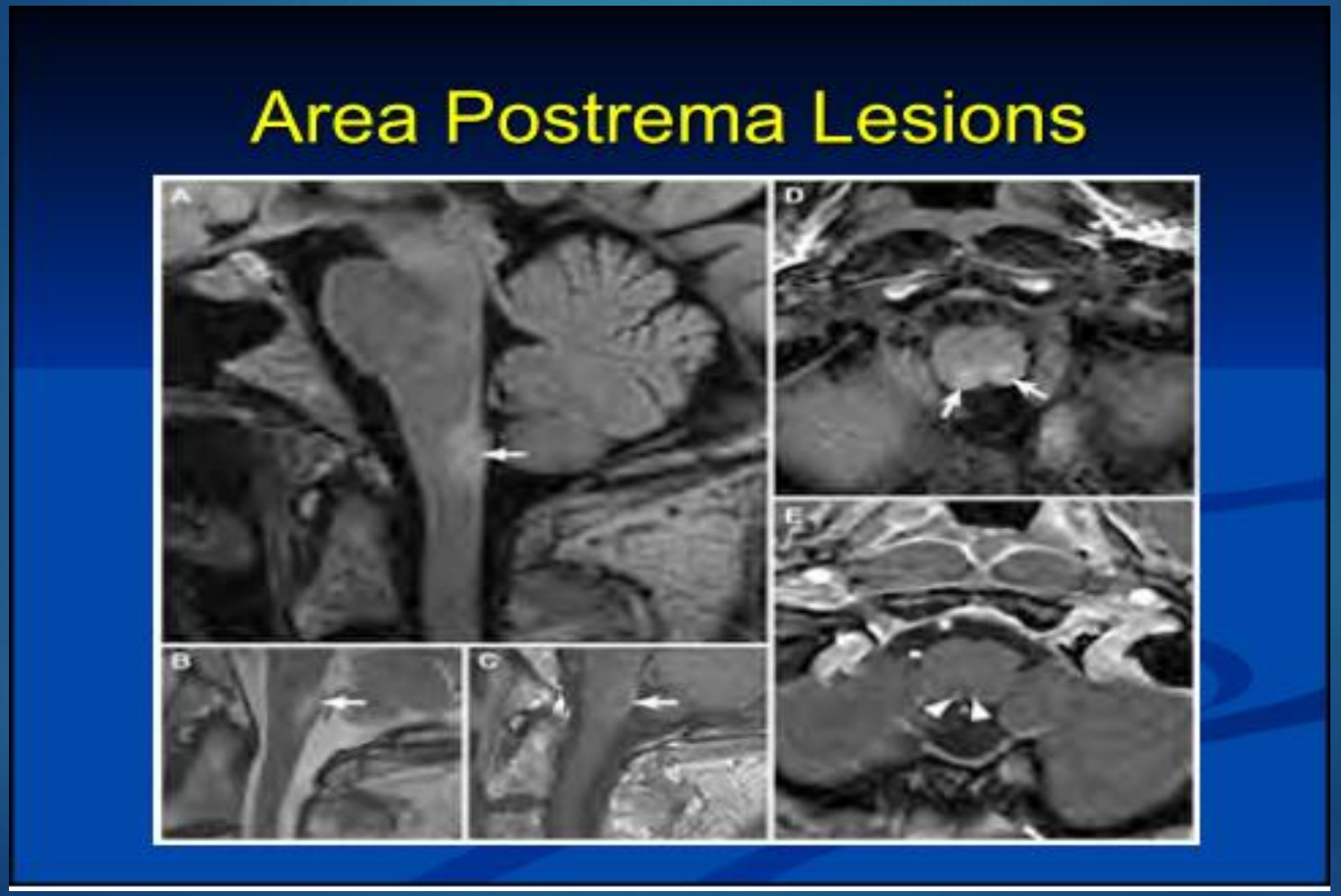
- Should also be considered in groups at higher risk of NMOSD (such as African American, Asian, Latin American, and pediatric populations).
- The treatments for MS and NMOSD are different (some MS treatments can exacerbate NMOSD).

NMOSD

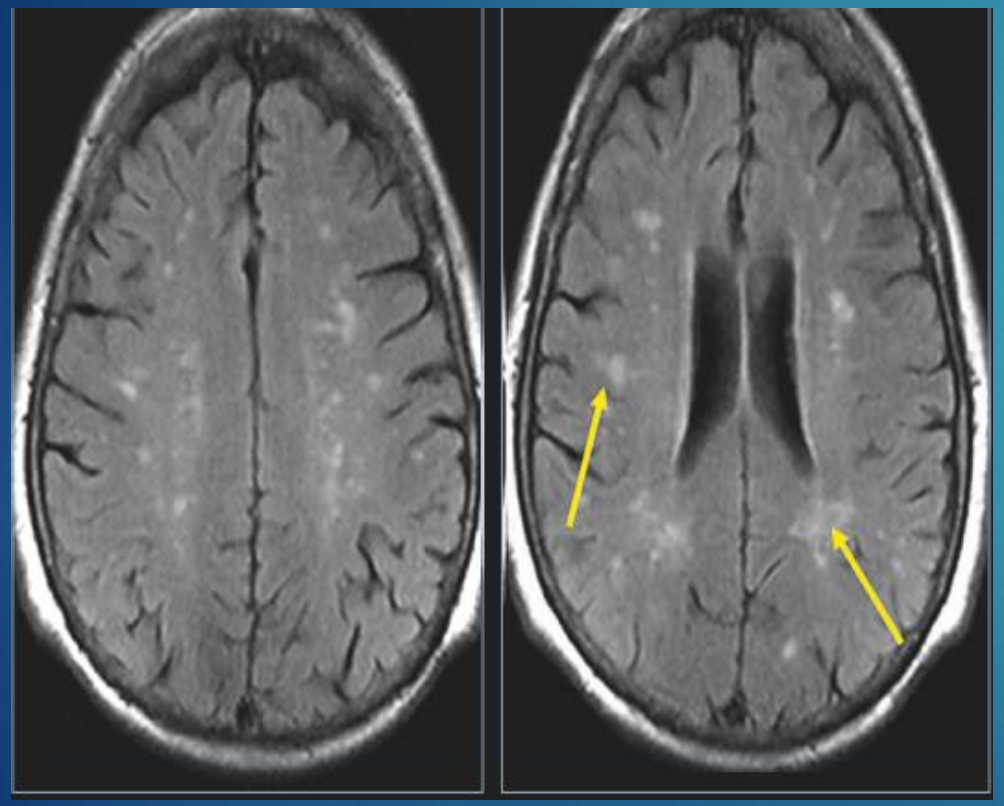




Typical of NMOSD-causes hiccups and vomiting

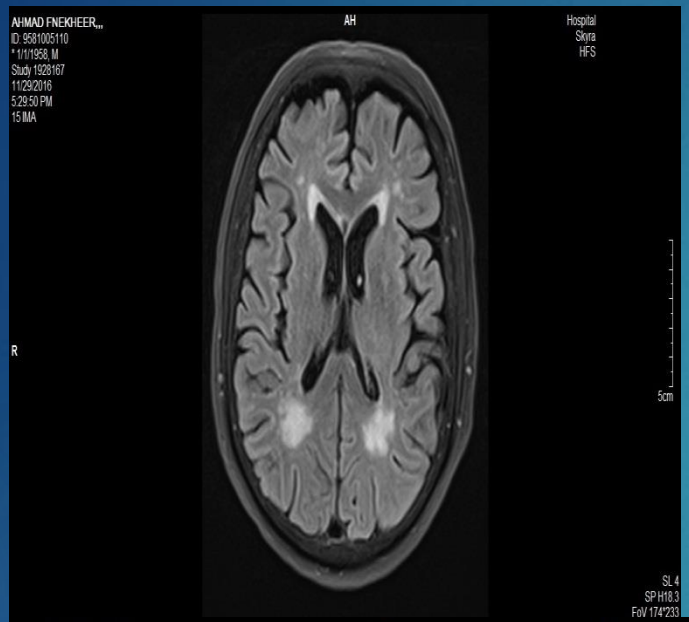


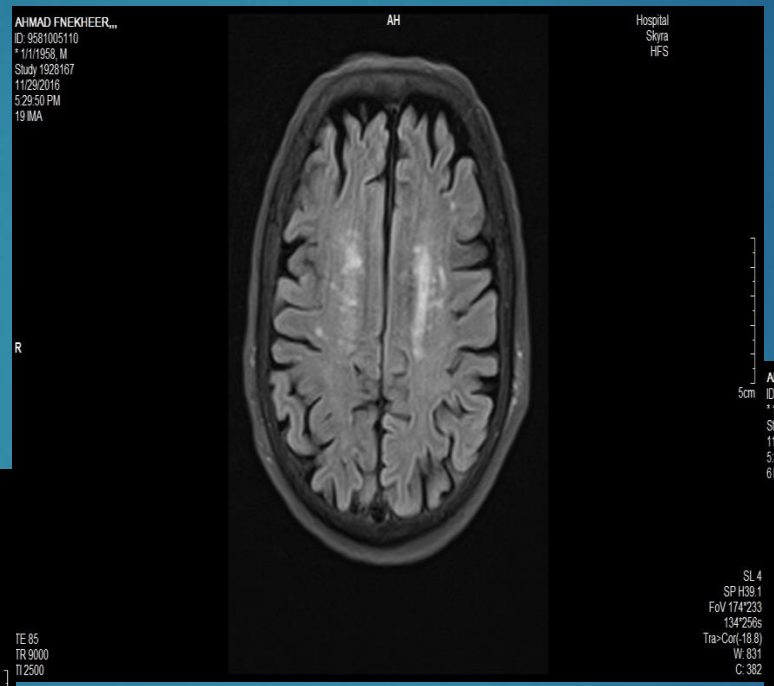
Normal aging phenomena

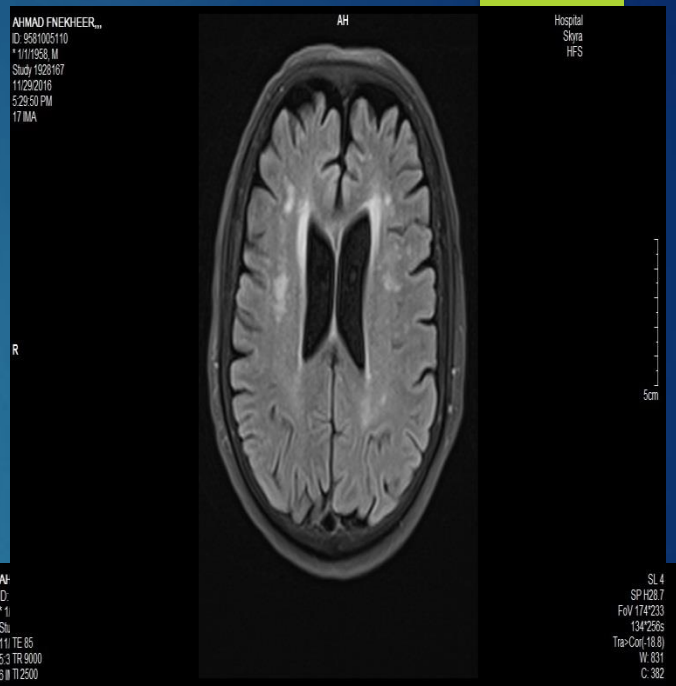


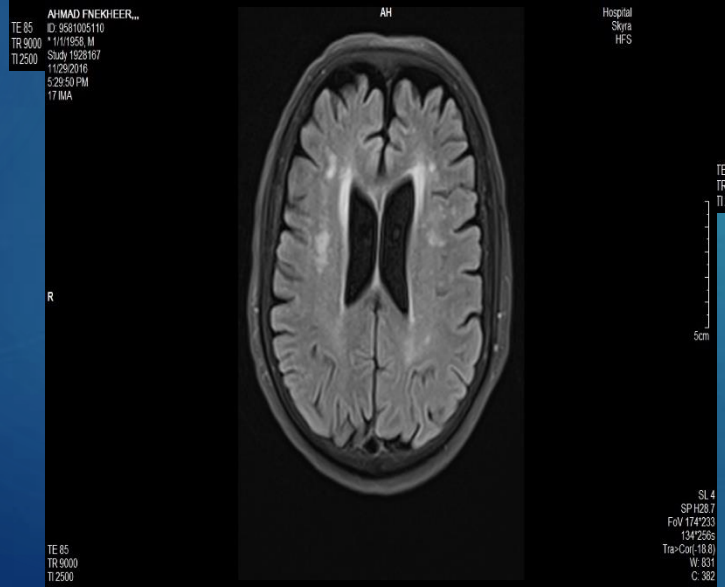
- Multifocal areas of T2 hyperintensity in the periventricular or deep white matter have been reported in around 35% of healthy individuals over the age of 60 years.
- Lesions may be small, multiple and punctuate or large and confluent.
- These non- specific, age-related, asymptomatic foci of ischemic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

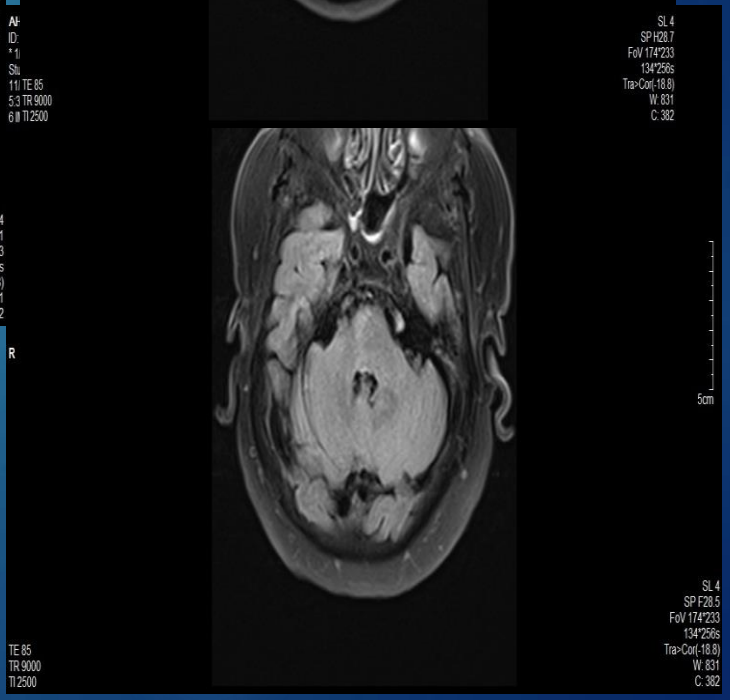
Small vessel disease





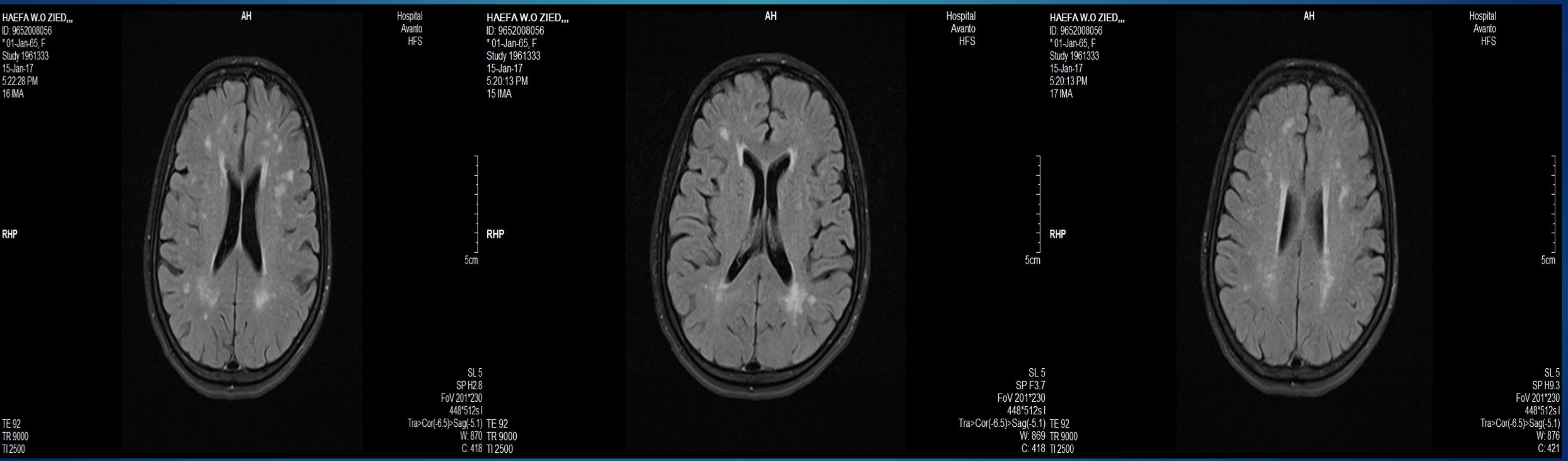




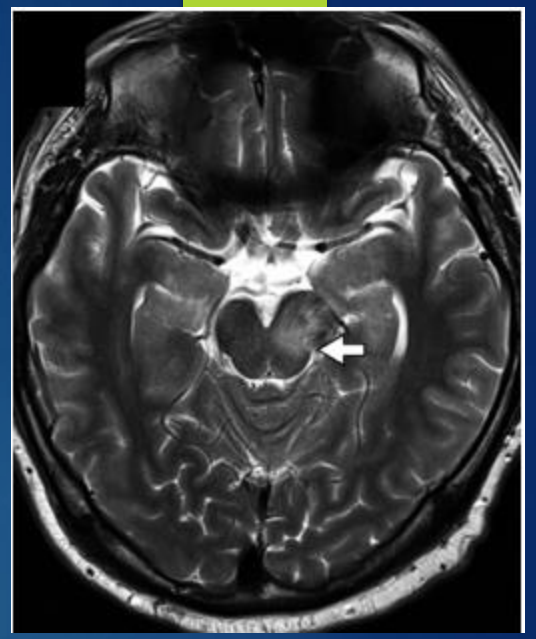


50 yr old lady seen last week with headache -2/12.
Arthralgia, dry mouth, ESR 80 mm/1st hr

? Sjogren's Disease with secondary CNS vasculitis

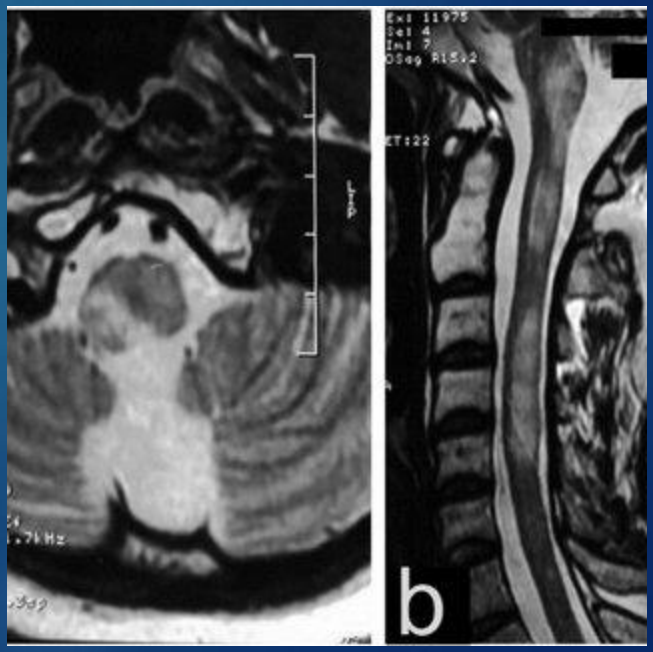


Behcet's Disease

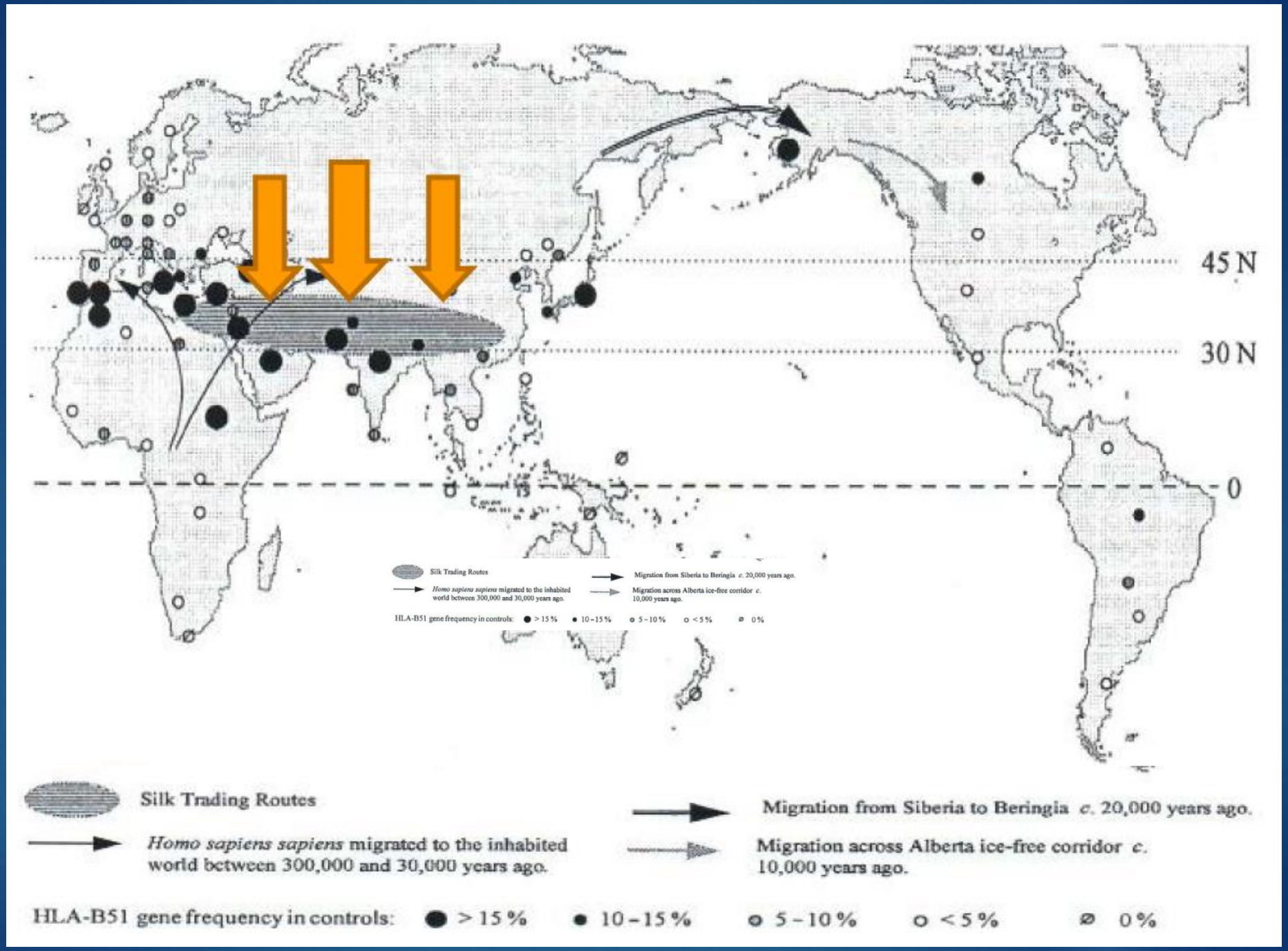


- A multi-system recurrent inflammatory disorder of unknown aetiology – strongly associated with HLA-B51 haplotype
- Variable vessel vasculitis (VVV)
- Can affect vessels of any size (small, medium, and large)
- Any type (arteries, veins, and capillaries).

Hulusi Behcet
1889-1948



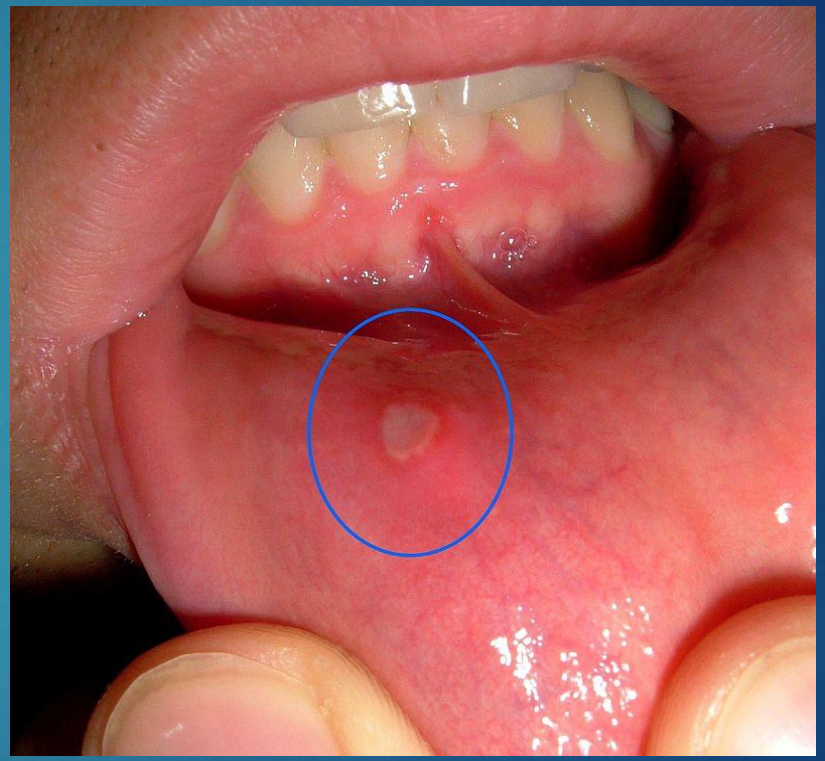
- Also called the "Silk Road Disease"


45 N
30 N
0
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

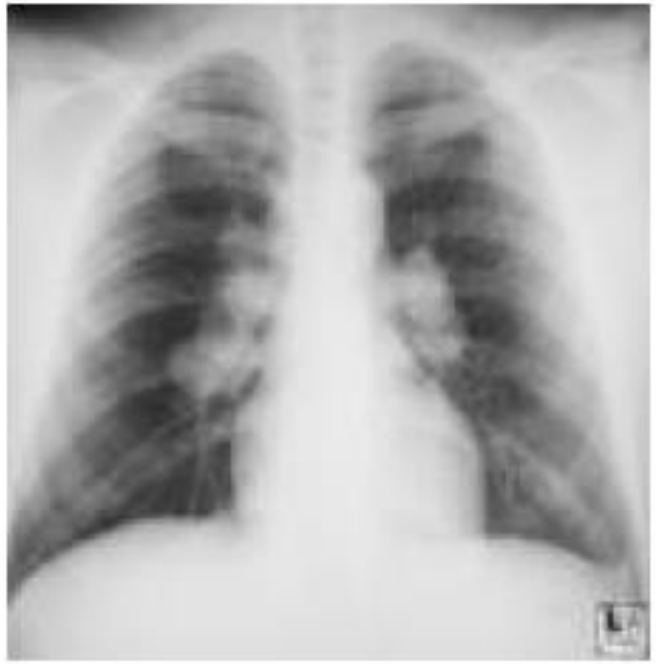
*Adapted from Yazici et al,[4] with permission from Nature Publishing Group.

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

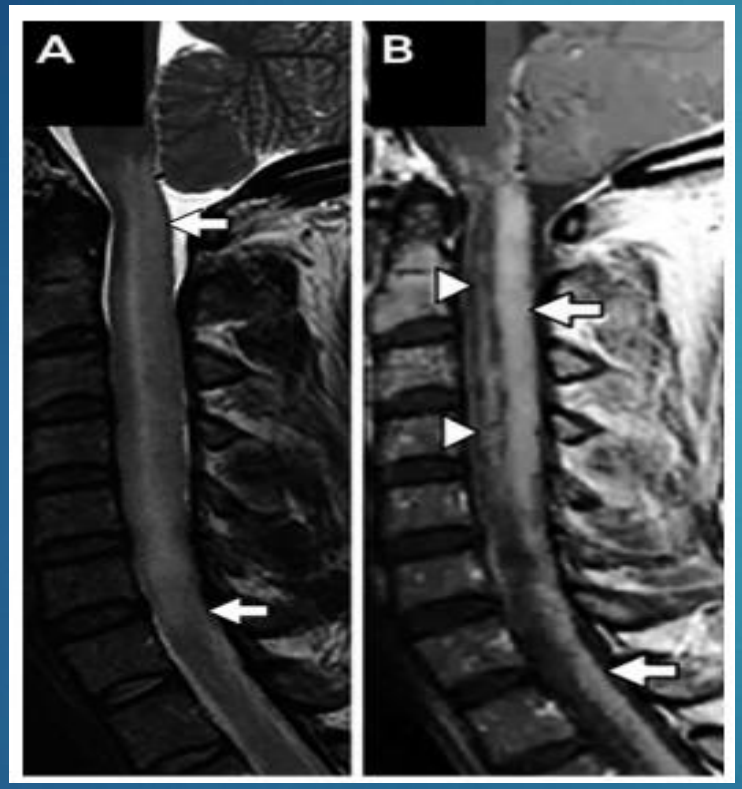


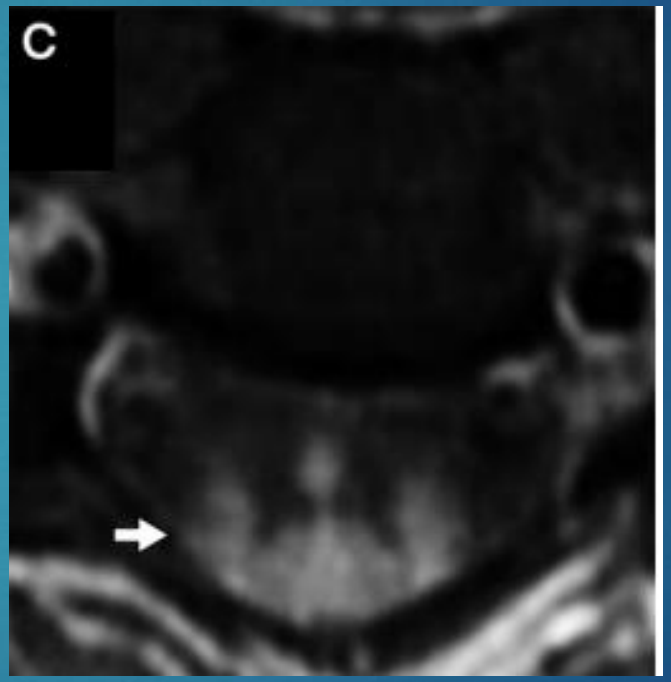
SYSTEMIC SARCOIDOSIS

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



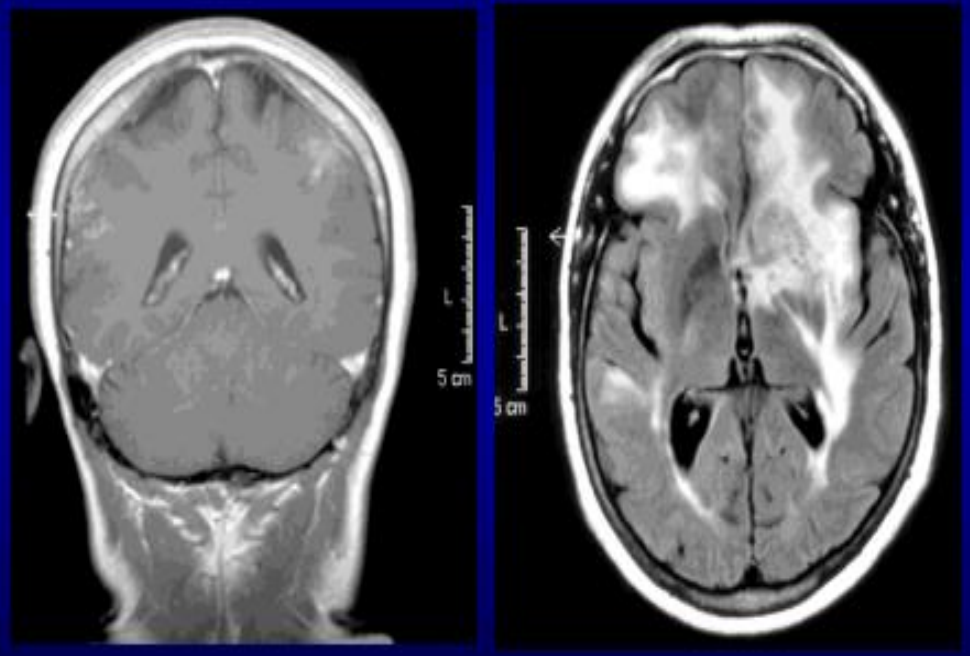
Neurosarcoidosis



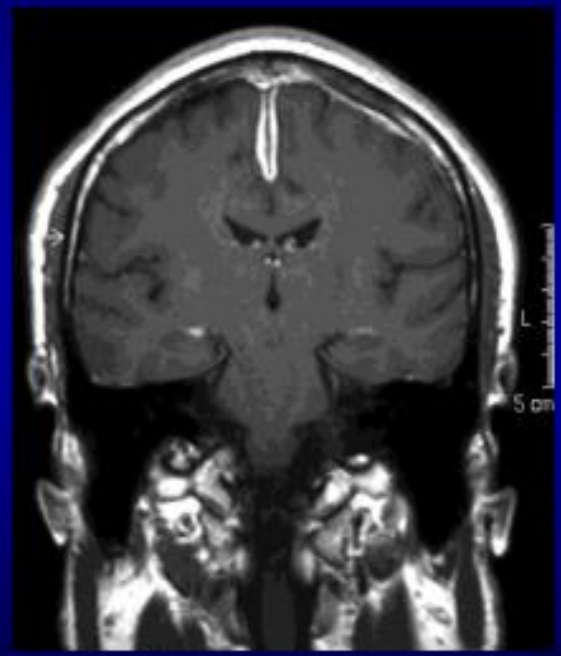


Neurosarcoidosis

Meningoencephalitis

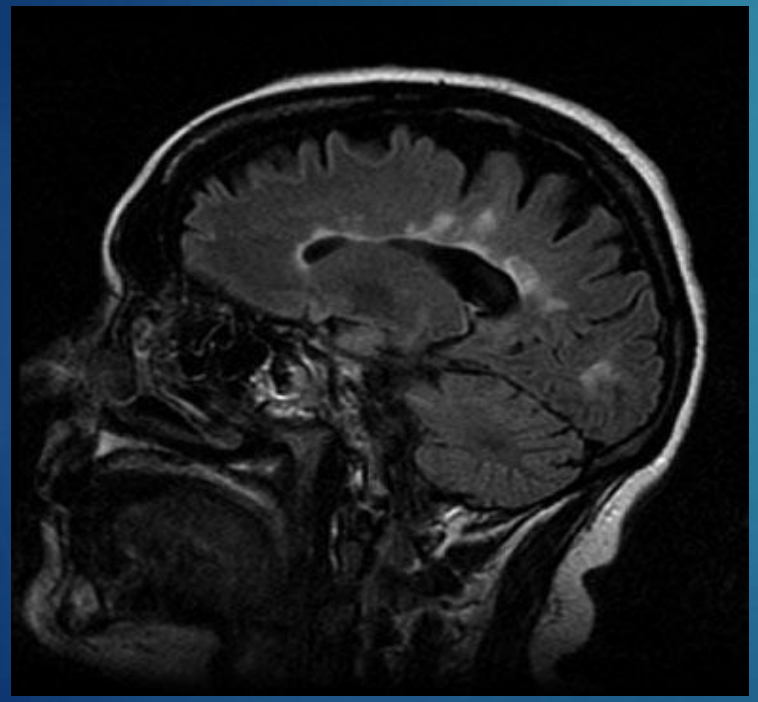


Pachymeningitis

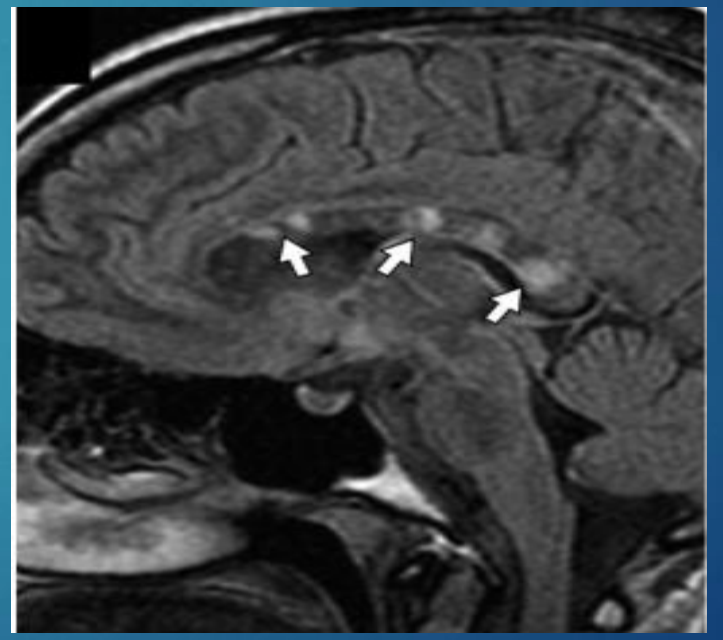


Susac’s Encephalopathy (confusion,deafness,visual problems)

MS



Susac’s



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

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

Life-style modifications

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)

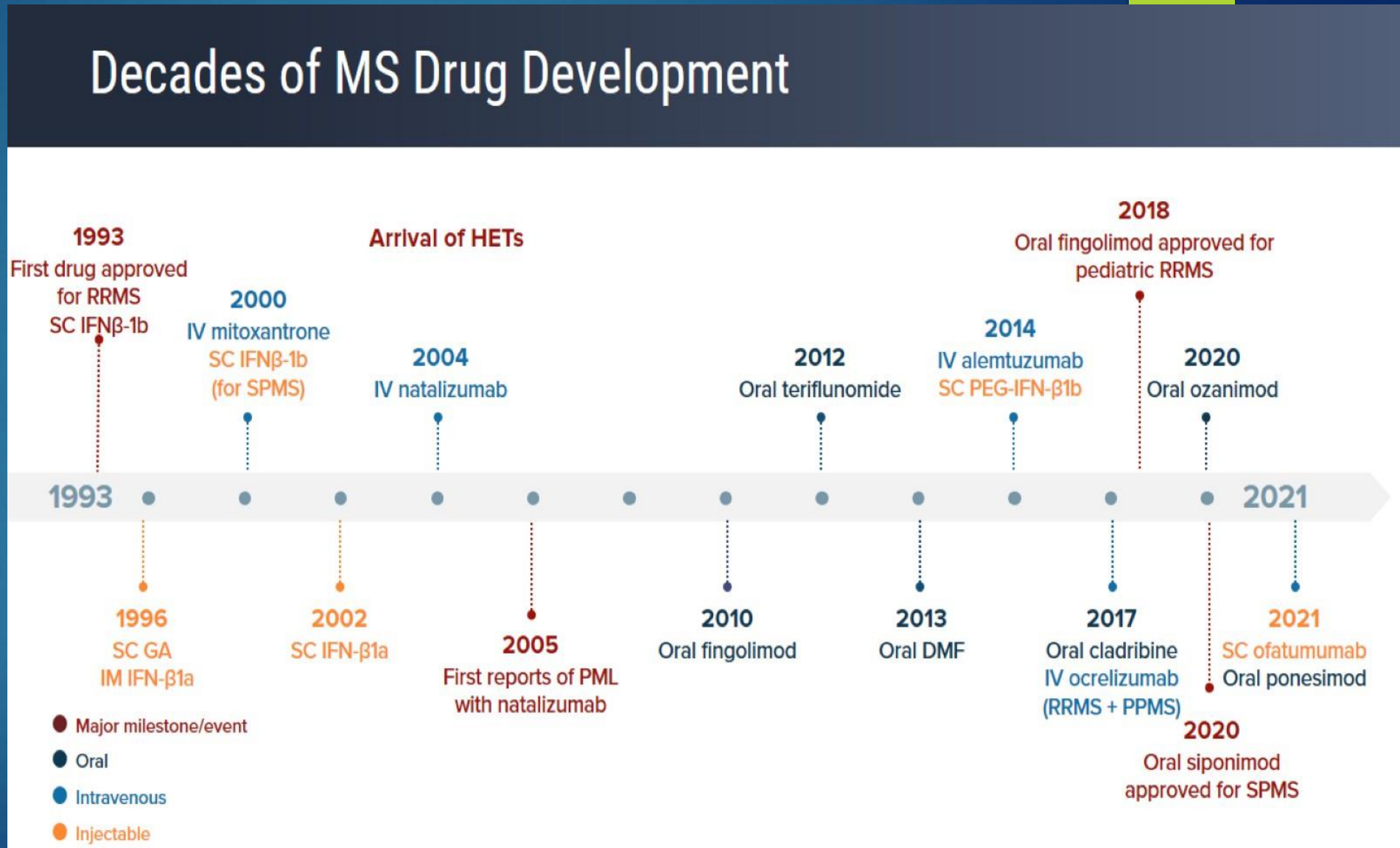
Relapse treatment

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 DMD

- The available treatment arsenal now contains up to 18 drugs



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.

Proposed MoA: Pleiotropic effects

IFNs → Activation of 100+ IFN-response genes → Modulation of Th1:Th2 balance

Glatiramer acetate → Modulation of Th1:Th2 balance

Dimethyl fumarate → Activation of 700+ Nrf2 responsive genes and HC-AR2

Proposed MoA: Targeted cell depletion

Alemtuzumab

Lysis of mature B and T cells

Cladribine Tablets

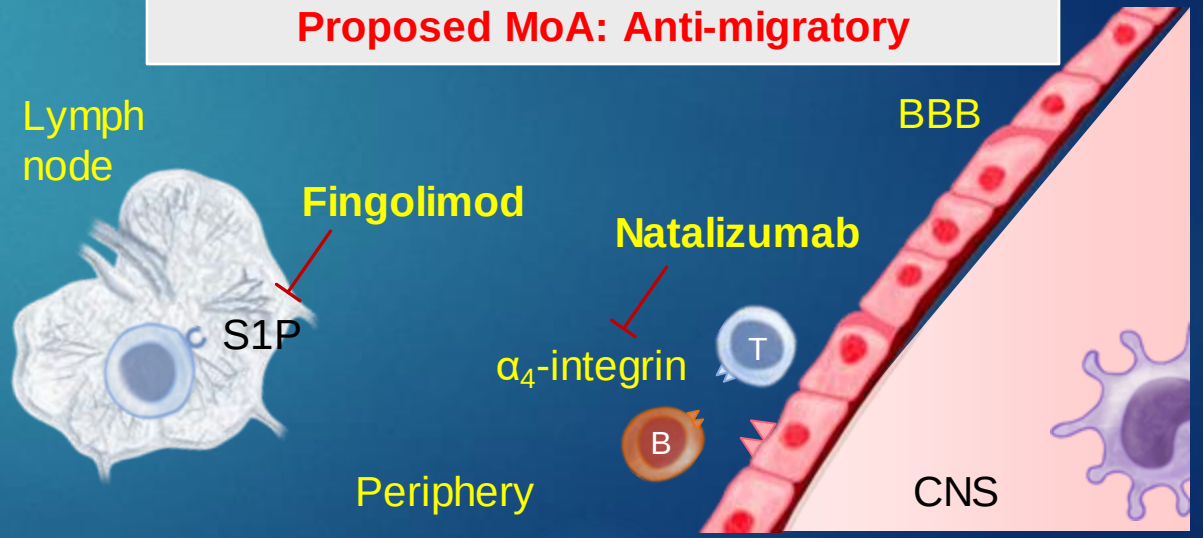
Ocrelizumab

Proposed MoA: Reduced proliferation

Teriflunomide ⊣ Limits pyrimidine availability for rapid cell division

Topoisomerase inhibitor ⊣ **Mitoxantrone**

Proposed MoA: Anti-migratory



S1P= Sphingosine-1 Phosphate

Goals of Treatment in MS

Benefit-Risk of Treatment Choice in MS

Safety/Risks

Reversibility

Long-term Safety

Tolerability

Efficacy

Relapses

Disability Progression

Freedom from MRI Activity

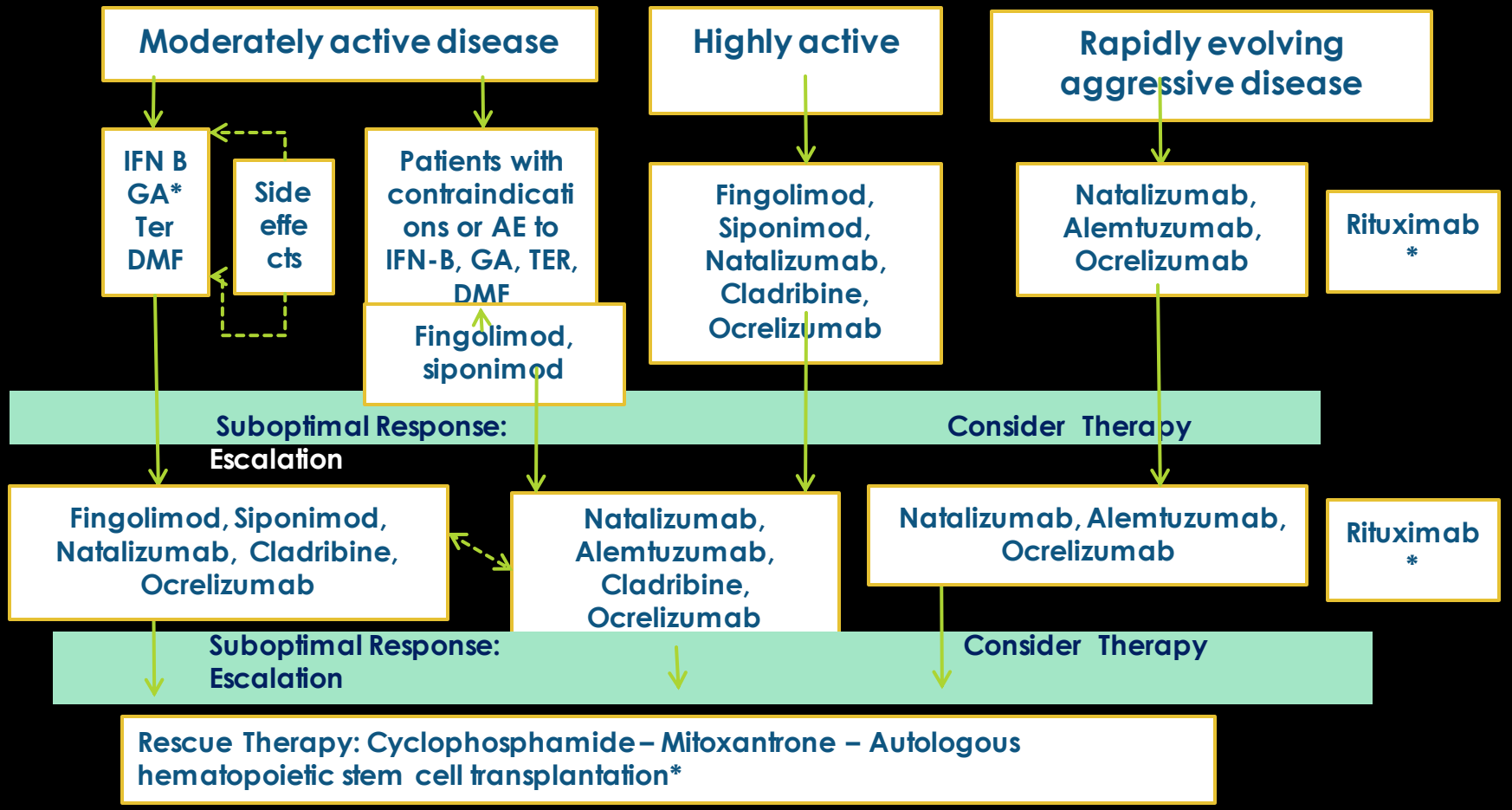
Adherence Potential

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	

MENACTRIMS Algorithm for treatment of RRMS



*Off label use

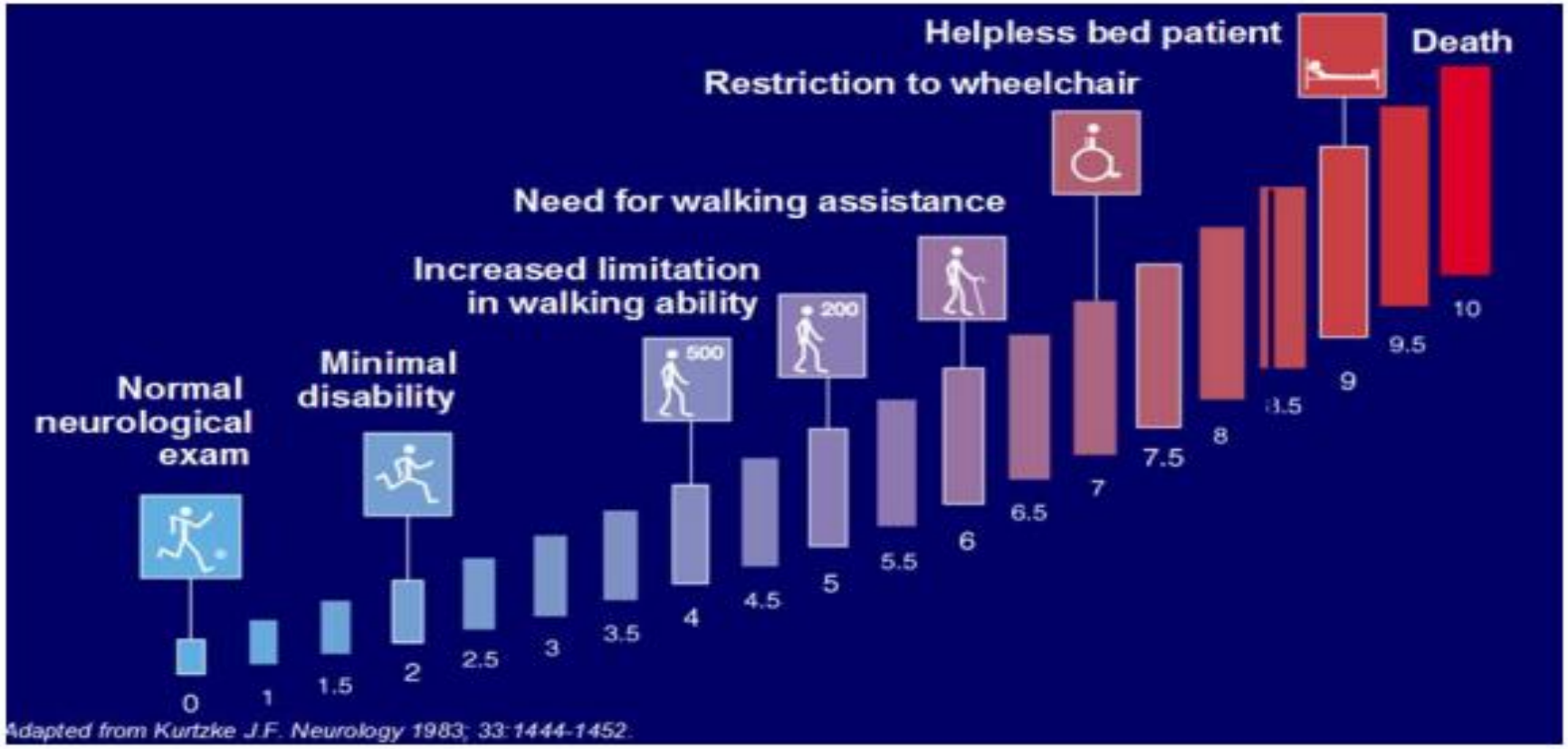
Accumulation of disability

- Disability in MS can occur because of
  - residual symptoms after a relapse , or
  - disease progression independent of a relapse (Progressive disease)

- Disability may relate to symptoms that are easy for others to see and measure (eg, ambulatory dysfunction), but much disability in MS is due to "silent symptoms," including fatigue, sensory disturbances/pain, depression/anxiety, and cognitive dysfunction.

- Relapsing MS does not have a major impact on life expectancy, so patients often live for many years with MS, during which they usually sustain significant neurologic disability.

Expanded Disability Status Scale (EDSS)

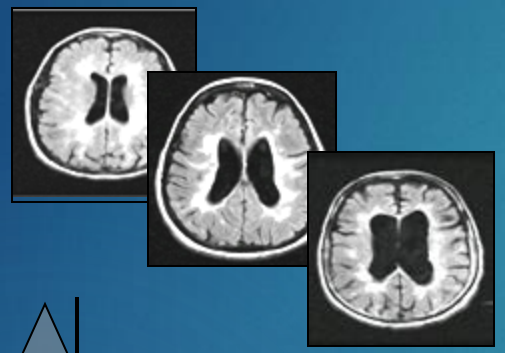


Progression from EDSS 0-4 (inflammatory phase): 1-32 years

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

Adverse Effects of HETs

DMT[a]	Key AEs
Natalizumab	Infusion-related reactions, PML
Fingolimod	Bradycardia (first dose), HT, bronchospasm, lymphopenia, opportunistic/ infections, BCC, lymphoma, macular edema, elevated LFTs
Siponimod	HT, bronchospasm, lymphopenia, opportunistic/infections, BCC, lymphoma, macular edema, elevated LFTs
Ozanimod	Bradycardia (first dose), HT, bronchospasm, lymphopenia, opportunistic/ infections, BCC, lymphoma, macular edema, elevated LFTs, PRES
Ponesimod[b]	Nasopharyngitis, elevated LFTs, HT, URTIs
Ocrelizumab	Infusion-related reactions, opportunistic/infections, hypogammaglobulinemia (prolonged use)
Ofatumumab	Infusion-related reactions, opportunistic/infections, hypogammaglobulinemia (prolonged use)
Alemtuzumab	Infusion-related reactions, opportunistic/infections, secondary autoimmunity (thyroid and others)
Cladribine tablets	Herpes reactivation (zoster)

a. Schmierer K, et al. *Curr Opin Neurol*. 2021;34:286-294; b. Ponvory™ (ponesimod) [PI]. EMA. June 2, 2021.

Summary of Main AEs

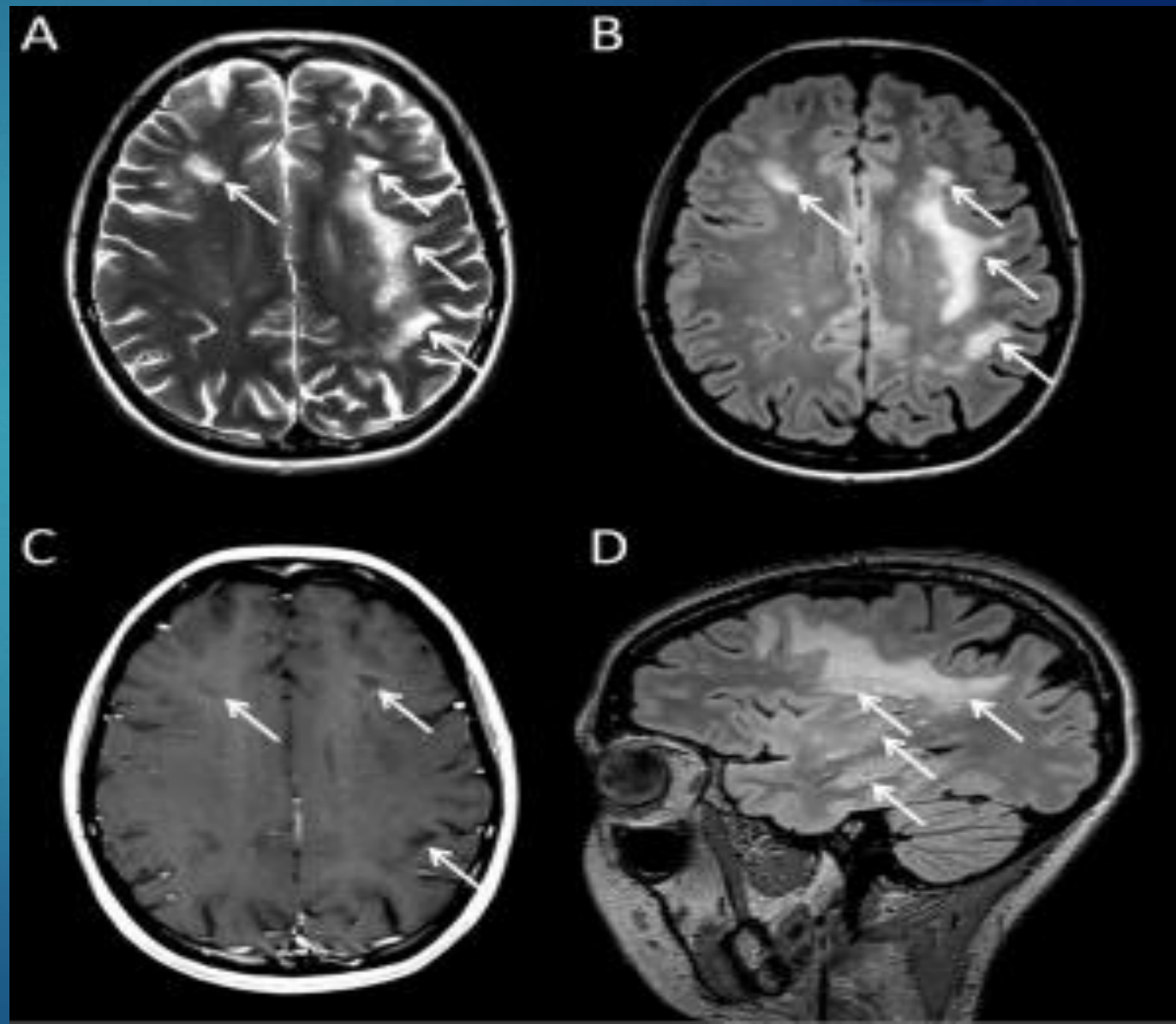
- Infusion reactions
- Infections
  - Opportunistic
  - Reactivation
- Cardiac effects
- Malignancies
- Secondary autoimmunity

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



Progressive MS

Diagnosing Progressive MS

2010 McDonald Criteria for Diagnosis of MS in Disease With Progression From Onset[1]

PPMS may be diagnosed in subjects with:

- One year of disease progression (retrospectively or prospectively determined)

Plus 2 or 3 of the following[a]:

- Evidence for DIS in the brain based on ≥1 T2[b] lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
- Evidence for DIS in the spinal cord based on ≥2 T2[b] lesions in the cord
- Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

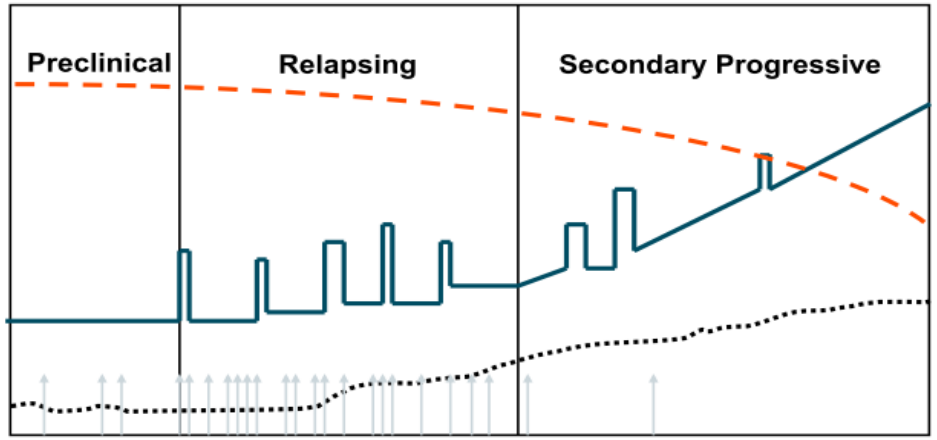
Currently, No Consensus on Diagnostic Criteria for SPMS, However…

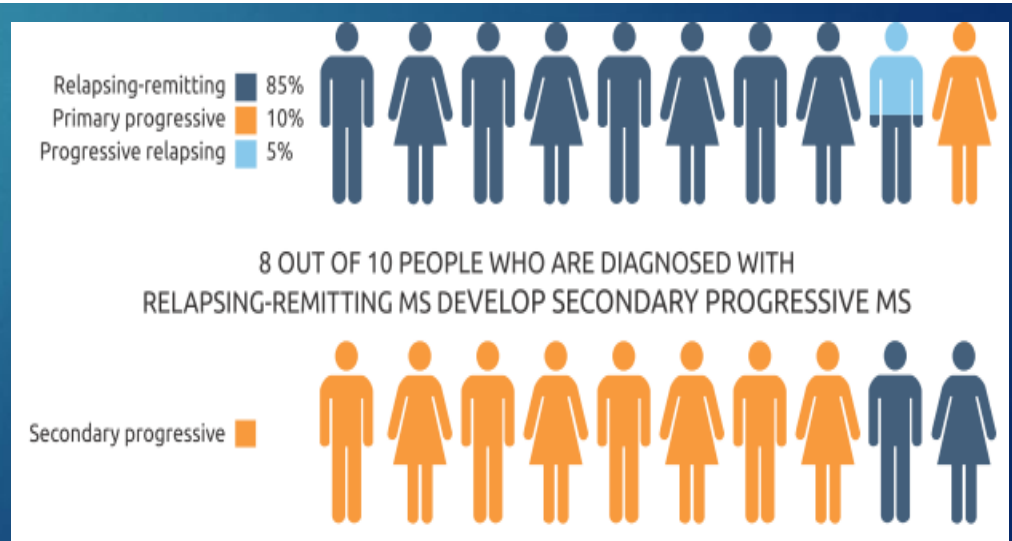
SPMS may be suspected in subjects with[2]:

- Change from baseline on neurological exam without evidence of ongoing relapses[2]

[a] If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria.
[b] Gadolinium enhancement of lesions is not required.

Natural History of MS





Diagnosis of SPMS

- **The different phases of MS commonly overlap.**
- **the unpredictable period of this overlap and the fact that relapses differ significantly in their duration make it difficult to mark the transition from relapsing–remitting disease to secondary progressive MS, and this is commonly done only in retrospect.**
- **At least 80% of MS patients develop secondary progressive disease within 25 yrs.**

Primary Progressive Multiple Sclerosis (PPMS)

- The mean age of onset is older than RRMS (~40 yrs vs. ~30 yrs - similar to the average age of onset of secondary progression in those with relapse onset disease), and it is almost never seen in childhood

- Interestingly, PPMS appears to exhibit only the slightest gender bias (1.2 to 1) unlike the 2.5:1 female to male predominance of MS overall

- PPMS most commonly presents with a spinal syndrome, a spastic paraparesis usually with no clear sensory level (80–85% of cases). Some 10–15% present with progressive cerebellar ataxia, and a smaller number with cognitive, other brainstem or visual symptoms.

The differential diagnosis of PPMS

- Degenerative
  - MND
  - Structural (c. spine/Chiari)
- Hereditary
  - HSP—SCAs
  - Leukodystrophies (AMN, Krabbe's), PKU
- Metabolic
  - Vitamins B12, E
  - Copper
  - Hypothyroidism
  - Toxic—phenytoin, lathyrism, nitric oxide
  - Alcohol
- Infective/Inflammatory
  - HIV
  - Syphilis
  - Prions
  - Vasculitis, sarcoid, lupus
  - Schistosomiasis, Brucellosis
- Neoplastic (paraneoplasia)
- Idiopathic/cryptic

Treatment of the Progressive stage of MS

- Treatment of progressive MS is very difficult and patients usually continue to deteriorate !

  - Siponimod is licensed for SPMS

  - Ocrelizumab is licensed for PPMS

- Treatment is focused on symptomatic therapy and rehabilitation

Good Luck !