Multiple sclerosis

Nora Alfugham

Consultant Autoimmune Neurology

King Khalid University Hospital

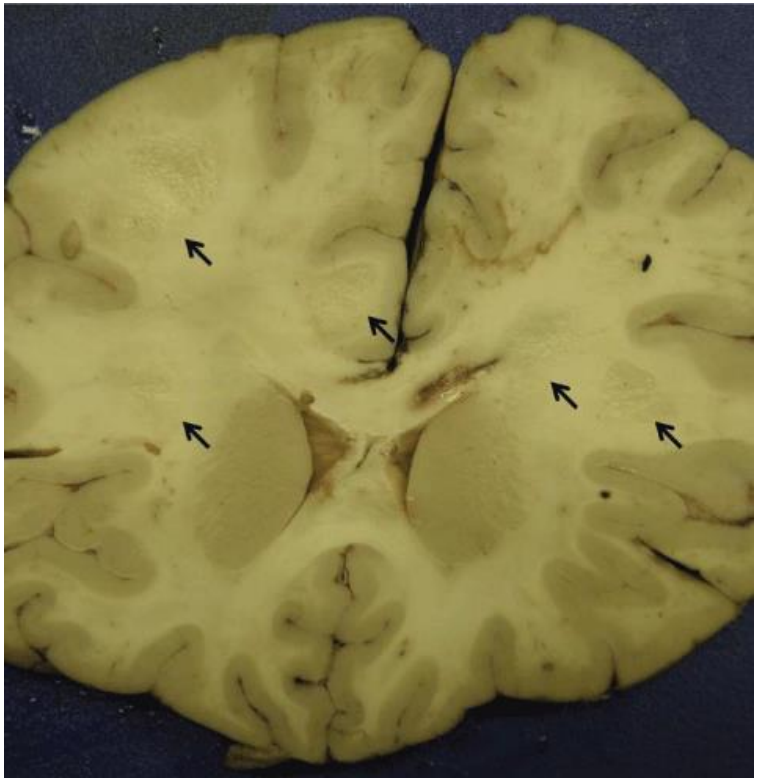
Jean- MARTIN charcot: The Father of Neurology

"To take away from neurology all discoveries made by charcot would be to render it unrecognizable"

Joseph Babiinski

Multiple Sclerosis

- An inflammatory demyelinating disease of the CNS where there is:
  - Dissemination in space
  - Dissemination in time
  - No alternative neurologic disease
- MS is a clinical diagnosis, no laboratory test in isolation confirms the diagnosis of multiple sclerosis



Immunopathology

several basic processes drive the formation of plaques:

- inflammation,
- myelin breakdown,
- Astrogliosis and oligodendrocyte injury
- neurodegeneration and axonal loss,
- remyelination

Immunopathology

- The pathologic hallmark of multiple sclerosis (MS) is multiple focal areas of myelin loss within the CNS called plaques or lesions
- Demyelination is accompanied by variable gliosis and inflammation and by relative axonal preservation
- **Demyelination with relative axonal sparing** is important for the diagnosis of demyelinating lesions, (whereas an infarct is more likely if axons and myelin in lesions are depleted to the same extent)
- acute axonal injury occurring in early multiple sclerosis lesions likely contributes to the relapse-related disability observed predominantly during the inflammatory disease phases

Immunopathology

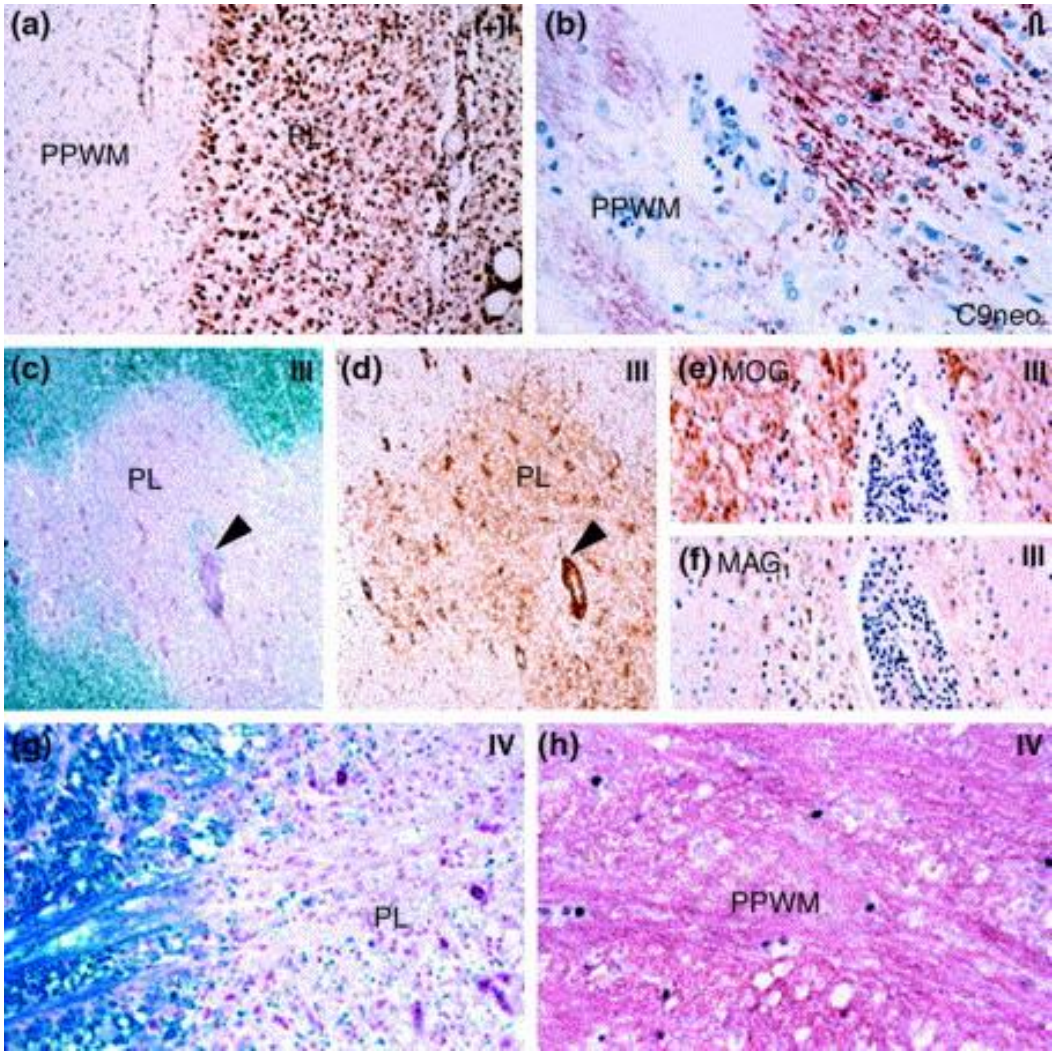
- Despite relative axonal sparing, axonal injury does occur, evidenced by the presence of axonal swellings (irregularly swollen axons with a beaded appearance), accumulation of amyloid-" precursor protein (a marker of focal accumulations of proteins that are typically moved along axons by fast axonal transport), and mild axonal loss.
- The extent of axonal damage in active lesions correlates significantly with the number of lymphocytes and activated microglia

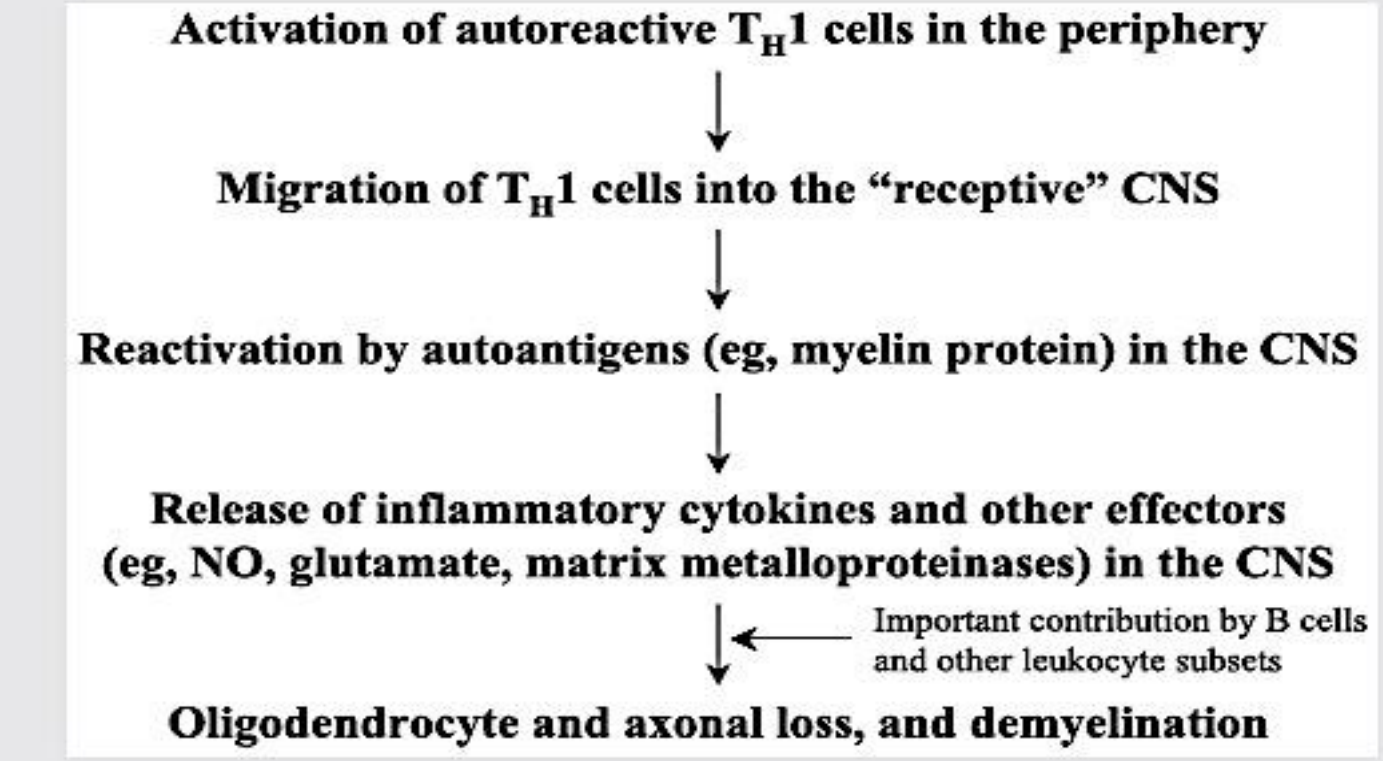
immunopathology

- Extensive remyelination, illustrated by the presence of newly formed myelin sheaths and oligodendrocyte precursor cells, is frequently encountered within active plaques of early multiple sclerosis

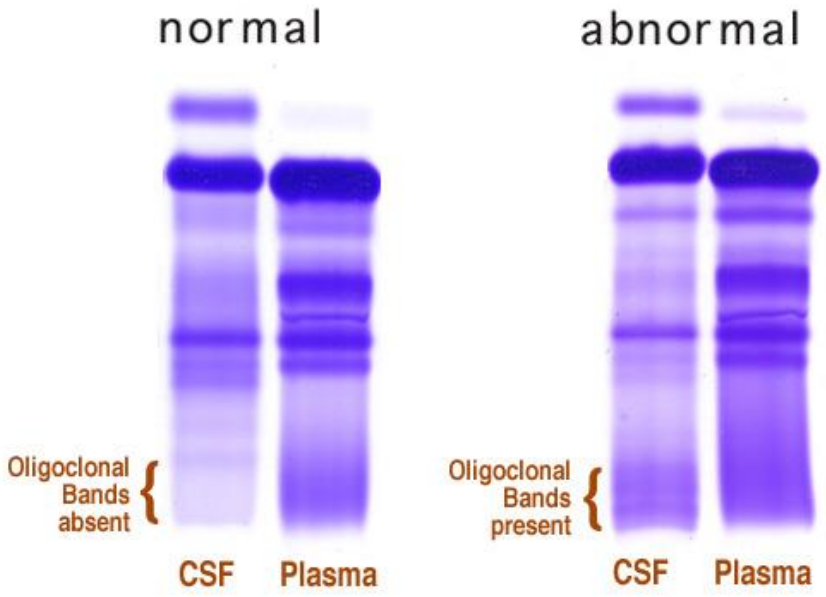
Immunopathology

- T cells comprise approximately 10% of the inflammatory cells populating active demyelinating lesions in MS
- Lymphocytic inflammatory infiltrate : mainly CD8-positive cytotoxic T lymphocyte
- EAE model can be adoptively transferred by injecting an animal with myelin-specific CD4+ T cells.


(a)
(+)I
PPWM
PL
(b)
II
PPWM
C9neo
(c)
III
PL
(d)
III
PL
(e) MOG
III
(f) MAG
III
(g)
IV
PL
(h)
IV
PPWM


Activation of autoreactive T_H1 cells in the periphery
Migration of T_H1 cells into the "receptive" CNS
Reactivation by autoantigens (eg, myelin protein) in the CNS
Release of inflammatory cytokines and other effectors (eg, NO, glutamate, matrix metalloproteinases) in the CNS
Important contribution by B cells and other leukocyte subsets
Oligodendrocyte and axonal loss, and demyelination

Oligoclonal Bands in CSF

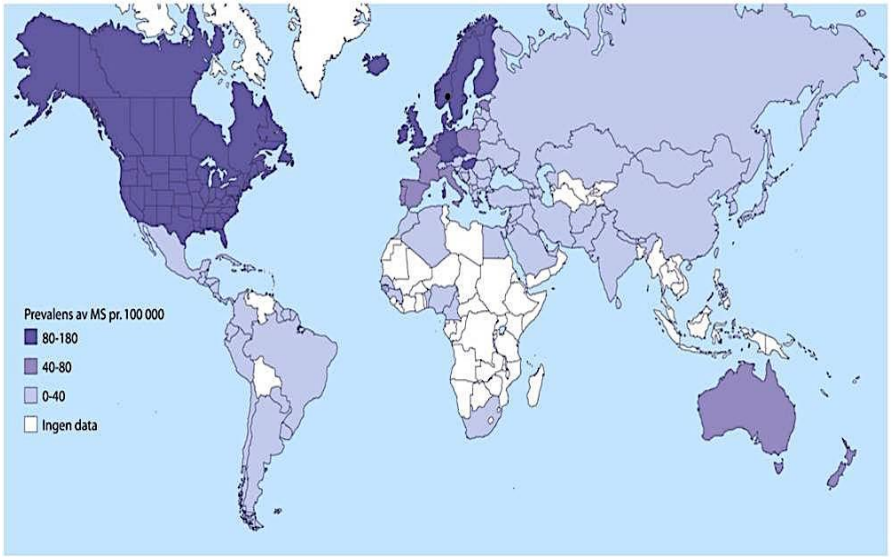


Immunopathology

- Direct proof of an autoimmune response is lacking
- No specific autoantibody or autoreactive T cells

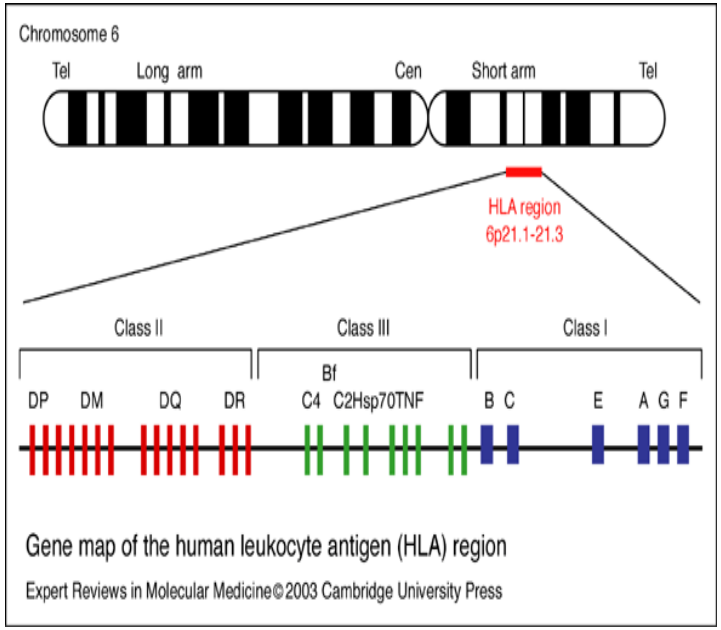
Epidemiology

- It is the second most common cause of neurological disability in young adults
- Female to male ratio 2.3:1
- Mean Age of onset 28-31 year (range:15-45 year)
- Ethnicity: white population(northern Europe)



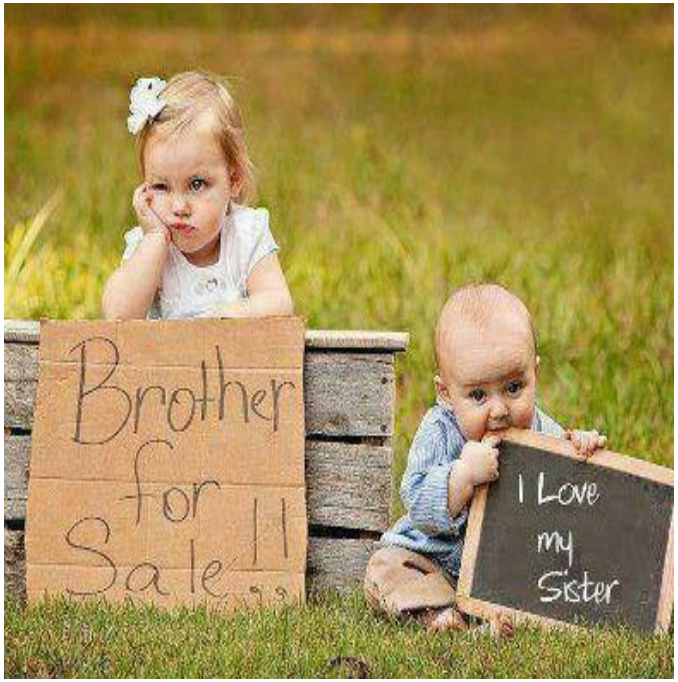
Genetics

- Polymorphism of HLA proteins is estimated to account for 17% to 60% of the genetic susceptibility to MS.1
- Single nucleotide polymorphisms in the chains of the interleukins 2 (IL-2) and 7 (IL-7) receptors



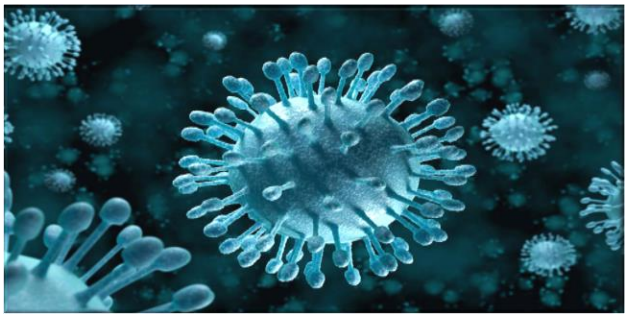
Concordance rate

Dizygotic: 3-5%



Monozygotic: 20%

Environmental Factors



Types of MS

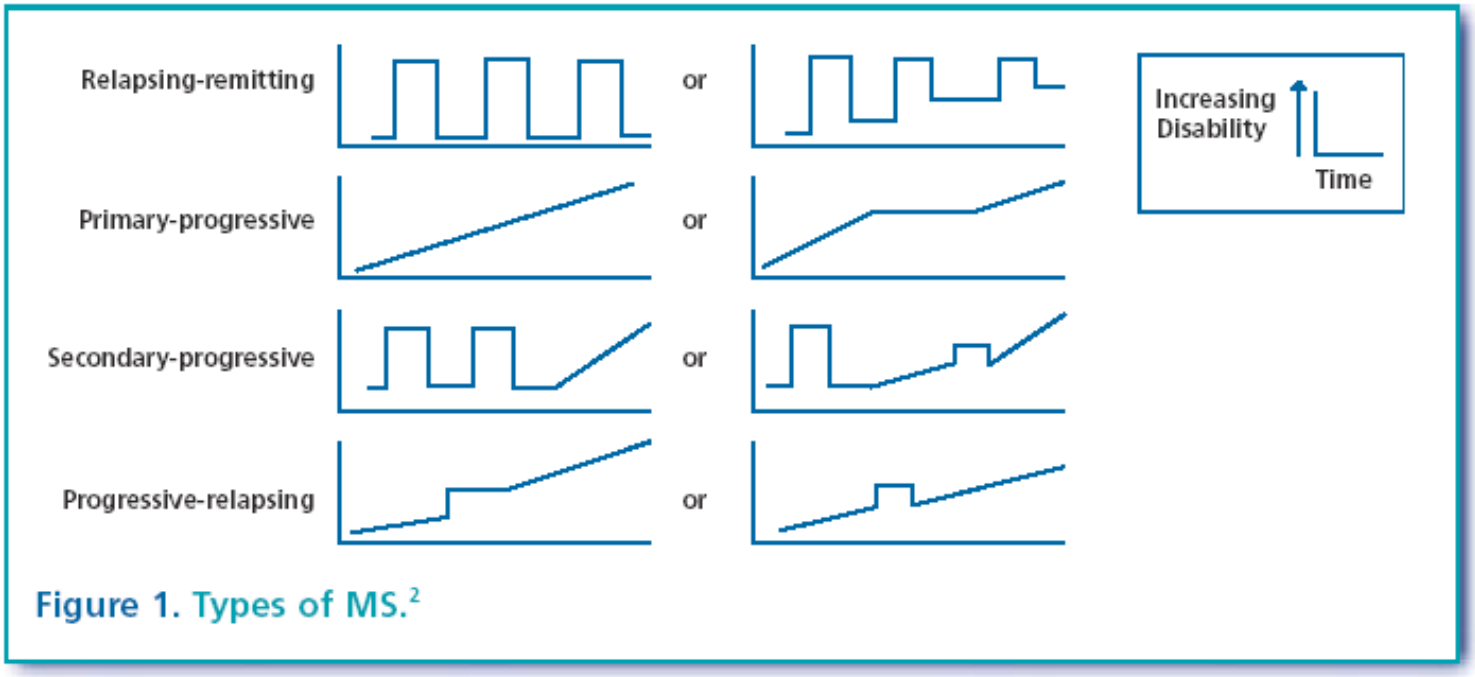


Figure 1. Types of MS.[2]

What is Clinical Attack (relapse, exacerbation)?

- focal disturbance affecting white matter that last for more than 24 hours and result in functional decline
- Preceded by more than 30 days of clinical stability
- No better explanation
- Role out **pseudorelapse**

Classic MS symptoms

- Sensory symptoms/ lermitte's phenomena
- Vision loss
- Eye movement abnormality (internuclear opthalmoplegia)
- Bowel and bladder dysfunction
- Incoordination
- Vertigo & dizziness
- Sexual dysfunction
- Poly-symptomatic onset

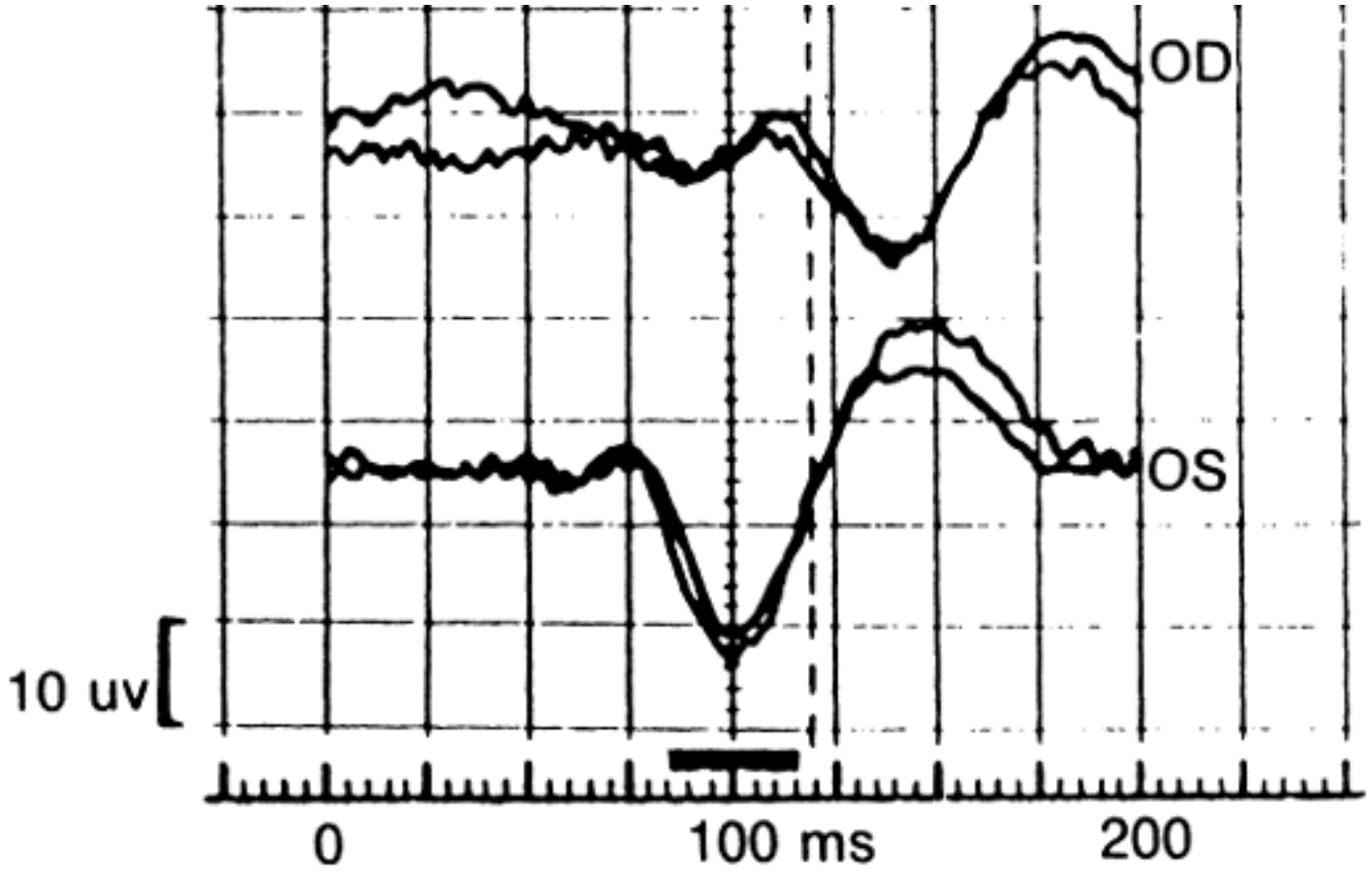
Classic MS symptoms

- Fatigue
- Heat sensitivity (uthoff phenomena)
- Cognitive dysfunction

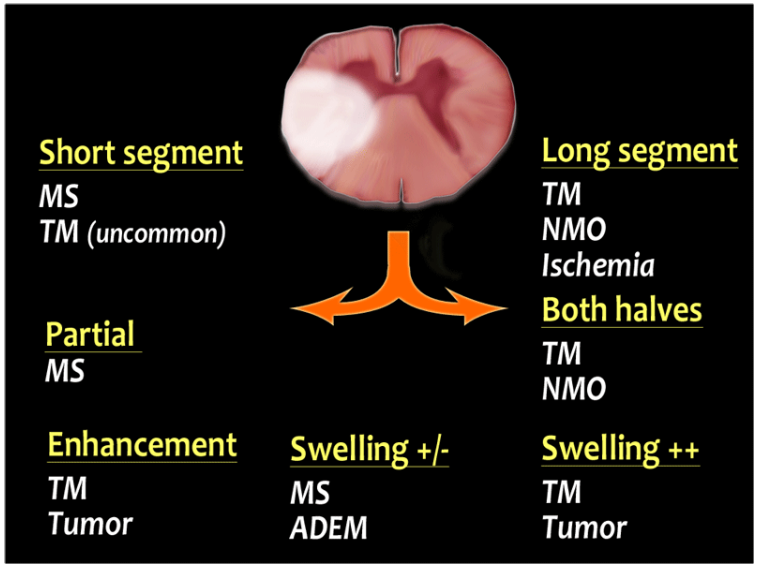
Optic neuritis

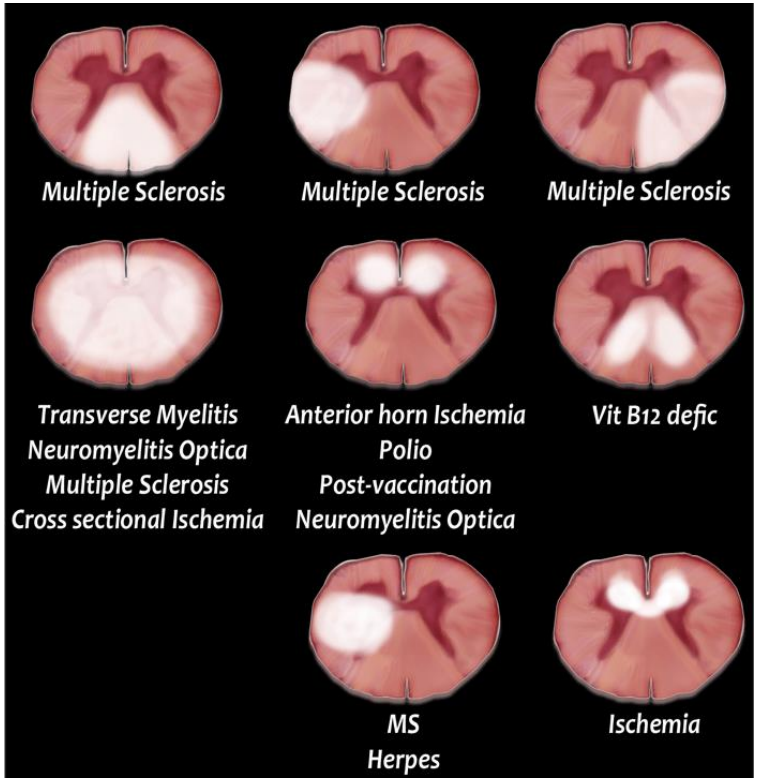
- Subacute onset (1-10 days)
- Unilateral eye pain accentuated by eye movement (92%)
- Mostly unilateral
- Median visual acuity 20/60
- Afferent pupillary defect

Delayed Visual Evoked Potentials response

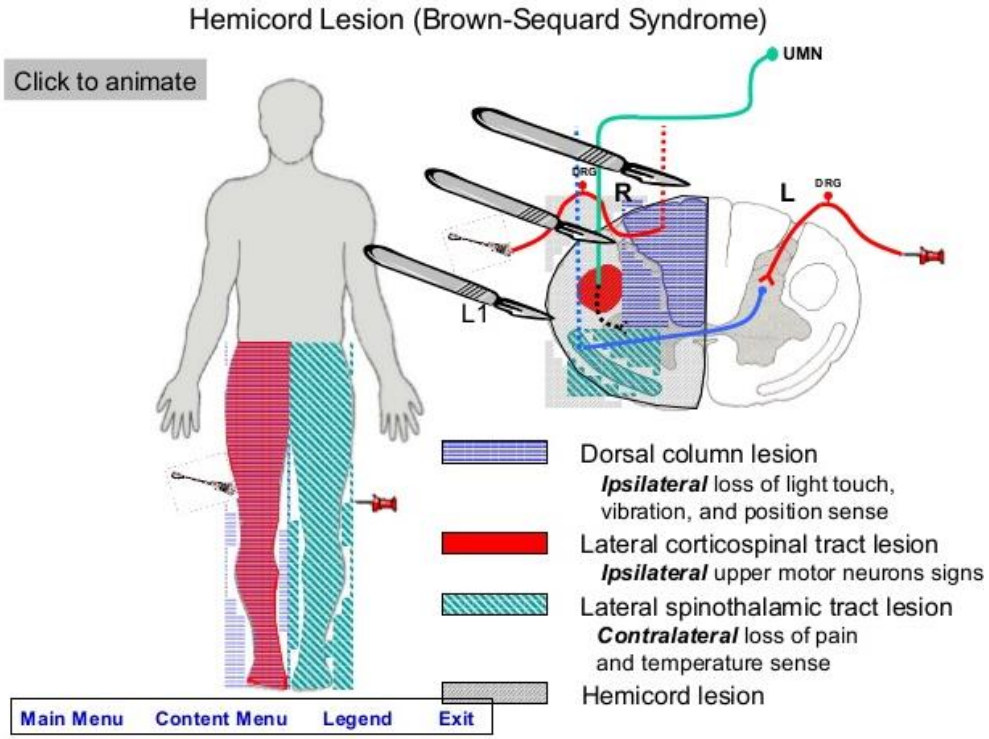


Myelitis

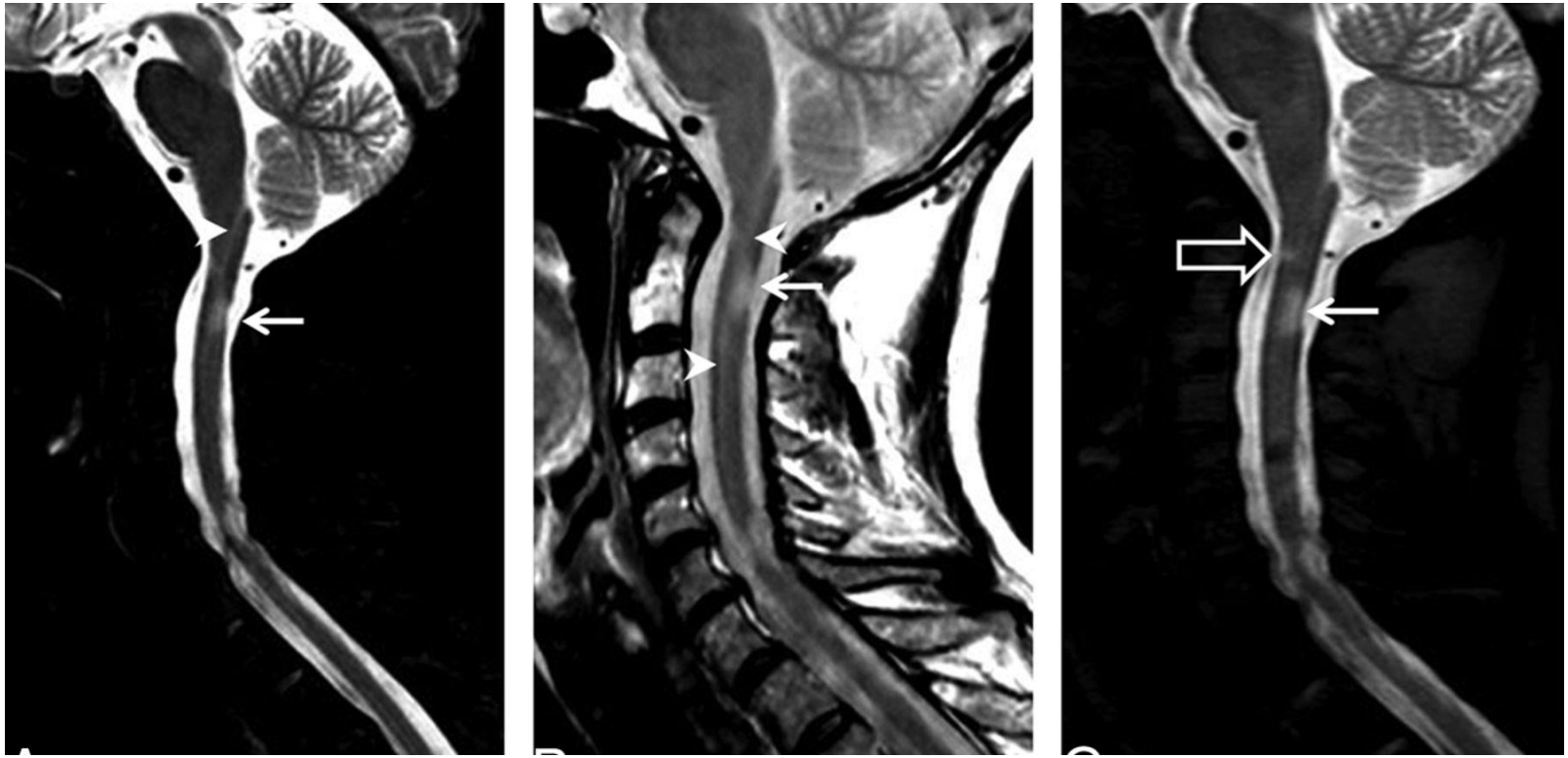

Short segment
MS
TM (uncommon)
Partial
MS
Enhancement
TM
Tumor
Swelling +/-
MS
ADEM
Long segment
TM
NMO
Ischemia
Both halves
TM
NMO
Swelling ++
TM
Tumor


Multiple Sclerosis
Multiple Sclerosis
Multiple Sclerosis
Transverse Myelitis
Neuromyelitis Optica
Multiple Sclerosis
Cross sectional Ischemia
Anterior horn Ischemia
Polio
Post-vaccination
Neuromyelitis Optica
Vit B12 defic
MS
Herpes
Ischemia

myelitis


Hemicord Lesion (Brown-Sequard Syndrome)
Click to animate
UMN
DRG
R
L
DRG
L1
Dorsal column lesion
Ipsilateral loss of light touch, vibration, and position sense
Lateral corticospinal tract lesion
Ipsilateral upper motor neurons signs
Lateral spinothalamic tract lesion
Contralateral loss of pain and temperature sense
Hemicord lesion
Main Menu
Content Menu
Legend
Exit

Myelitis in multiple sclerosis



McDonald Diagnostic Criteria

- The McDonald criteria, first developed in 2001 and revised in 2005,and in 2010.
- Final revisions of McDonald criteria was in 2017
- Diagnosis of **"Clinically definite MS"** needs demonstration of **dissemenination of space and time**

Dissemination in space (by MRI brain)

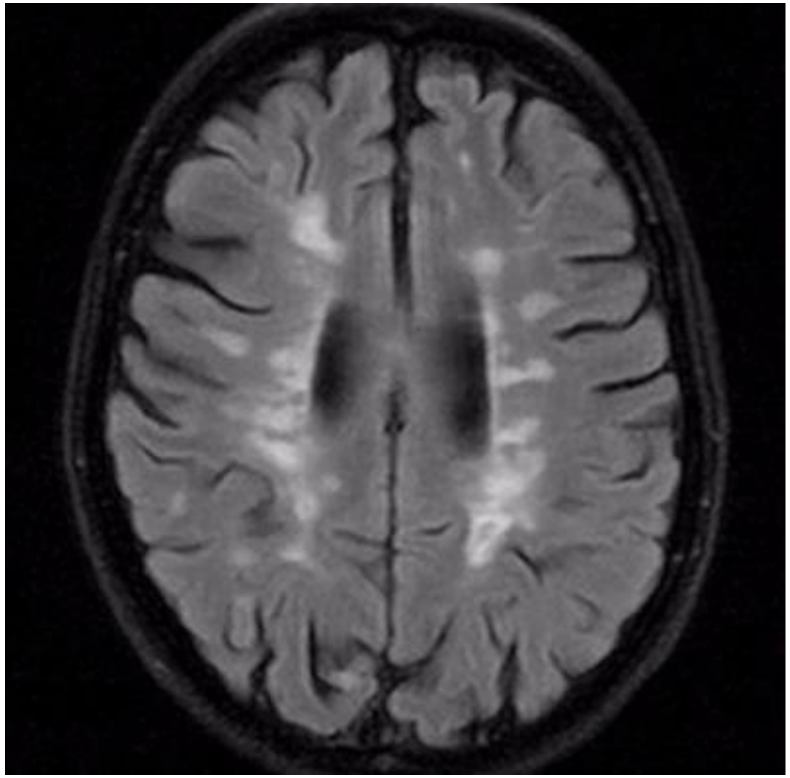
- are disseminated throughout the CNS but have a predilection for optic nerves, subpial spinal cord, brainstem, cerebellum, and juxtacortical and periventricular white matter regions
- demyelinated lesions are also commonly found in the cortical gray matter of MS patients

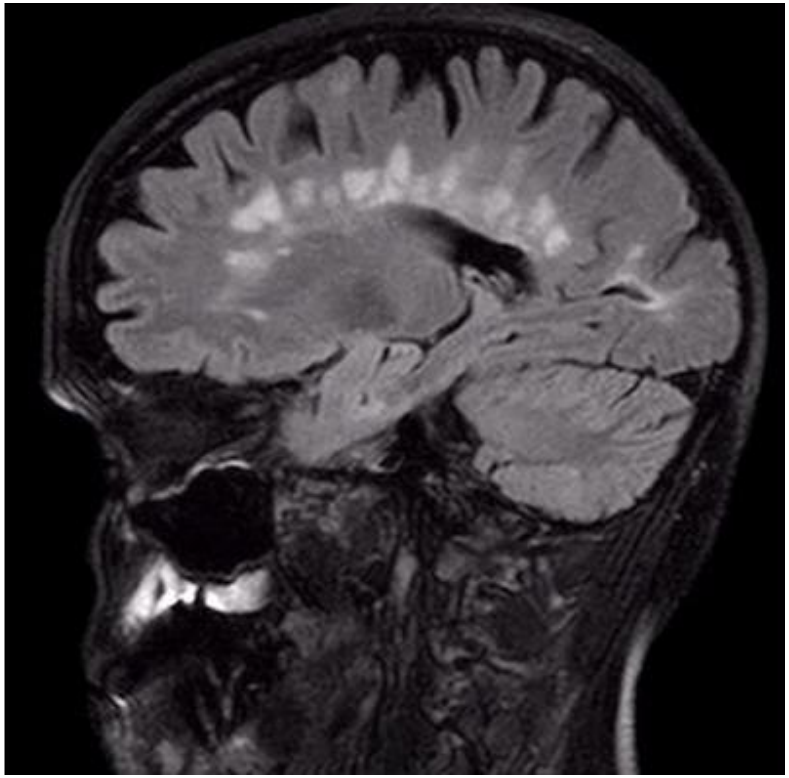
Dissemination in space (by MRI brain)

T2 lesion in ≥ 1 of the following locations:

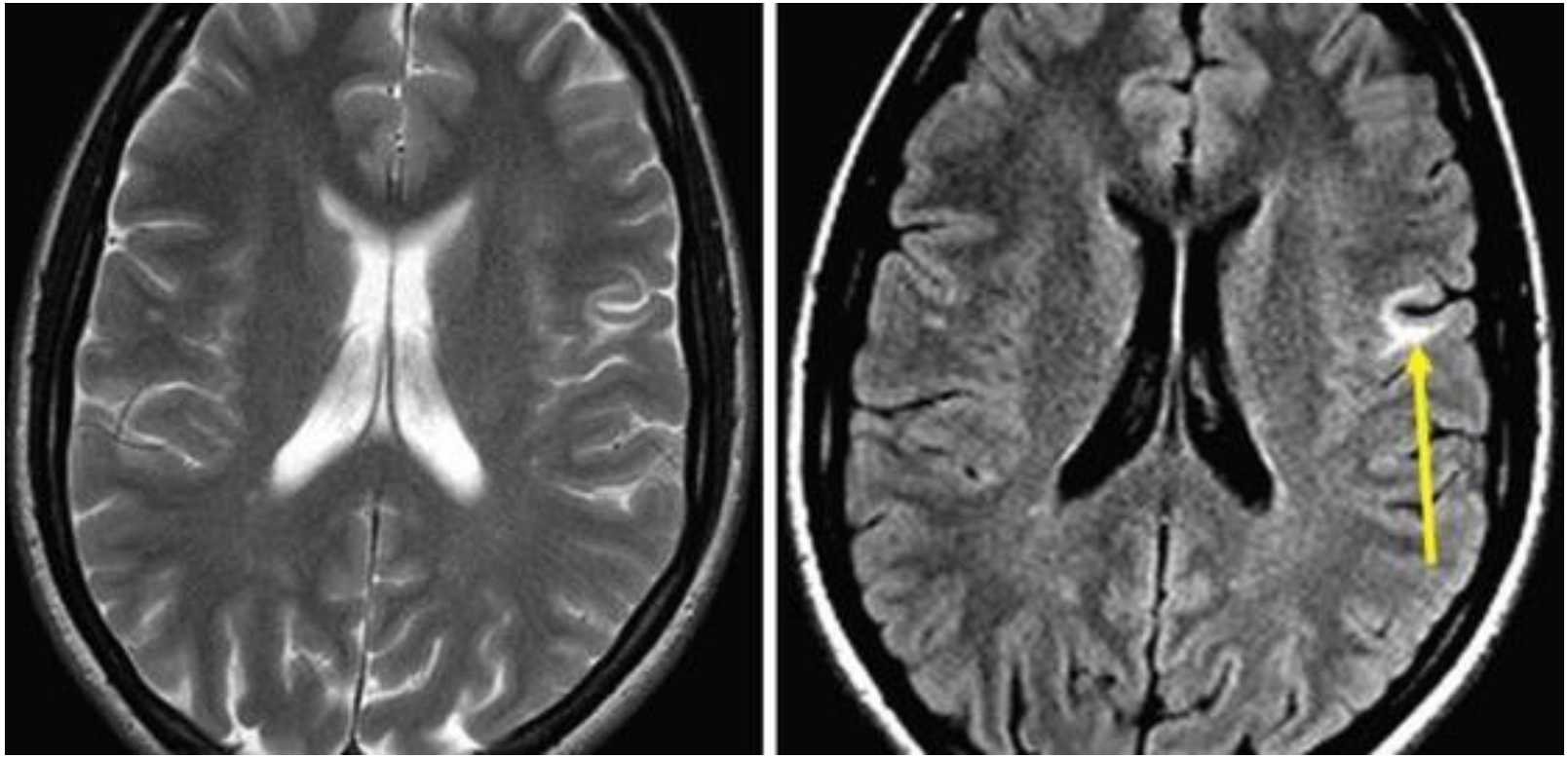
- Cortical /Juxtacortical
- Infratentorial
- periventricular
- Spinal cord

Perivenricular (Dawson finger)

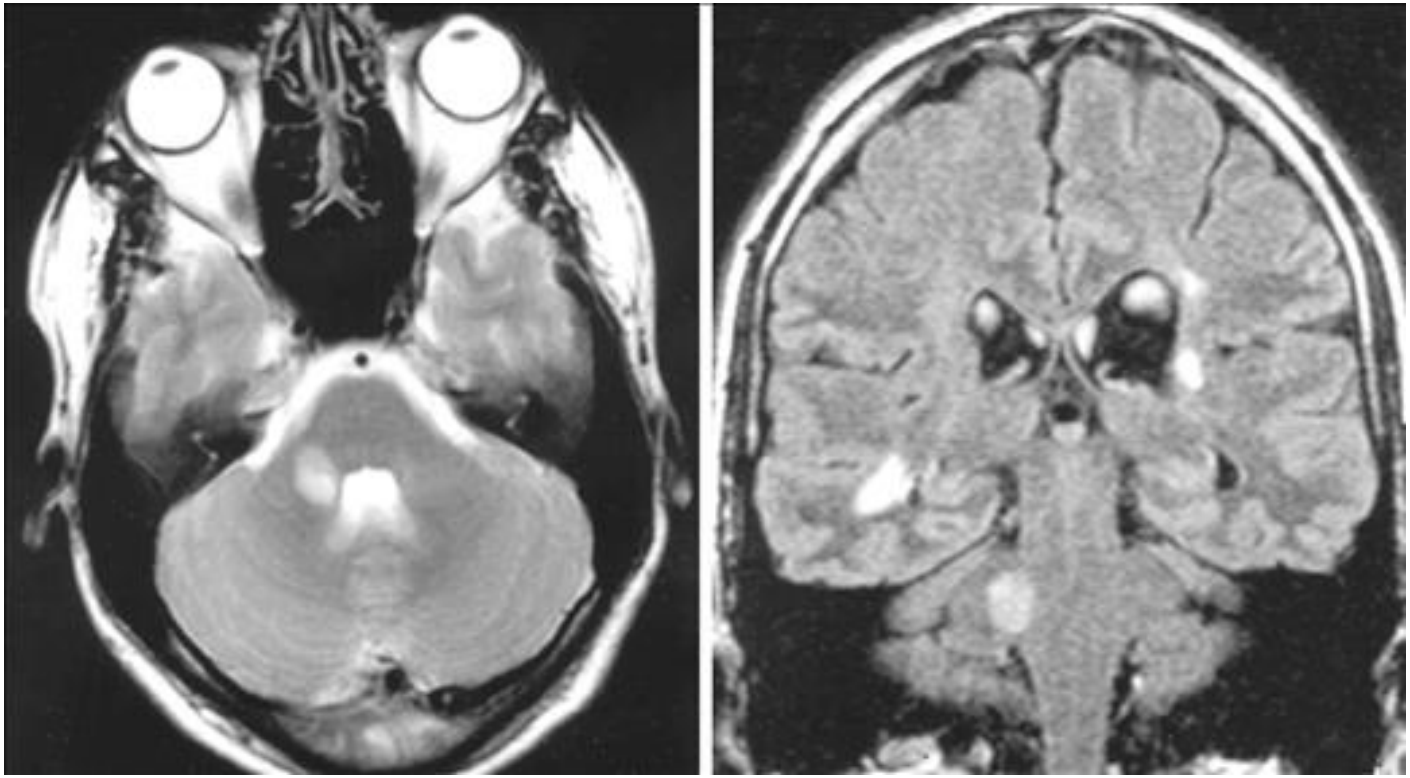




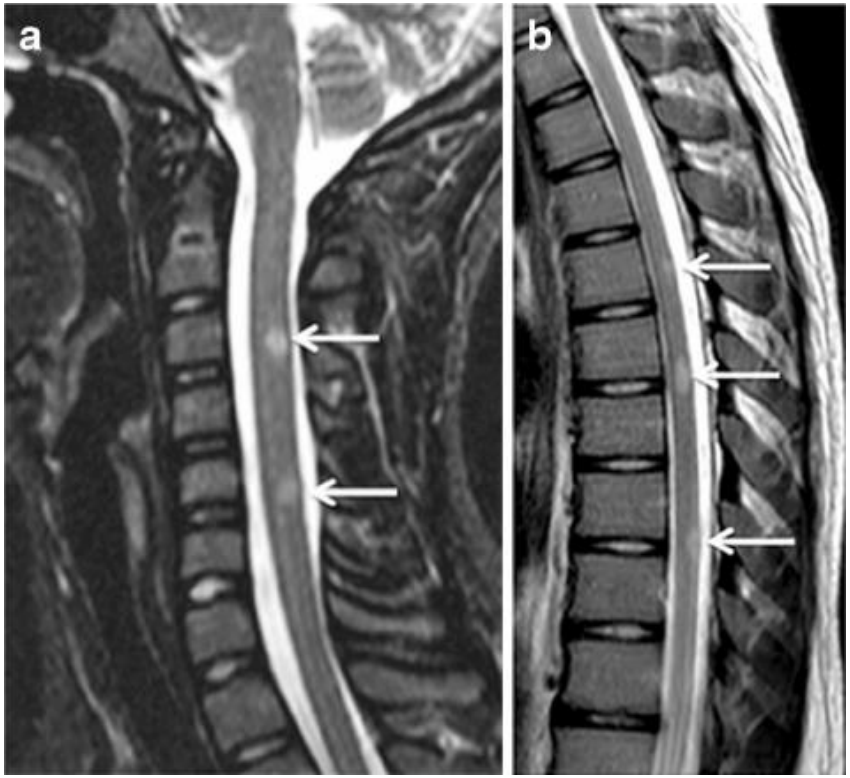
Juxtacortical lesion



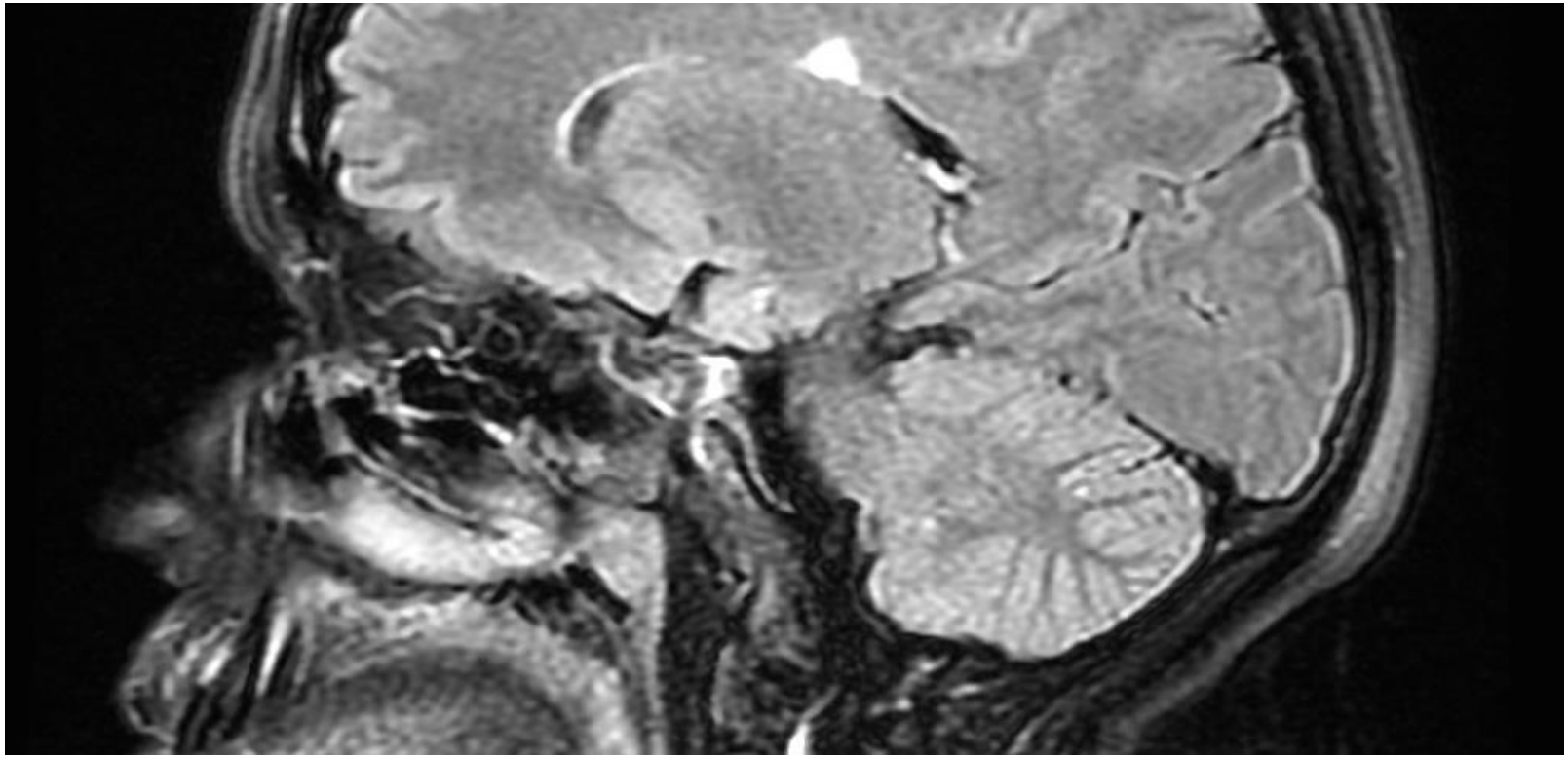
Infratentorial lesion



Spinal lesion



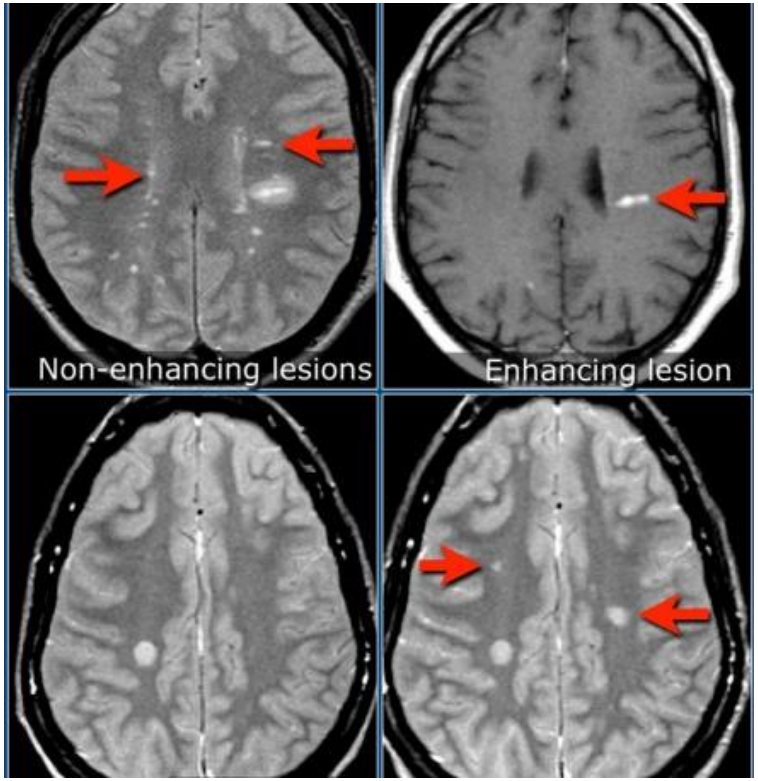
Corpus callosum lesion



Dissemination in time (MRI)

- simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time

- new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI



The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	none
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	none
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands

Primary progressive MS

1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

- **Plus two of the following criteria:**
- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions in the spinal cord
- Presence of CSF-specific oligoclonal bands

Clinically isolated syndrome

- A monophasic clinical episode with patient-reported symptoms and objective findings developing acutely or subacutely, with a duration of **at least 24 h**, with or without recovery, and in the absence of fever or infection; similar to a typical multiple sclerosis relapse (attack and exacerbation) but in a patient not known to have multiple sclerosis.
- can be monofocal (reflecting pathology in a single location) or multifocal; the specific manifestations of a clinically isolated syndrome depend on the anatomical location (or locations) of the pathology.
- Typical presentations include unilateral optic neuritis, focal supratentorial syndrome, focal brainstem or cerebellar syndrome, or partial myelopathy;

Atypical for CIS

- bilateral optic neuritis
- complete ophthalmoplegia
- complete myelopathy
- encephalopathy
- headache
- alteration of consciousness
- meningismus
- isolated fatigue.

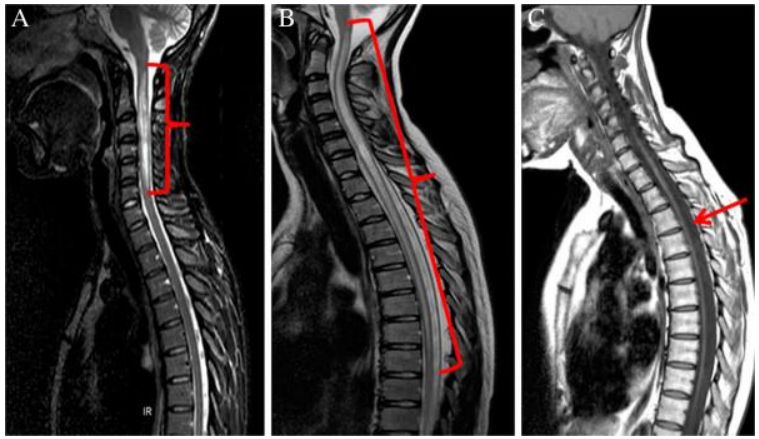
MS mimicker

- Sarcoidosis
- Behcet disease
- B12 deficiency
- Lyme/brucleeosis

Other Disorders

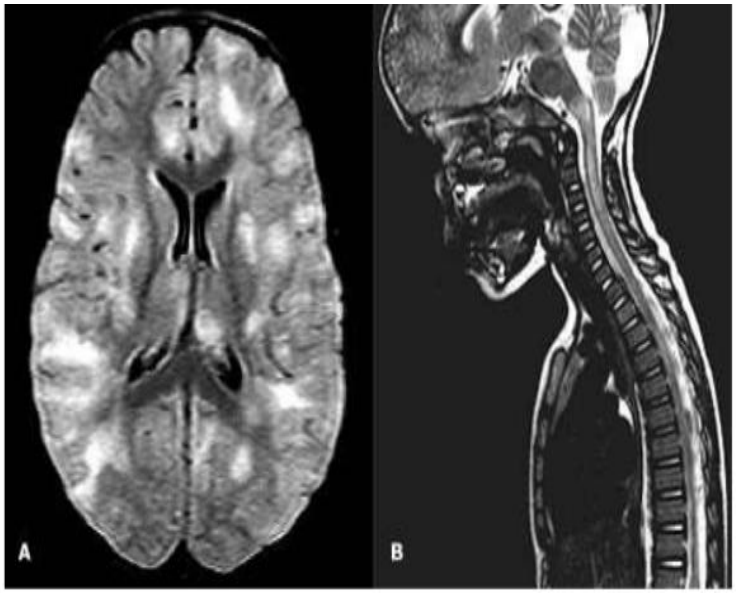
Neuromyelitis Optica (Devic Syndrome)

- Relapsing (55%), monophasic (35%)
- MRI: cord lesions, chiasmal signal changes
- CSF: generally >100 wbc, ↑ protein, rare OCB



Other Disorders

- **Postinfectious encephalomyelitis or ADEM**
  - Monophasic with preceeding event common (70%)
  - Most common in children
  - Altered LOC and seizures common
  - MRI: bilateral lesions, grey matter involvement



Management of relapsing-remitting multiple sclerosis

- Acute attacks (relapses) of MS are typically treated with glucocorticoids (IV methylprednisolone for 5 days).
- Indications for treatment of a relapse include functionally disabling symptoms with objective evidence of neurologic impairment.

	ROUTE	Mechanism of action
Interferon	S/C, IM	Cytokine modulator, decrease expression of matrix metalopproteases
Natalizumab	IV	Alpha-4 integrin monoclonal antibody
Fingolimod	oral	Inhibit egress of lymphocyte from lymph nodes
Dimethyl fumarate	oral	Anti-oxidative, anti-inflammatory
Teriflunamide	oral	Inhibit lymphocytre proliferation (anti-metabolite)
Alemtuzumab	IV	Anti-CD52 (B, T and NK cells)
Ocrelizumab	IV	B cell depletion
Caldribine	oral	Inhibit lymphocytre proliferation (anti-metabolite)

Side effects of MS treatment

- Injection site reaction (Interferons)

Increase liver enzyme

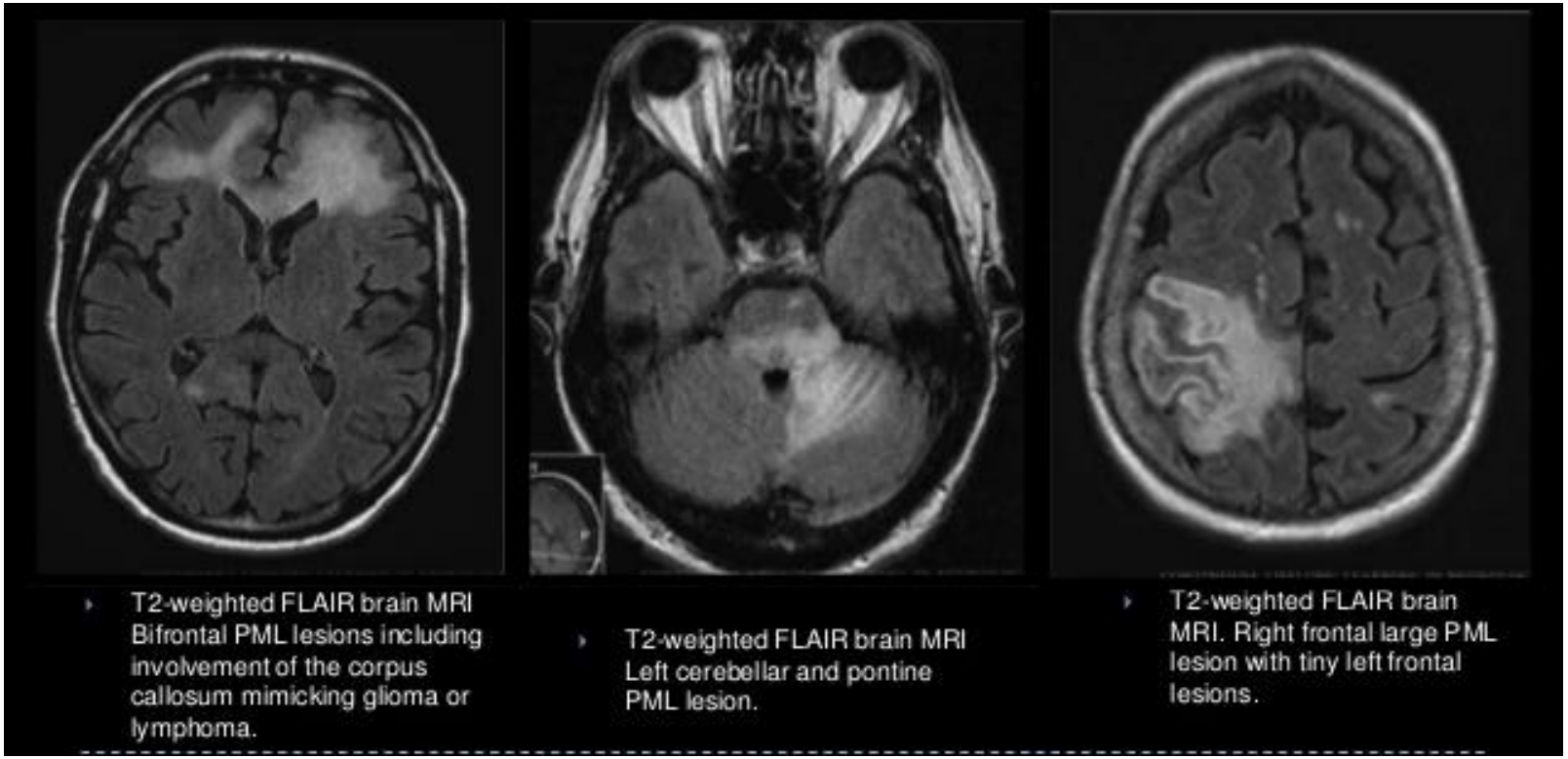
Lymphopenia

Cardiac conduction abnormalities (fingolimod)

Autoimmunity (alemtuzumab)

Progressive multifocal leukoencephalopathyPML (natalizumab)

Progressive multifocal leukoencephalopathy



- T2-weighted FLAIR brain MRI Bifrontal PML lesions including involvement of the corpus callosum mimicking glioma or lymphoma.
- T2-weighted FLAIR brain MRI Left cerebellar and pontine PML lesion.
- T2-weighted FLAIR brain MRI. Right frontal large PML lesion with tiny left frontal lesions.

Thank you