

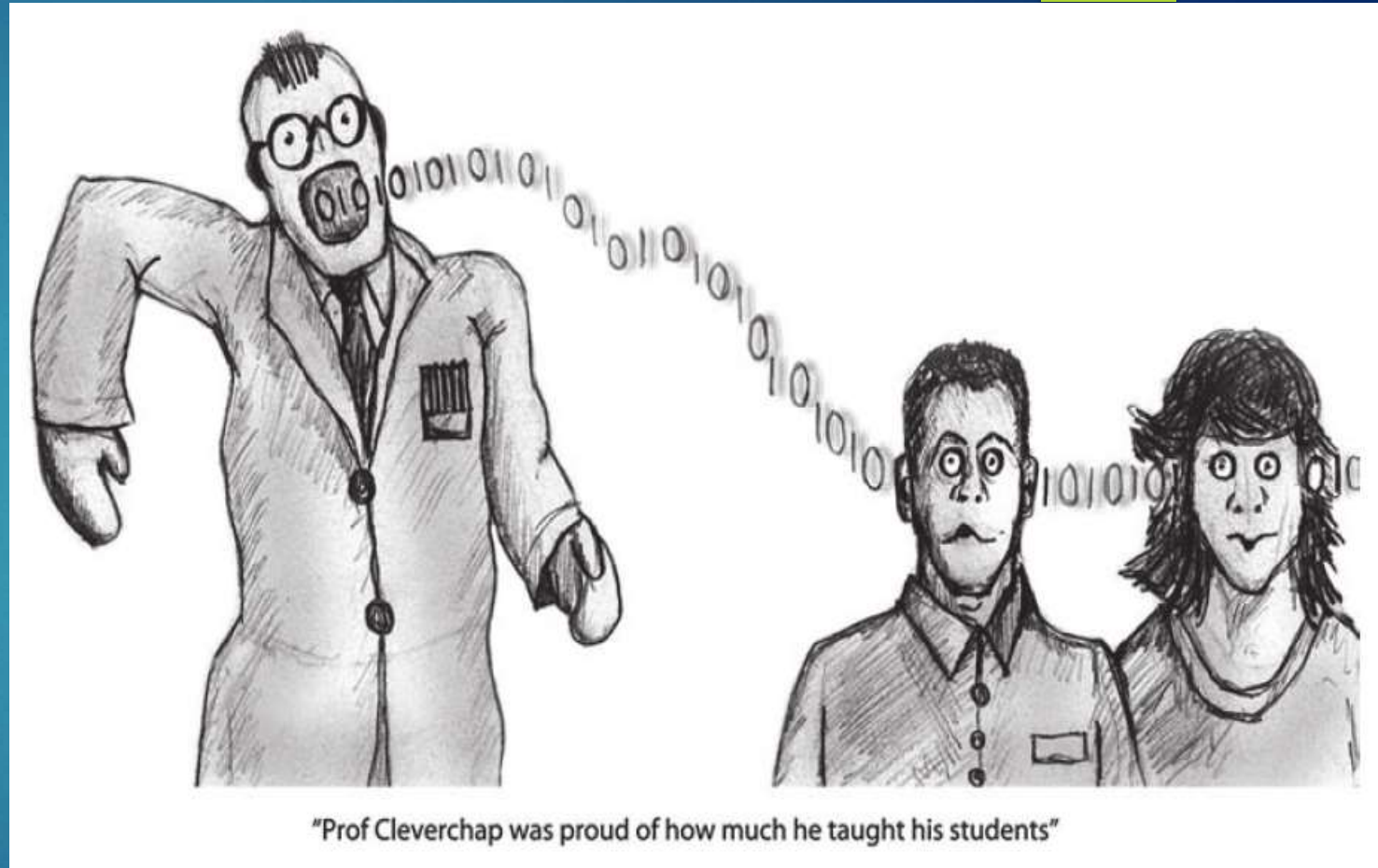


Multiple Sclerosis and related disorders

Dr Majed Habahbeh FRCP FRCS

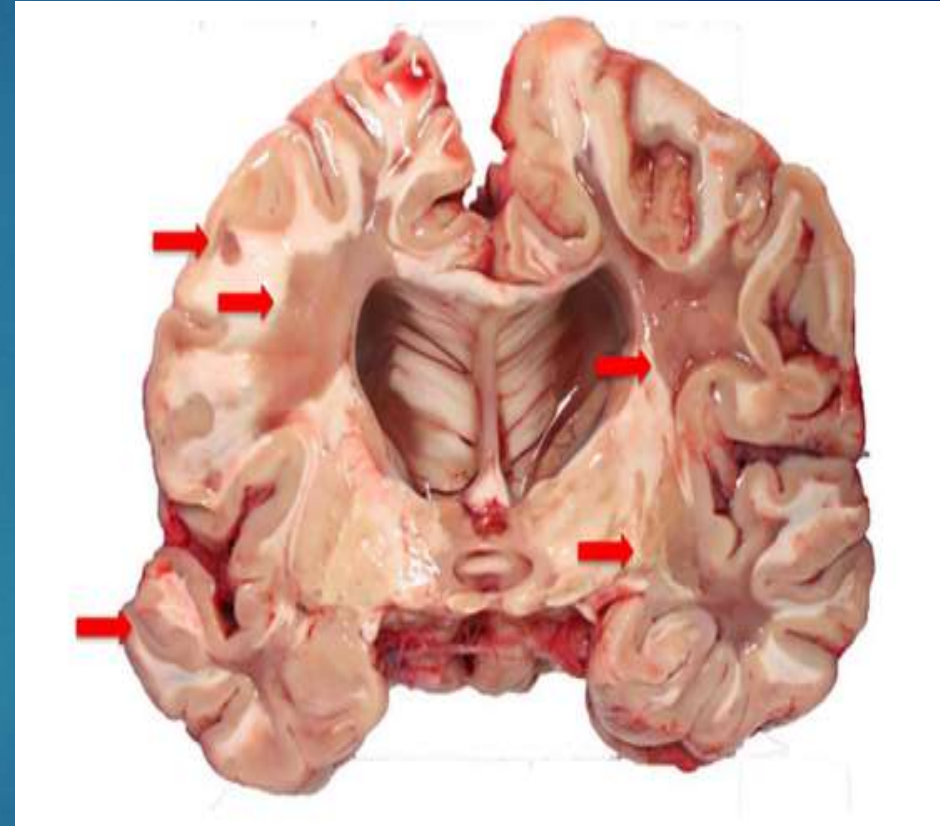
Multiple Sclerosis

- ▶ Pathology
- ▶ Pathogenesis
- ▶ Epidemiology/Etiology
- ▶ Clinical course and stages
- ▶ Diagnosis/ Differential diagnosis
- ▶ Management/Prognosis



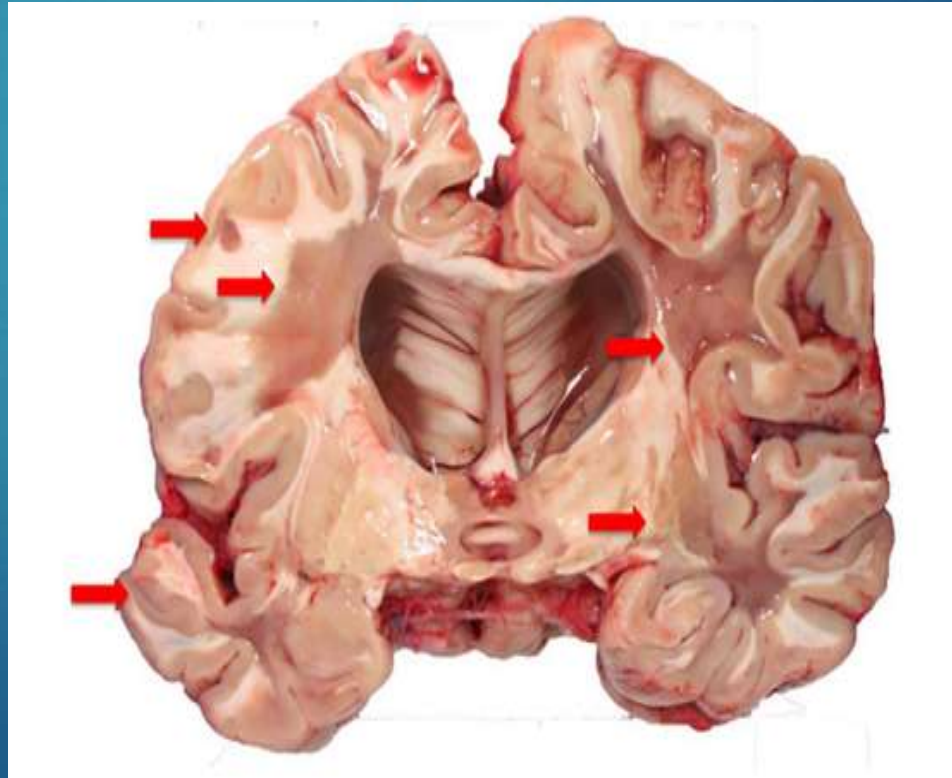
Pathology

- MS is an autoimmune disease in which lymphocytes migrate out of lymph nodes into the circulation, cross the blood–brain barrier, and target antigens in the central nervous system, causing inflammation, demyelination, neuroaxonal injury, astrogliosis, and ultimately neurodegeneration.
- White matter + 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.



Pathophysiology

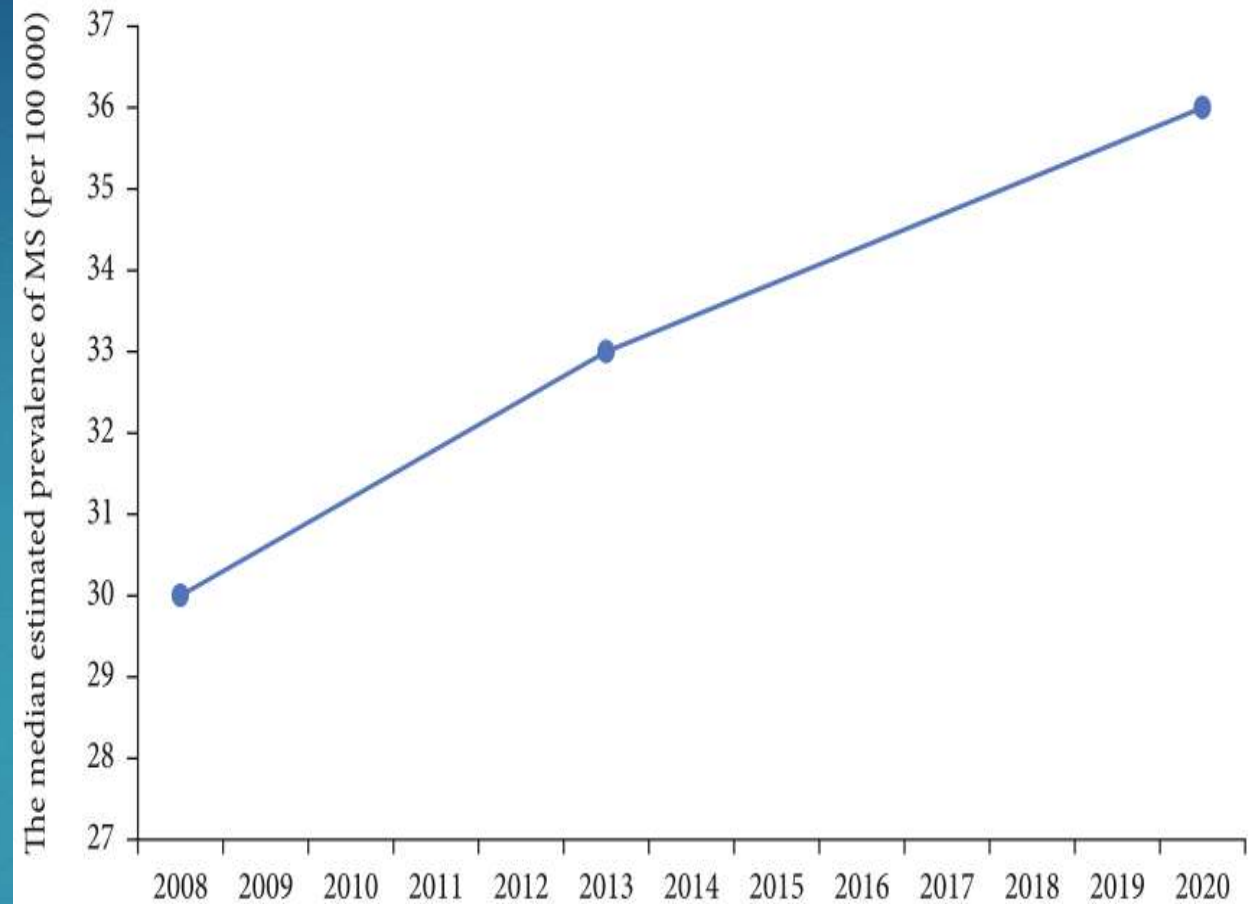
- ▶ Multiple sclerosis is an autoimmune disease in which lymphocytes migrate out of lymph nodes into the circulation, cross the blood–brain barrier, and aggressively target putative myelin antigens in the CNS , causing inflammation, demyelination , neuroaxonal injury, astrogliosis, and ultimately neurodegeneration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

- ▶ 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)

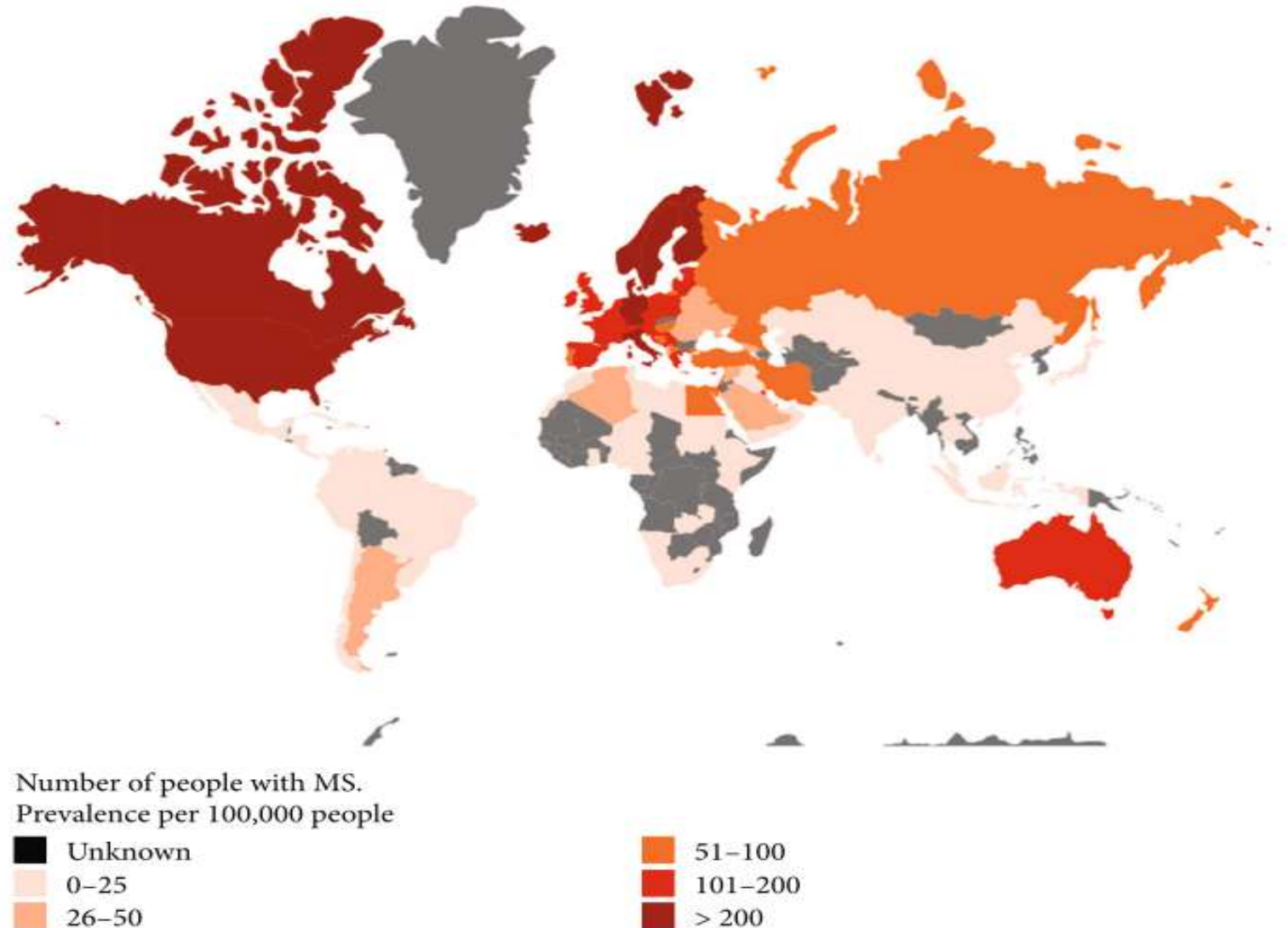
MS Epidemiology

- ▶ There is a clear trend **towards increasing prevalence (and possibly incidence)** 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**.



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**.



Unproven Theories

- ▶ The ‘**Viking theory**’ suggested 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.
- ▶ Interestingly, in a small area on the southern peninsula of China, which the Vikings managed to conquer, the incidence of MS is relatively high compared with the remainder of mainland China

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

Journal of the Neurological Sciences, 100 (1990) 137–141
Elsevier

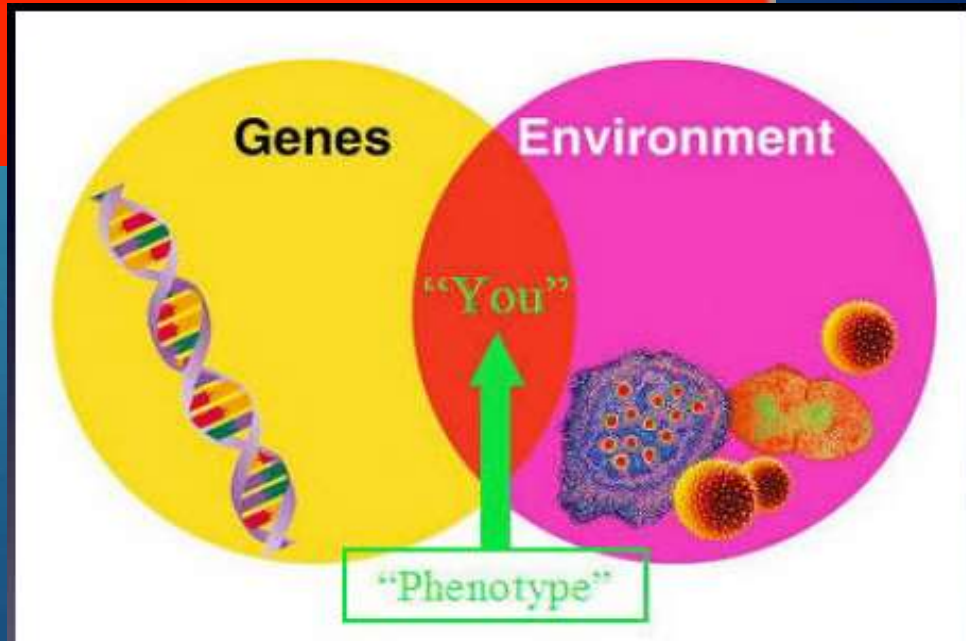
JNS 03436

Epidemiology of multiple sclerosis in Arabs in Kuwait: a comparative study between Kuwaitis and Palestinians

A.S. Najim Al-Din¹, M. Khogali², C.M. Poser³, K.E. Al-Nassar⁴, R. Shakir¹, J. Hussain¹, K. Behbahani⁵ and G. Chadha¹

Departments of ¹Medicine, ²Community Medicine, ⁴Biochemistry, ⁵Microbiology, Faculty of Medicine, University of Kuwait, Safat (Kuwait), and
³Department of Neurology, Harvard Medical School, Boston, MA (U.S.A.)

Etiology of MS



Genetic factors

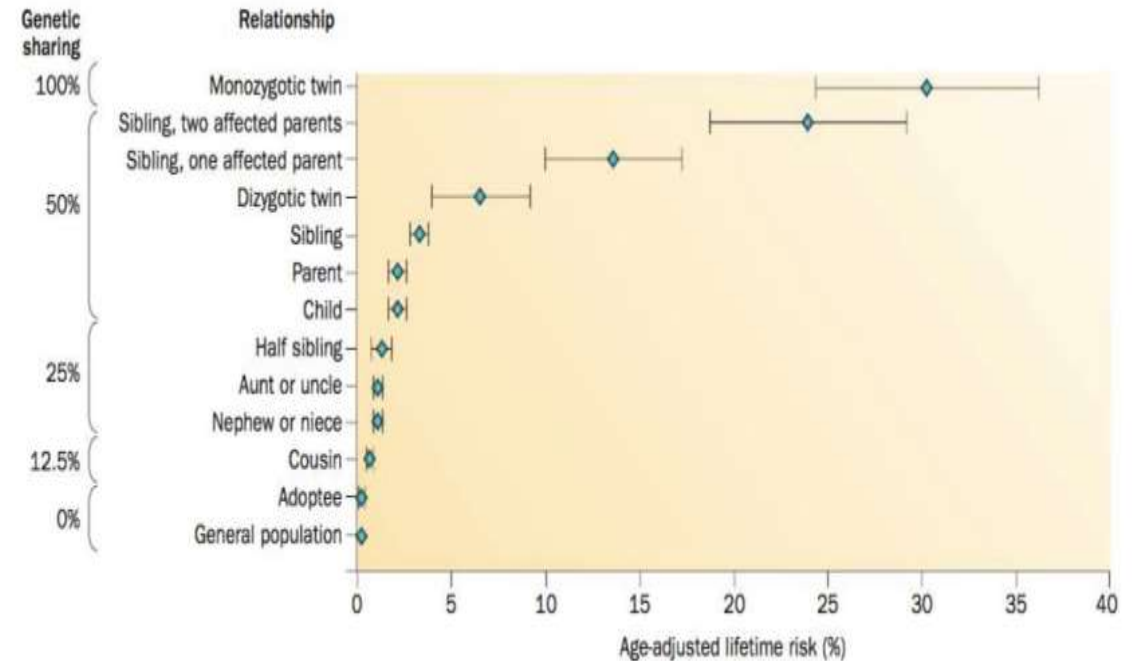
class 2 major histocompatibility complex gene
DRB1*15:01 and its extended haplotype
carrying the greatest risk

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%

But what about the risk of MS in my baby?



...there is an **increased risk of her child developing MS** compared to the general population (from roughly 0.2% to 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 (HHV-6)
- Air pollution

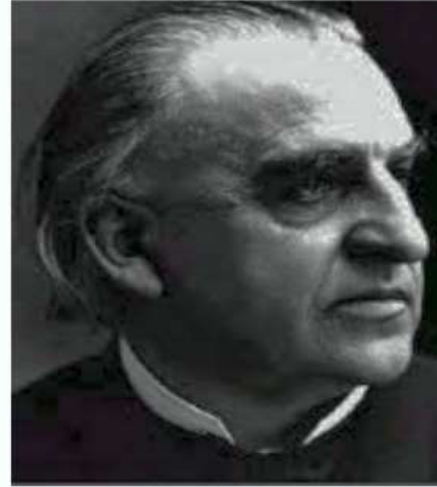
“Urbanization and western life-style”

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

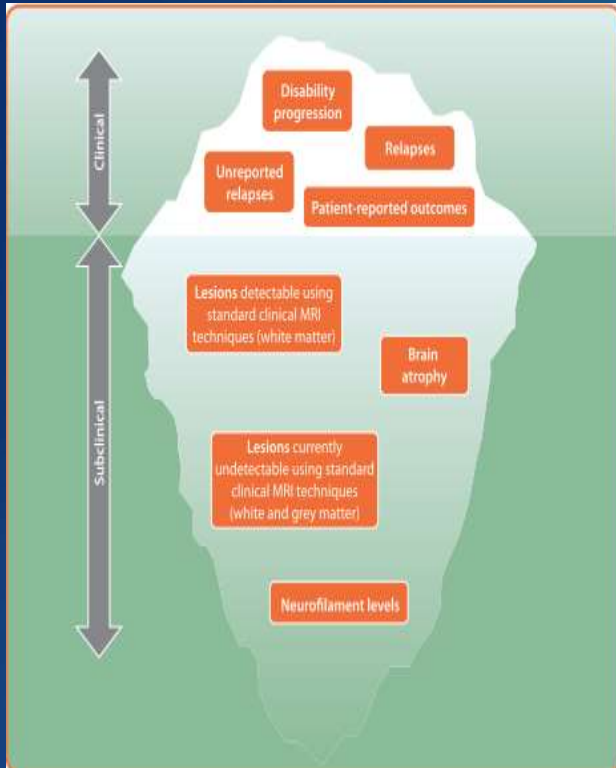
- ▶ Classically, a diagnosis of relapsing MS is made when a patient exhibits typical inflammatory neurologic episodes (relapses) disseminated in time and space.
- ▶ Relapses are defined as new or worsening neurologic symptoms that occur in the absence of fever or infection, **last over 24 hours**, and are preceded by 30 days of relative neurologic stability
- ▶ **No alternative explanation for the episodes.**



Jean Martin Charcot
1825-1893

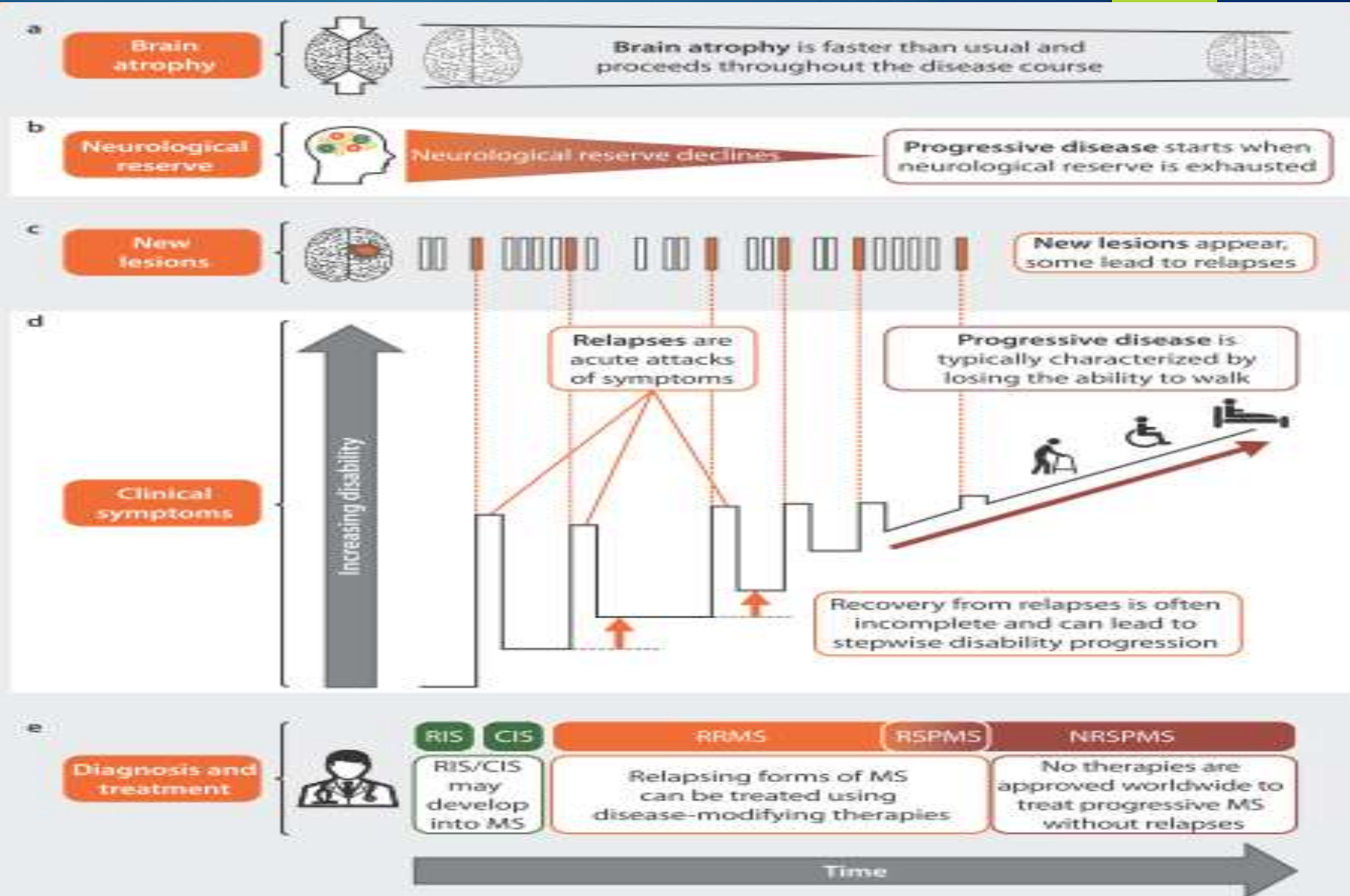
To learn how to treat disease, one must learn how to recognize it. The diagnosis is the best trump in the scheme of treatment.

Evolution of RRMS



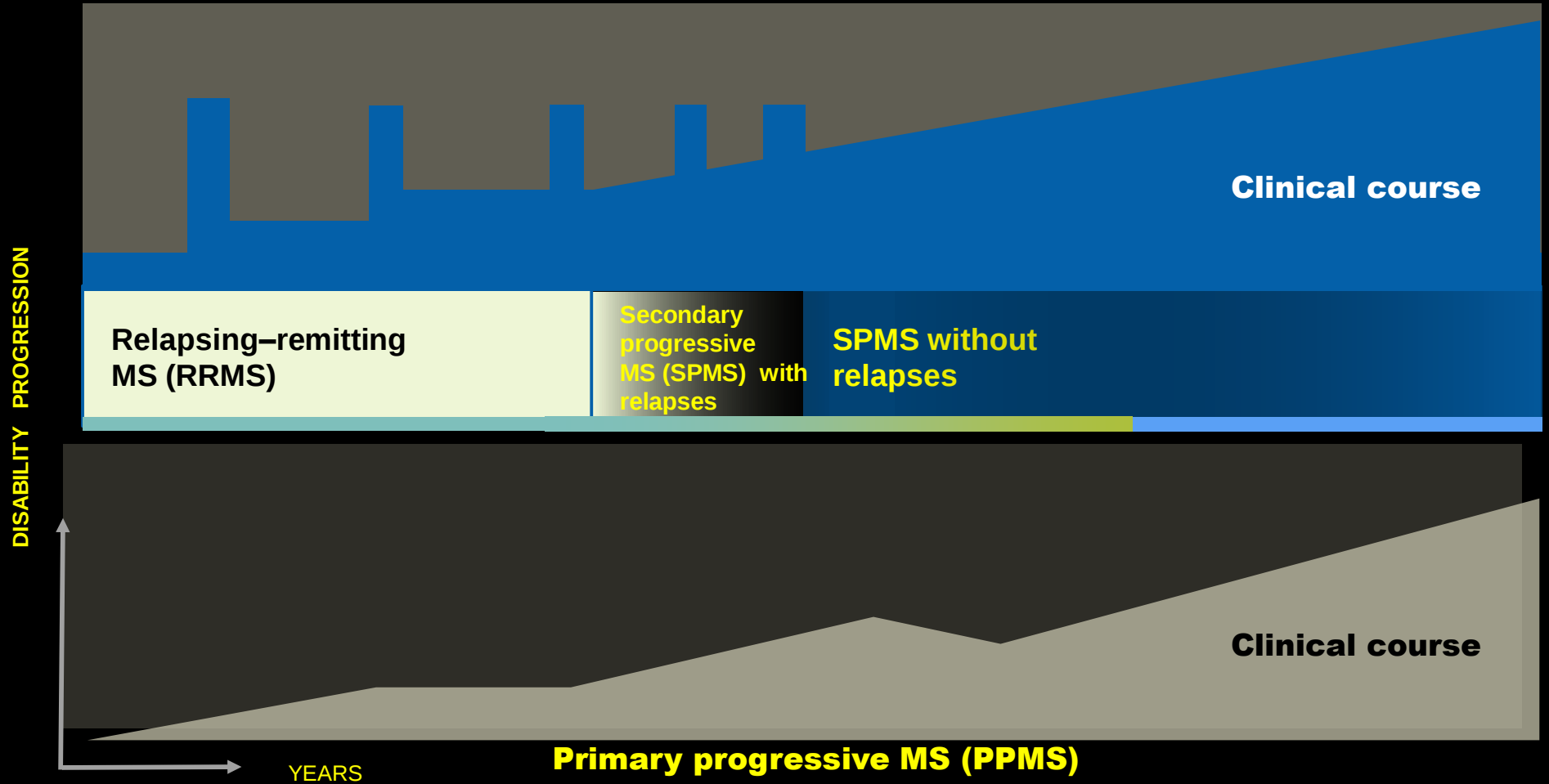
RIS- Radiologically Isolated Syndrome

CIS- Clinically Isolated Syndrome (first clinical relapse)



MS disease continuum

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



~10%
of patients have
primary progressive
onset of MS

Common Relapses

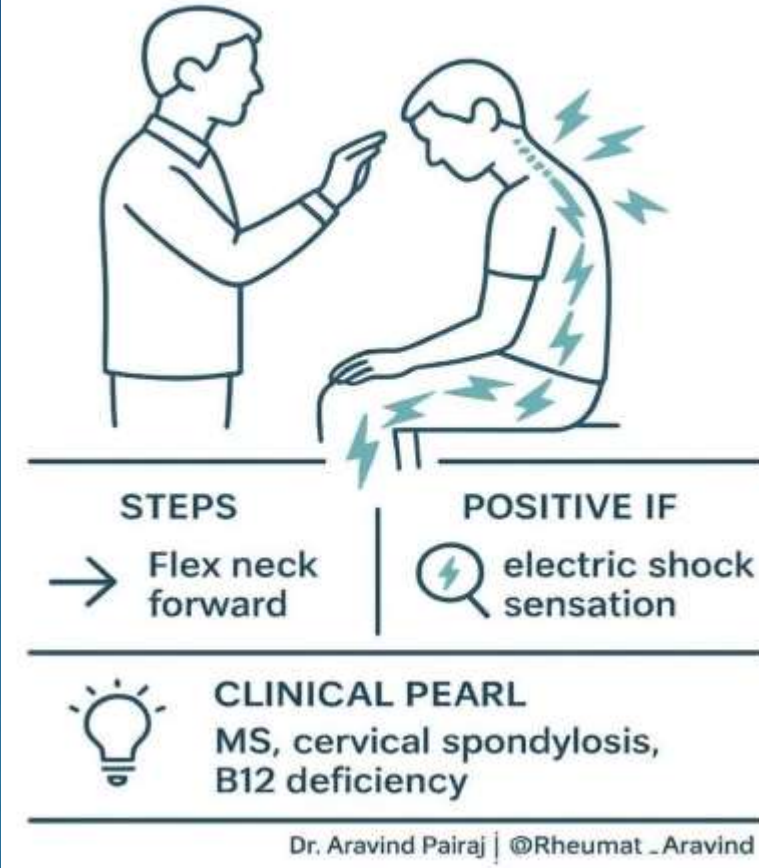
Part of CNS affected

- ▶ Optic nerve
- ▶ Spinal cord
(partial myelitis)
- ▶ Brain stem

Clinical Presentations

- ▶ Optic neuritis
- ▶ Numbness/tingling
- ▶ Mild hemi- or paraparesis
- ▶ Bowel/bladder dysfunction
- ▶ Lhermitte's sign
- ▶ Diplopia/ Internuclear ophthalmoplegia (Medial Longitudinal Fasciculus)
- ▶ Dizziness/vertigo
- ▶ Trigeminal neuralgia
- ▶ Facial palsy

Lhermitte's Sign – Cervical Spinal Cord Involvement



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



What is an RAPD?

No Light



Normal Response to Light

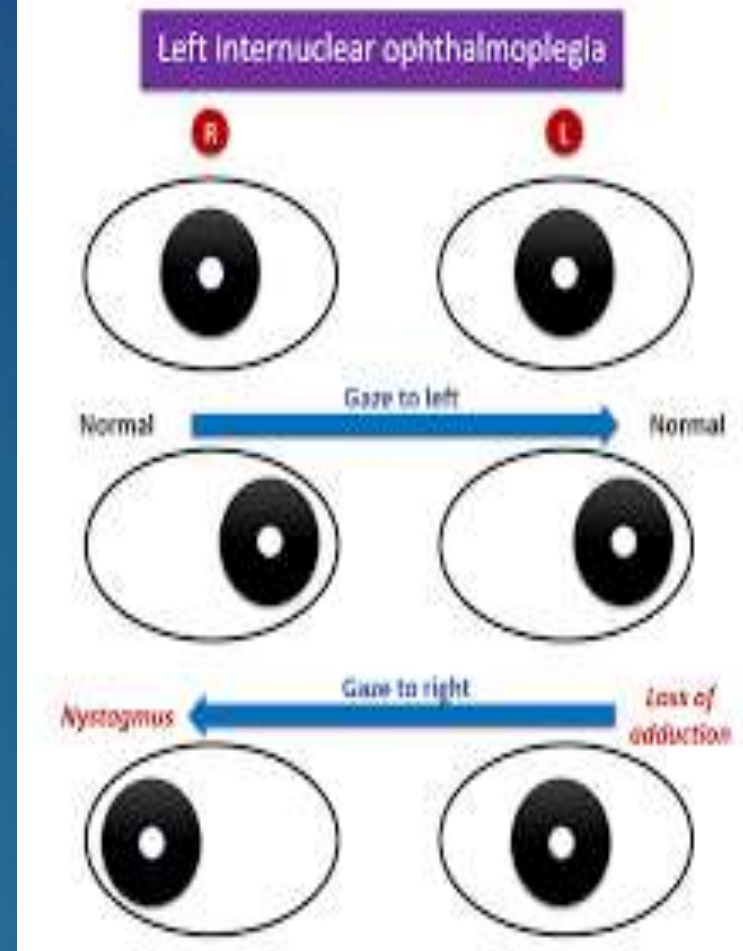
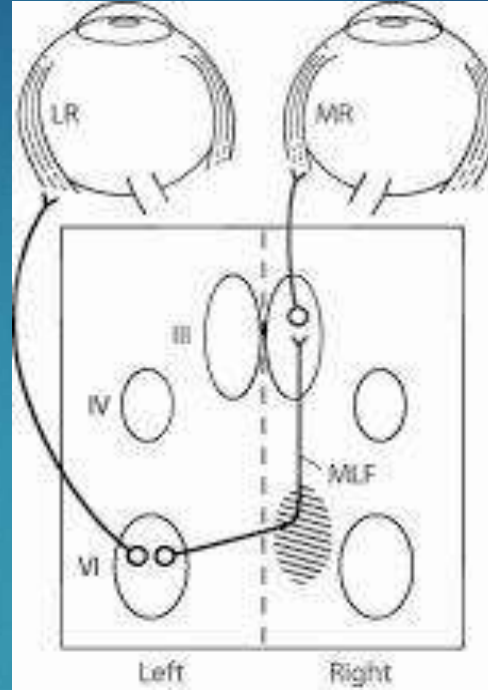


Positive RAPD of Right Eye



- Elicited during a swinging flashlight test
- Dilation of both pupils when the light is swung from the normal eye to affected eye

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

Clinical features atypical for MS

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



William Osler (1849-1919)

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



“He who knows syphilis knows medicine”
“The great imitator”



"It was always difficult to give young Jones positive feedback on his technique"

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



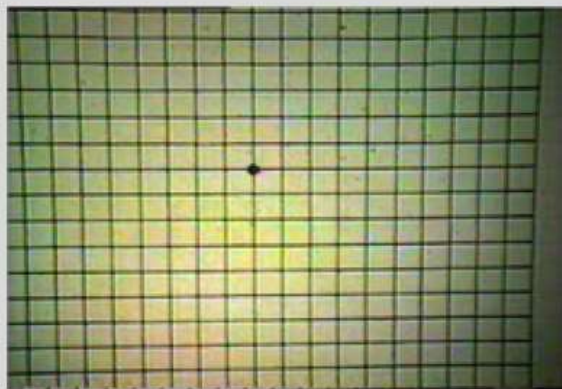
3 weeks later after IV Methylprednisolone

► Video 3

Purpose & Properties of Eye Movements

Eye movements evolved to serve vision in 2 ways

First: To hold images of the world steady on the retina



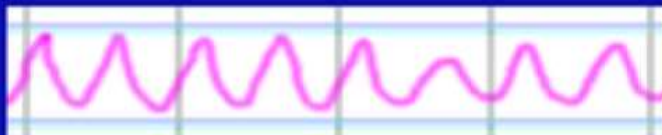
If images are in constant motion on the retina, then vision deteriorates and oscillopsia may occur

Nystagmus

- **Jerk**



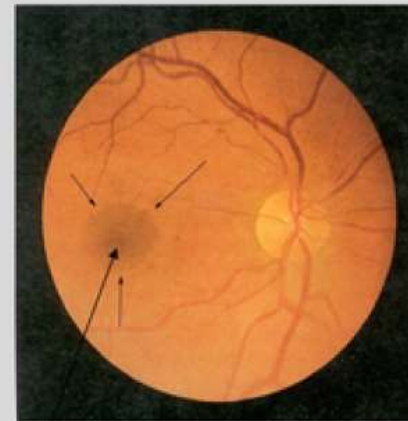
- **Pendular**



Purpose & Properties of Eye Movements

Eye movements evolved to serve vision in 2 ways

Second: To point the fovea at features of interest



Fovea: highest density of photoreceptors (macula)



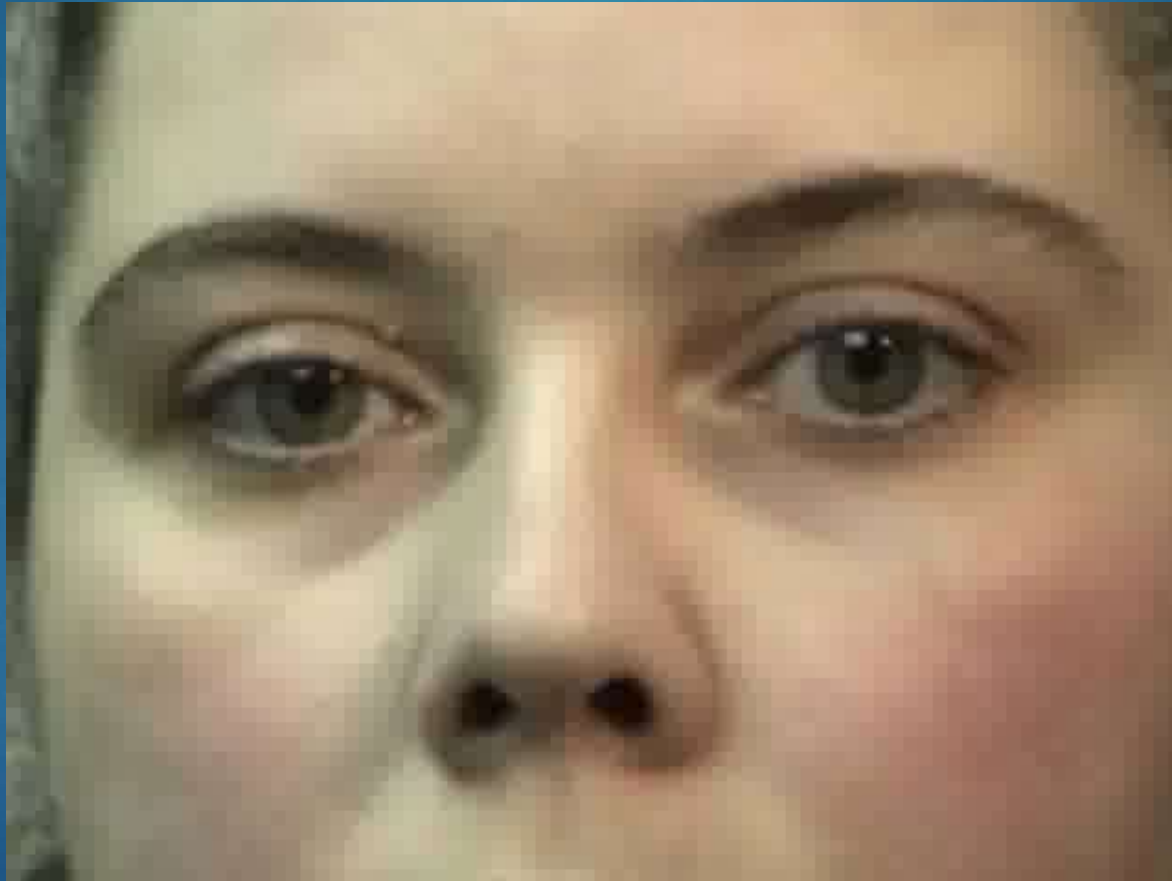
If images are displaced from the fovea, then visual acuity deteriorates

Saccades are rapid eye movements by which we point the fovea at salient details in our visual world



Video 4-Pendular nystagmus - Brainstem + ON pathology

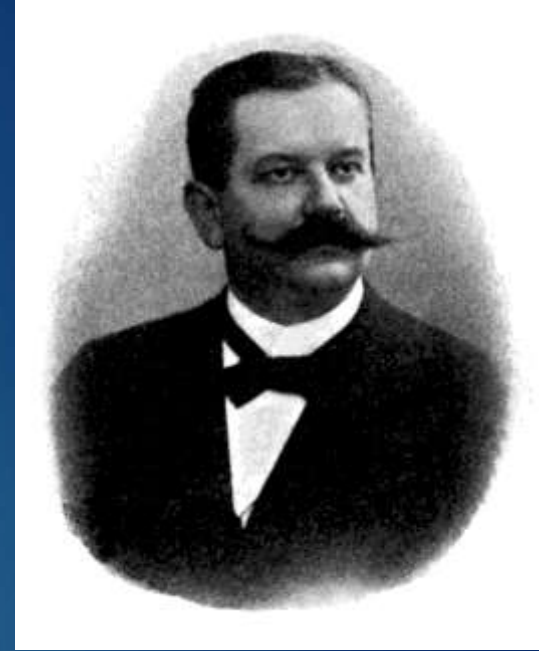
- Infantile /Albinism



MS symptoms (not relapses)

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

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



Para-clinical tests

► MRI

► CSF- OCB's

► 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 exclude other diseases

► Normal systemic inflammatory markers (ESR, CRP).

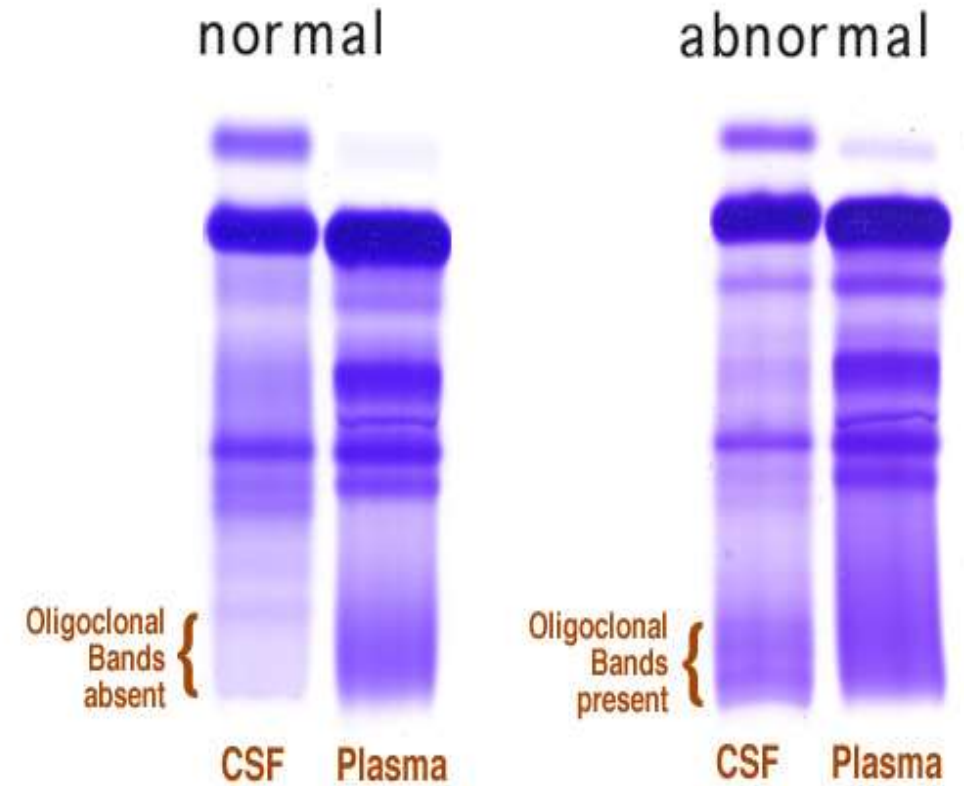
► Negative Autoantibodies, but low-titre ANA may occur

► B12, TFT, LFT, serum ACE/CXR

Frequencies of abnormal CSF variables in clinically definite MS

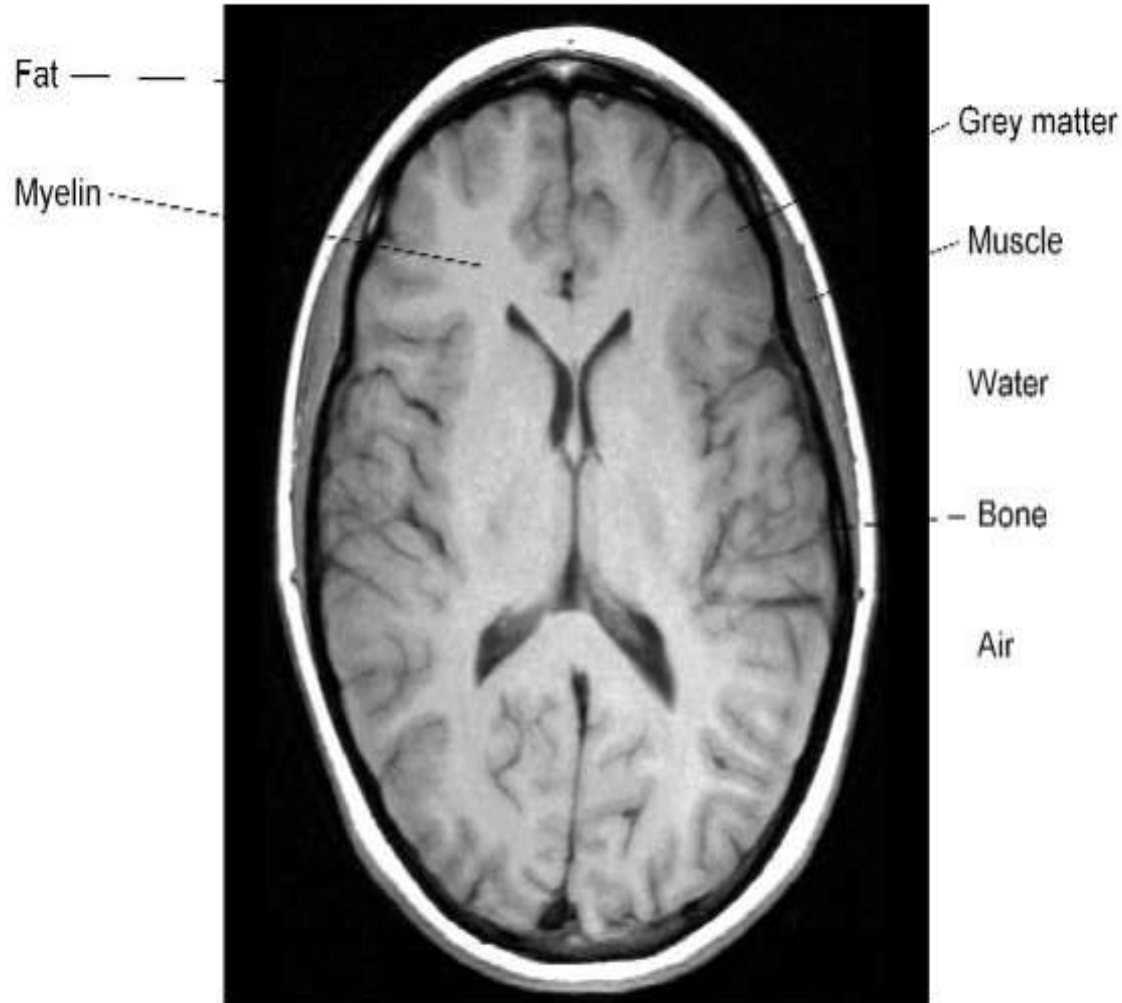
- ▶ Oligoclonal IgG bands >95% by isoelectric focusing technique
- ▶ Increased IgG index 75%
- ▶ Increased WBC count > 5 cells in 1/3 of patients (very rarely > 35)
- ▶ Mildly increased protein in 1/2 of patients (very rarely > 70)
- ▶ If protein >100 and/or low glucose unlikely to be MS

Oligoclonal Bands in CSF

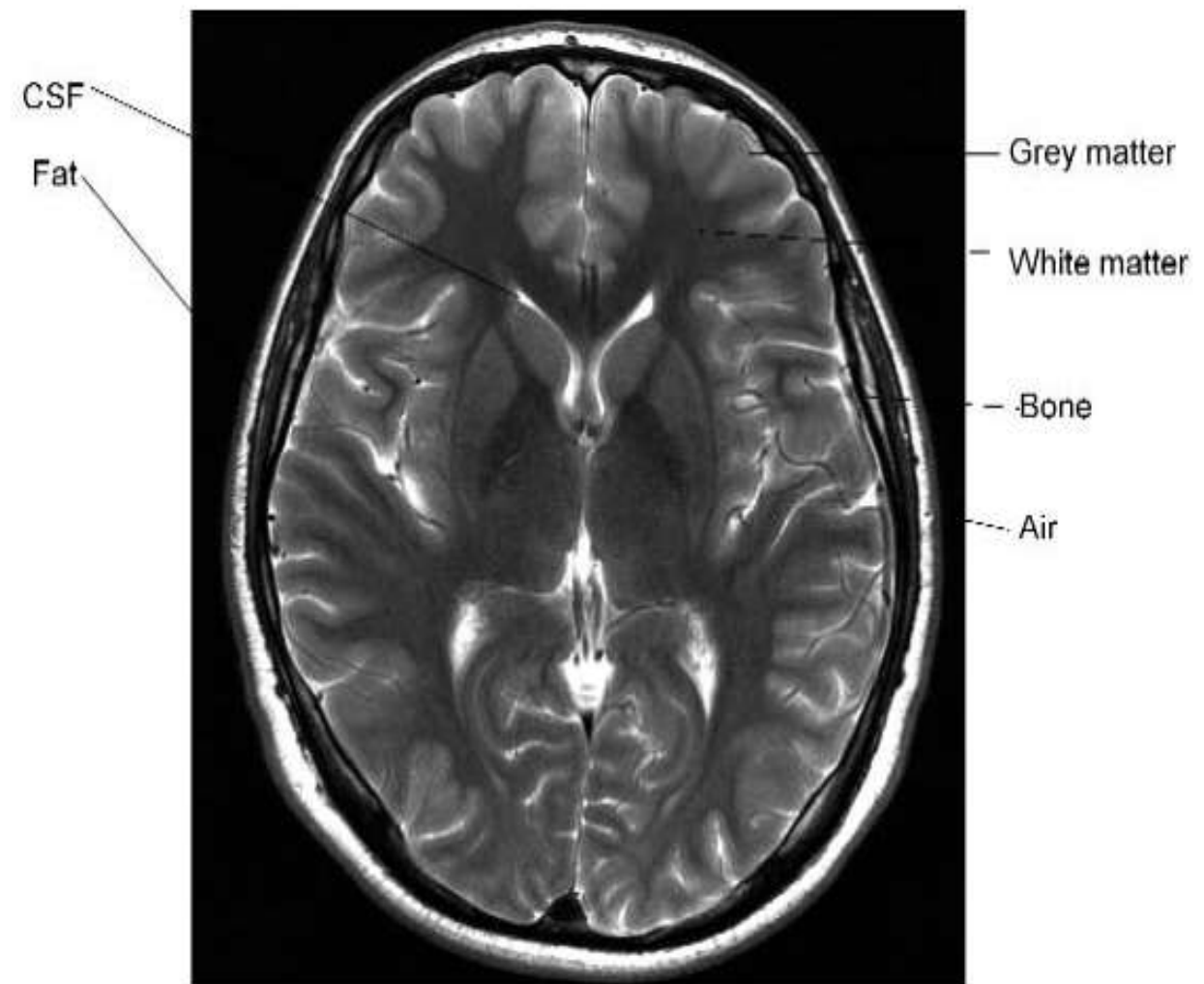


MRI –main sequences

T1-weighting



T2-weighting



MS brain lesion characteristics

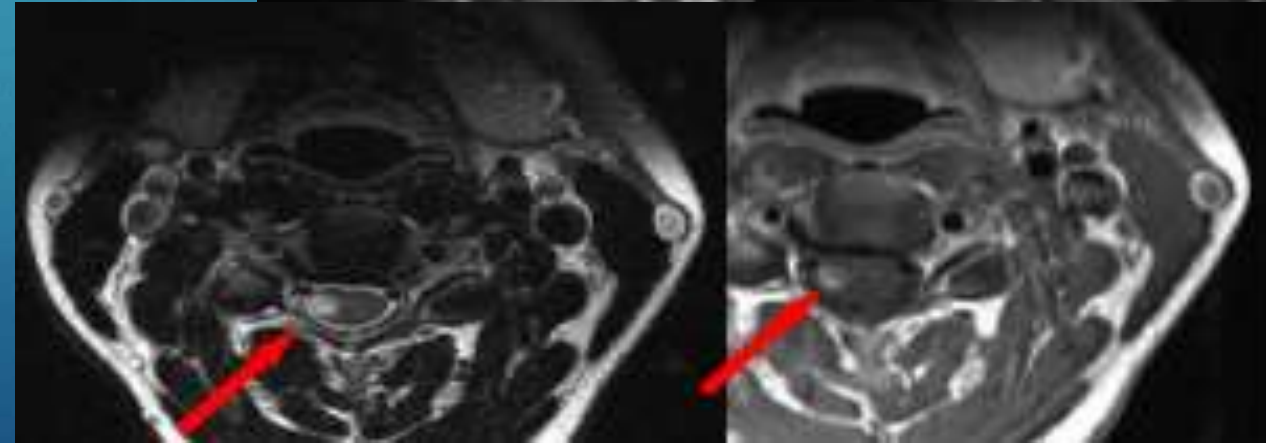
Lesion configuration	ovoid (round shape)
Size of lesions	> punctate
Typical lesion location	periventricular, juxtacortical, infratentorial
Lesion pattern	random, asymmetric
Tissue destruction	variable
Contrast enhancement	frequent



MS spinal cord lesion characteristics

- ▶▶ Cigar shaped (in sagittal plane)
- ▶▶ Extension < 2 vertebral bodies in length and < $\frac{1}{2}$ spinal cord diameter
- ▶▶ Eccentric location
- ▶▶ Mass effect rare
- ▶▶ Cervical cord and posterior columns preferentially affected

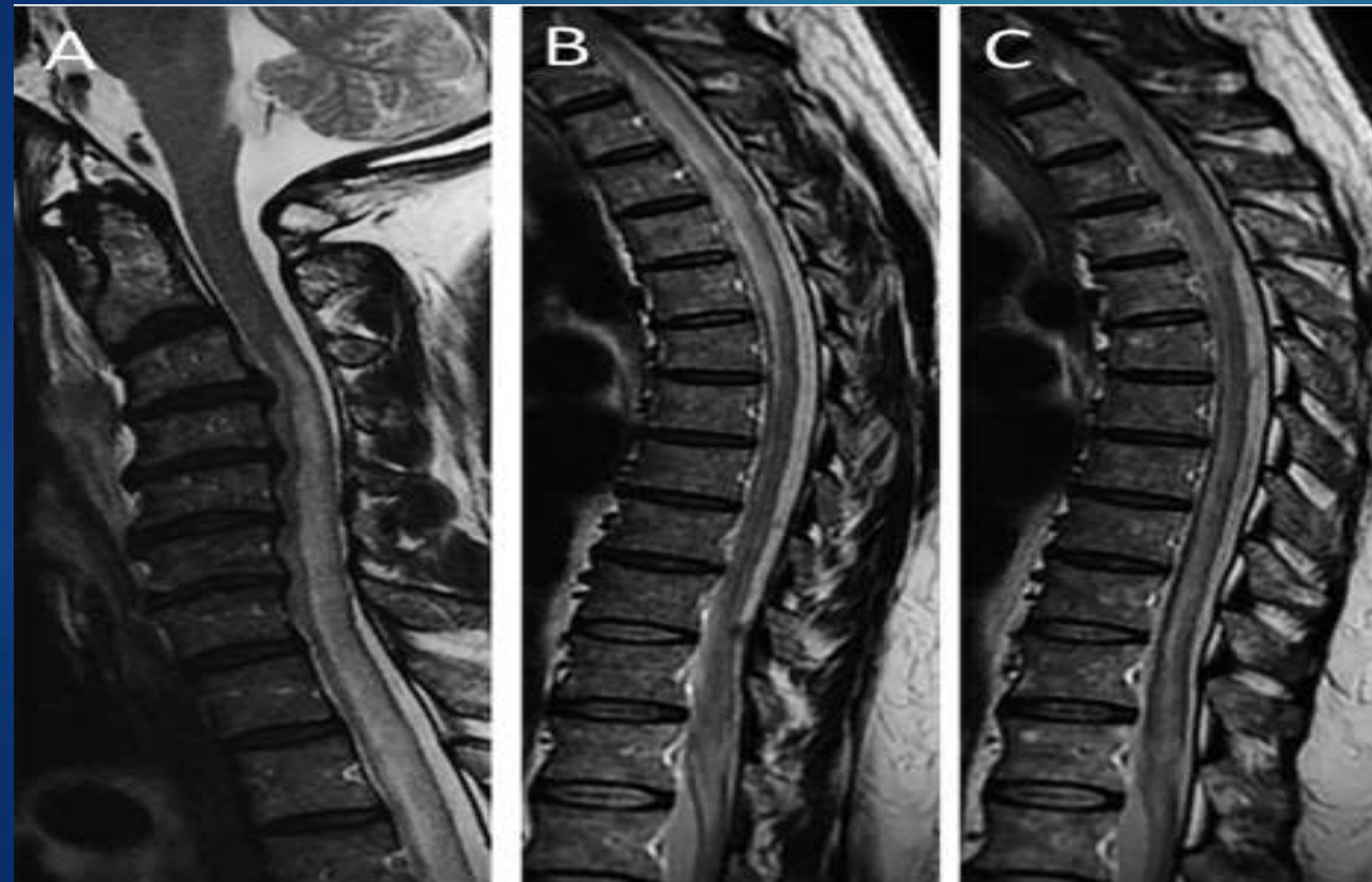
No incidental age-related / vascular spinal cord lesions



Differential Diagnosis

- ▶ MS is the most common **primary** demyelinating disease of the CNS, but other primary demyelinating/inflammatory disorders should be considered
 - Acute Disseminated Encephalomyelitis (ADEM)- most common in children
 - Neuromyelitis Optica /NMO spectrum disorder (NMOSD)- strictly speaking this is not demyelinating
 - Myelin Oligodendrocyte Glycoprotein-associated Disease (MOGAD)

NMOSD



Demyelination Secondary to systemic diseases

Ischemic/inflammatory...

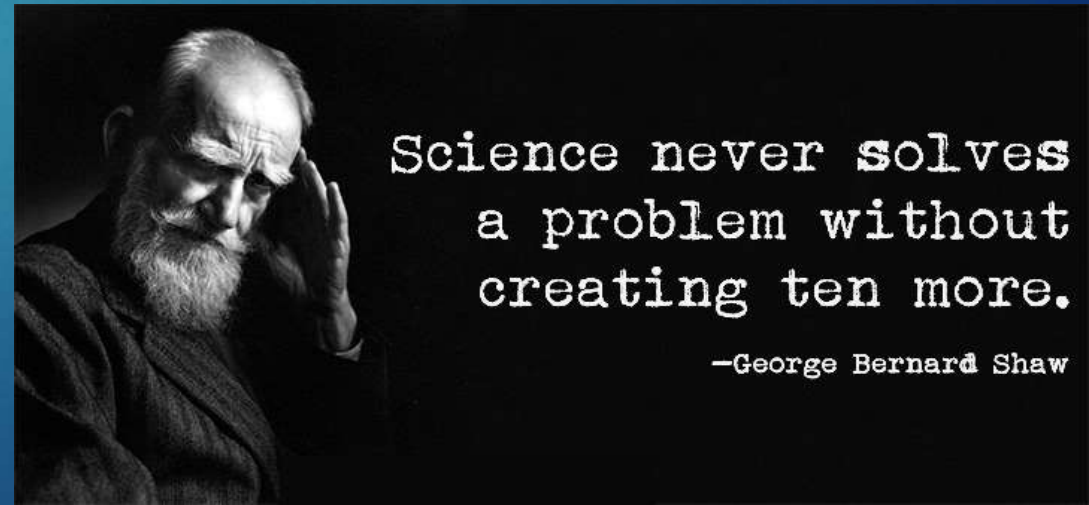
- ▶ Ischemia / Small vessel disease
- ▶ Vasculitis (SLE, APLA syndrome*, Sjogren's , Behcet's)
- ▶ Infection (Lyme disease)
- ▶ Sarcoidosis, Susac's syndrome
- ▶ B12 deficiency/ Hyperhomocystinemia
- ▶ Non-specific WM lesions/ Migraine



*Livedo reticularis

Differential Diagnosis

- ▶ Excluding diseases that can mimic MS clinically or radiologically is very important and can be very challenging.
- ▶ Late diagnosis and overdiagnosis are common.
- ▶ Late diagnosis due to many non-specific symptoms
- ▶ Over-diagnosis of non-specific MRI changes !!



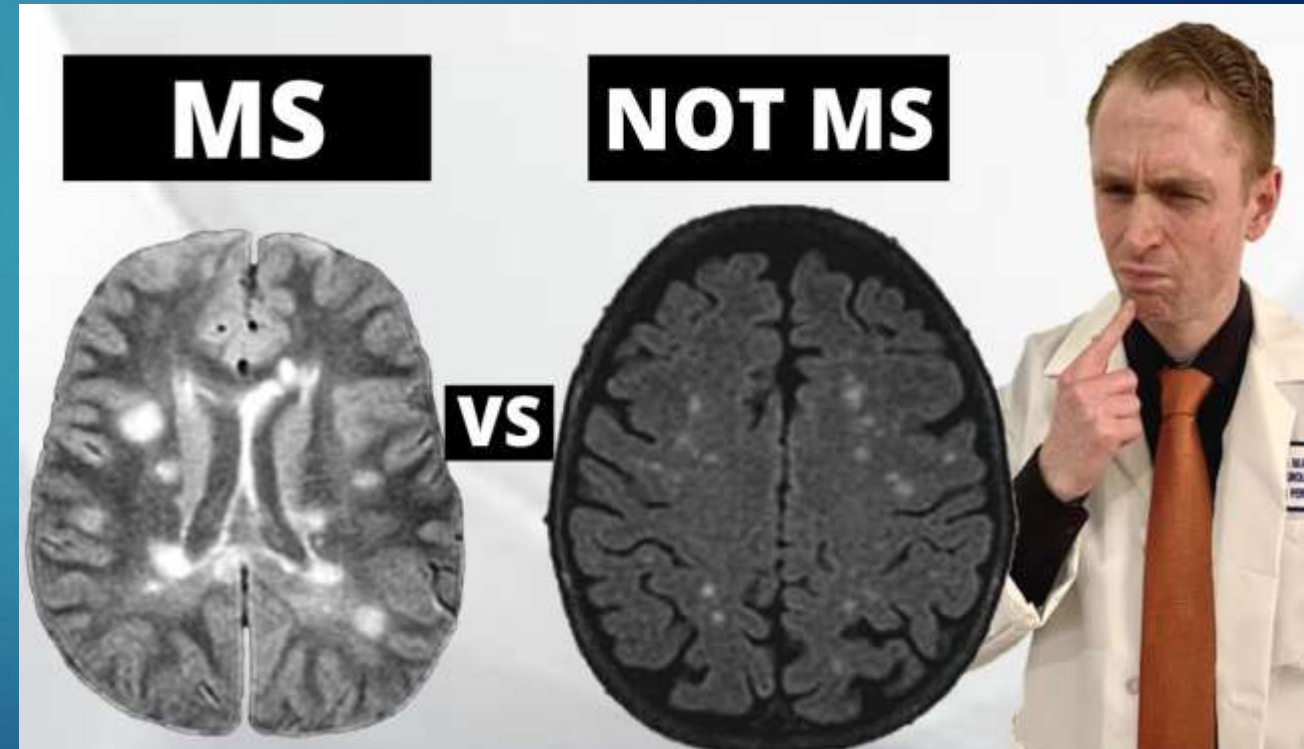
Science never solves
a problem without
creating ten more.

—George Bernard Shaw

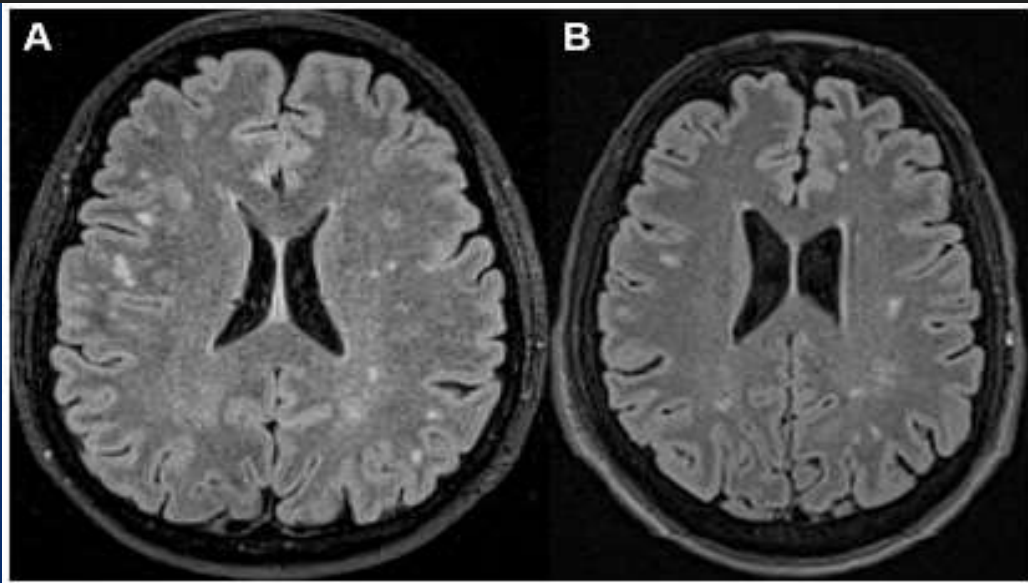
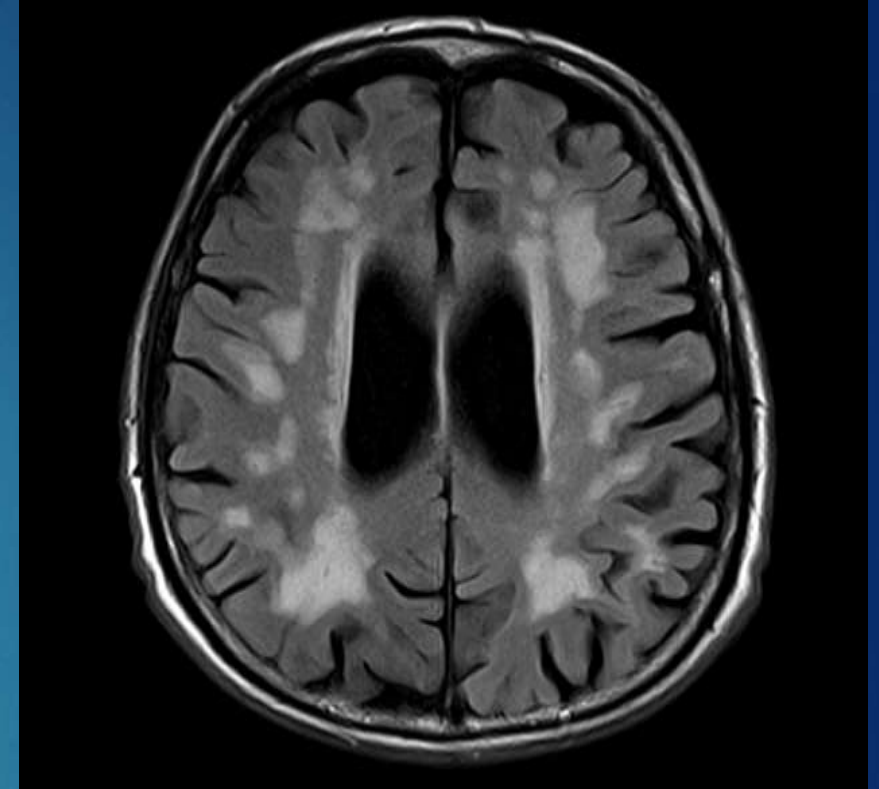
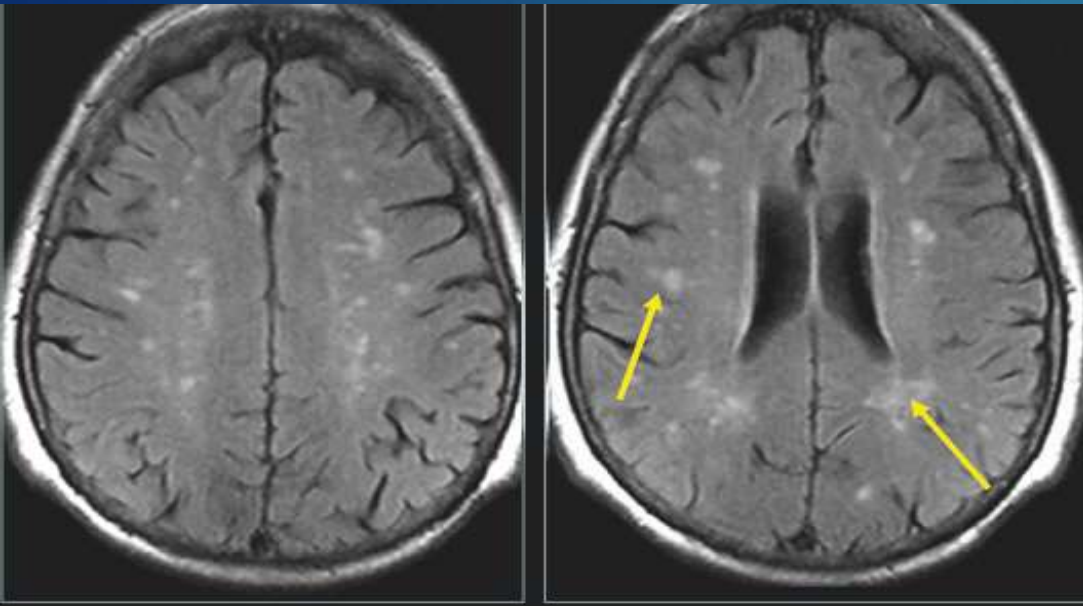
Non-specific WM lesions

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 in Ageing/Migraine



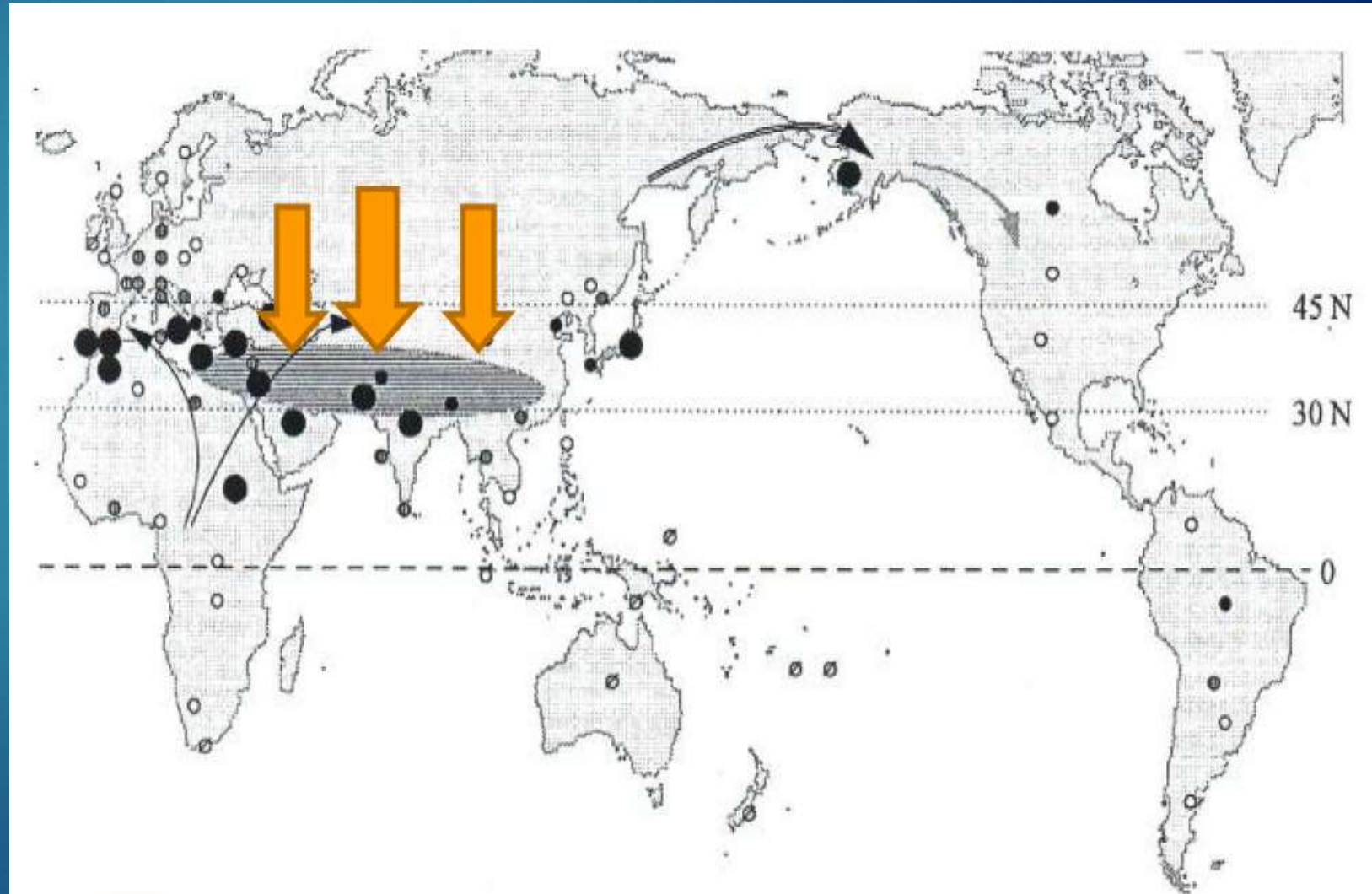
Ischemic lesions/Small vessel disease

Subcortical

Affect central brainstem

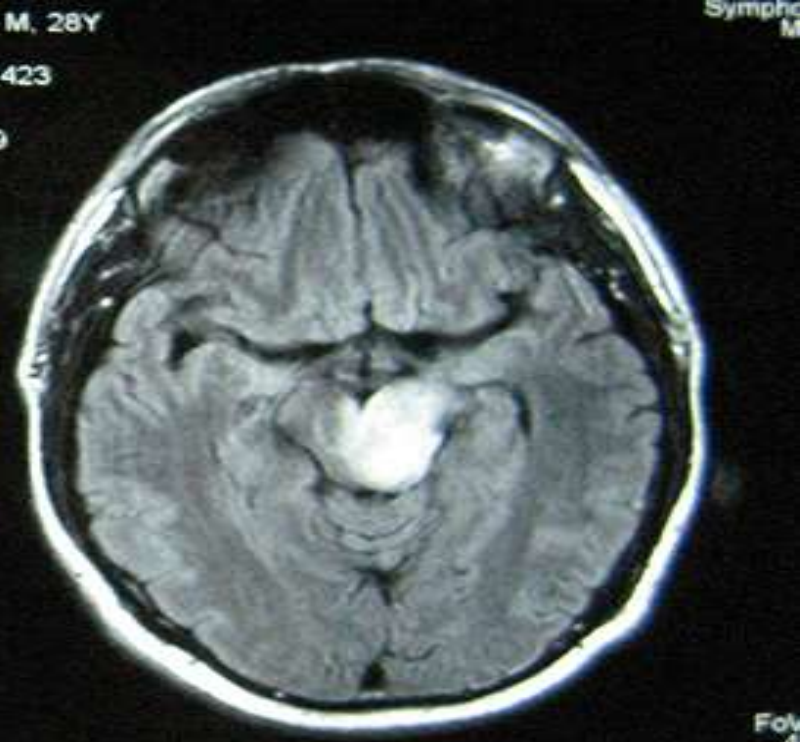
May be associated with lacunes

???

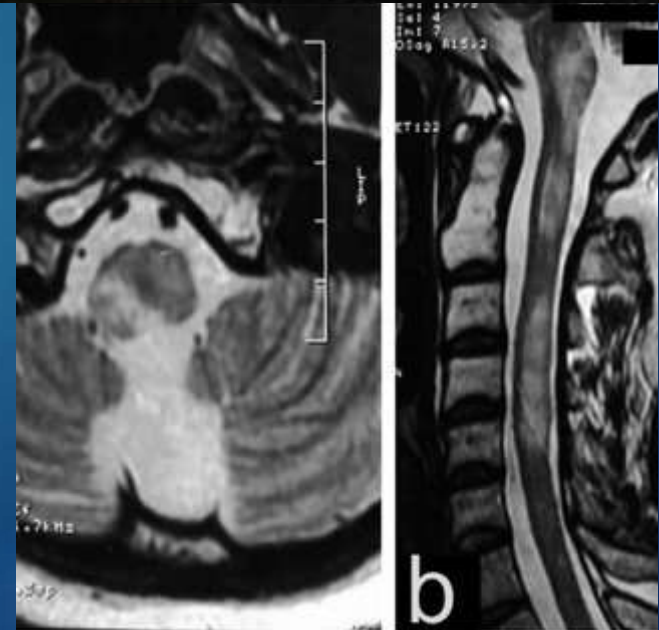


Behcet's Disease

- ▶ 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*

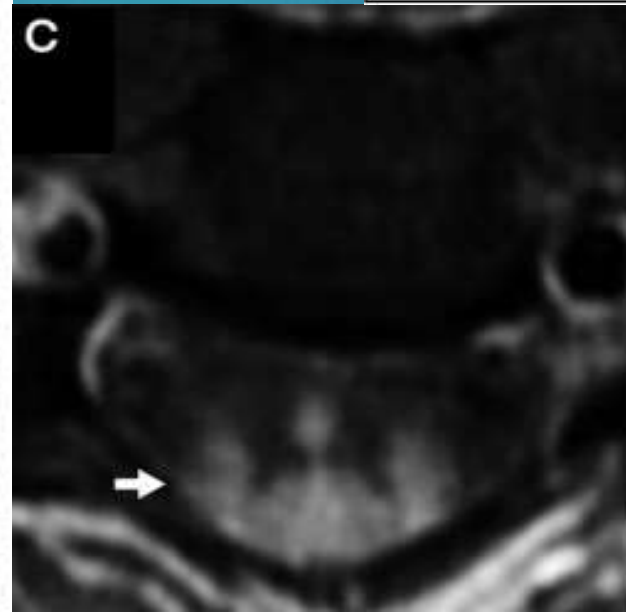
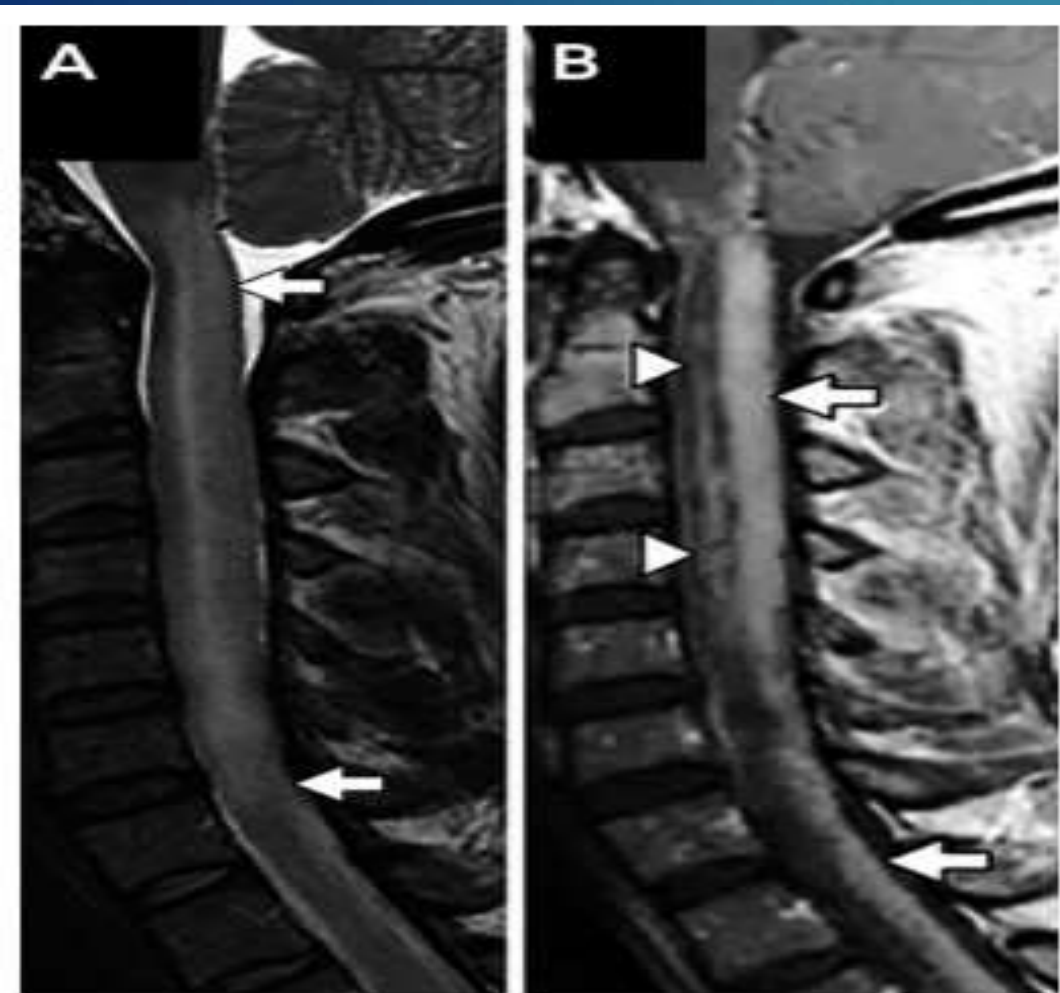


Neurosarcoidosis- trident sign

On axial contrast-enhanced spinal cord MRI

SYSTEMIC SARCOIDOSIS

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



► Photos

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



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Less likely to have a benign course if :

- Adolescent overweight and obesity
- Infrequent fish consumption
- Infectious mononucleosis

Relapse treatment

Faster recovery but no evidence of decreasing residual disability

- High-dose steroids is first line treatment
 - IV/oral Methylprednisolone 1 g daily for 3-5 days
 - 30-50 % do not respond adequately
- Plasma exchange for refractory relapses

Management

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

Expanded Disability Status Scale (EDSS)



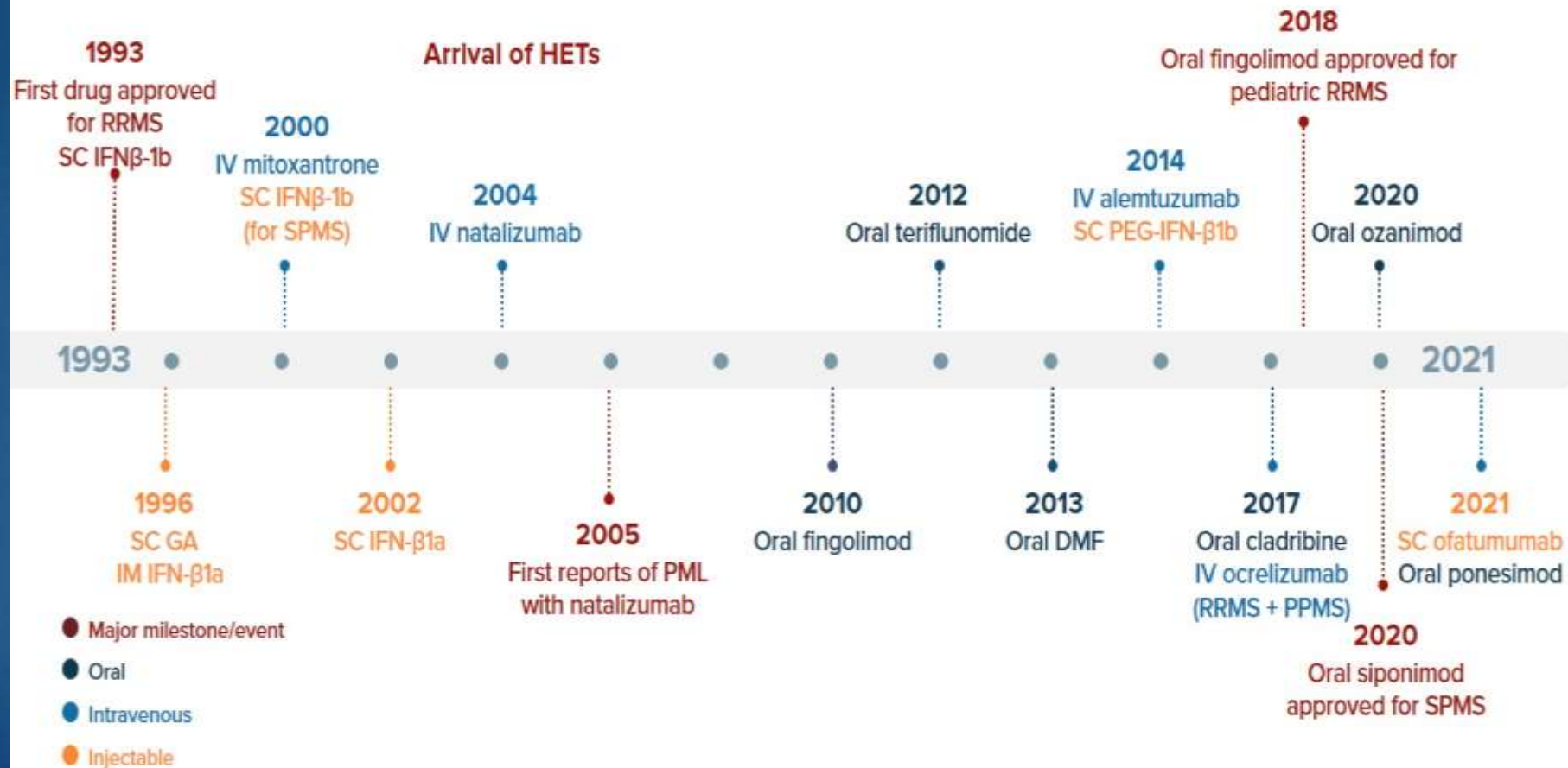
Progression from EDSS 0-4 (inflammatory phase): 1-32 years

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

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.

Benefit-Risk Balance of Treatment Choice in MS

Safety/Risks

Reversibility

Long-term
Safety

Tolerability



Efficacy

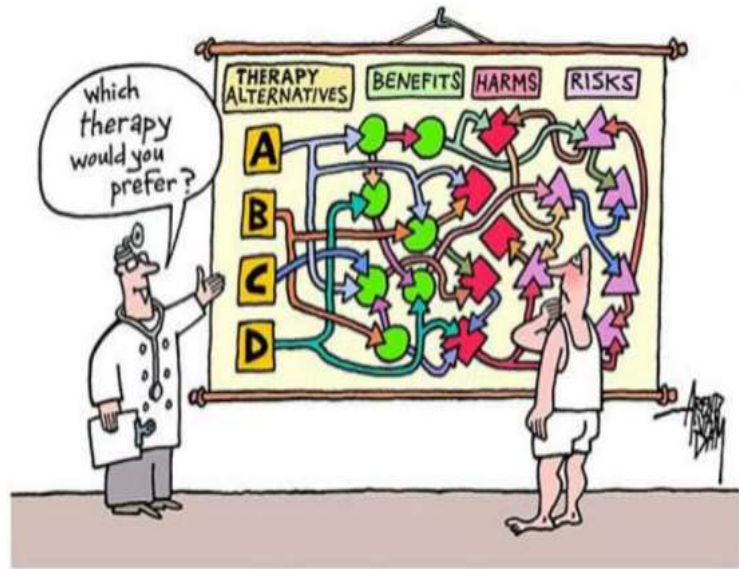
Relapses

Disability Progression

Freedom from
MRI Activity

Adherence Potential

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 lesions ,
age and polysymptomatic presentations

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The Burden of MS-without treatment



*mean time for development

Counselling patients about unpredictable long-term prognosis: Hope/optimism vs. Honesty/Truth



Versus



Questions ?

