Demyelinating Disorders of Central Nervous System

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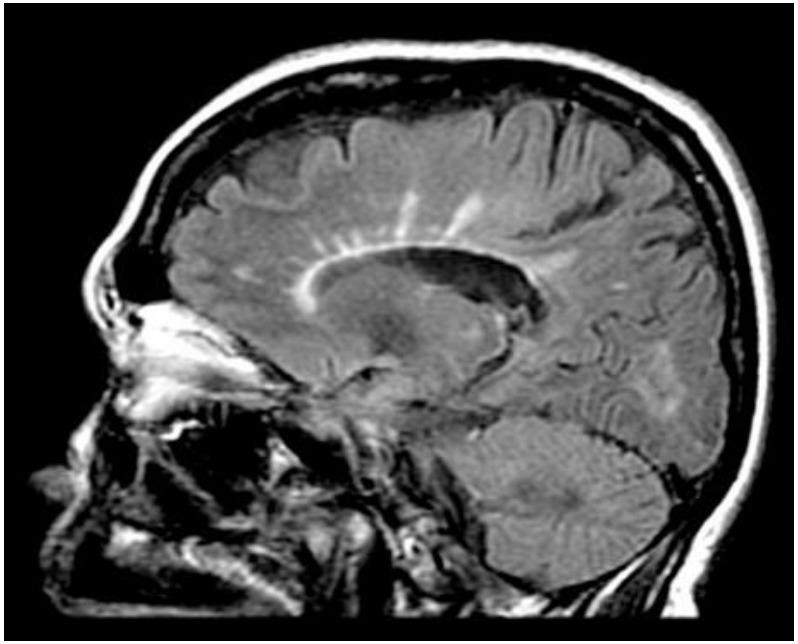
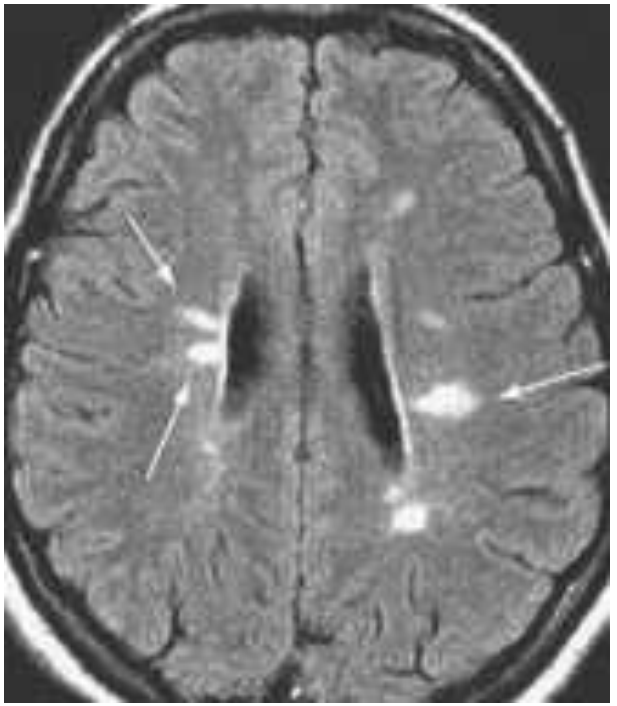
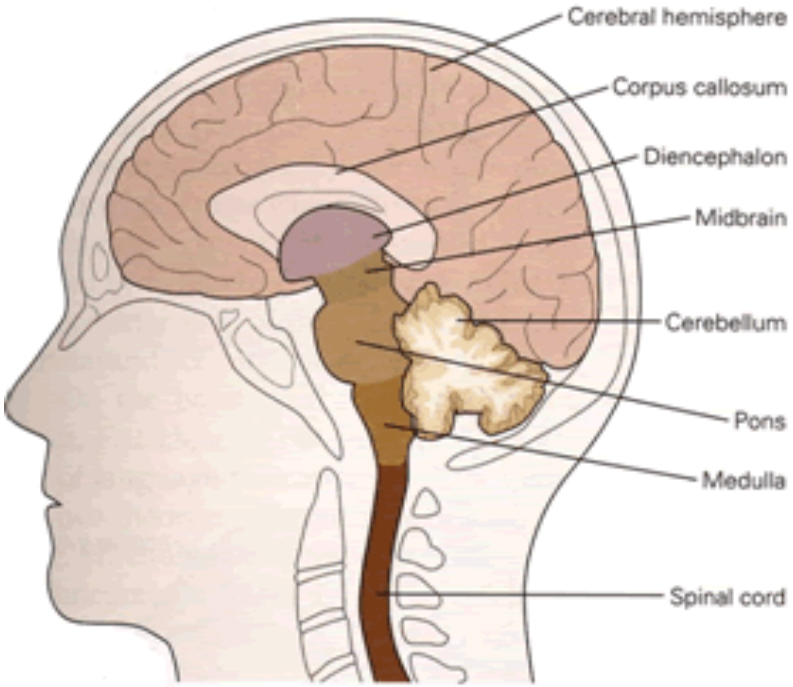
What is multiple sclerosis?

- Chronic, immune mediated demyelinating disease of central nervous system






Cerebral hemisphere
Corpus callosum
Diencephalon
Midbrain
Cerebellum
Pons
Medulla
Spinal cord

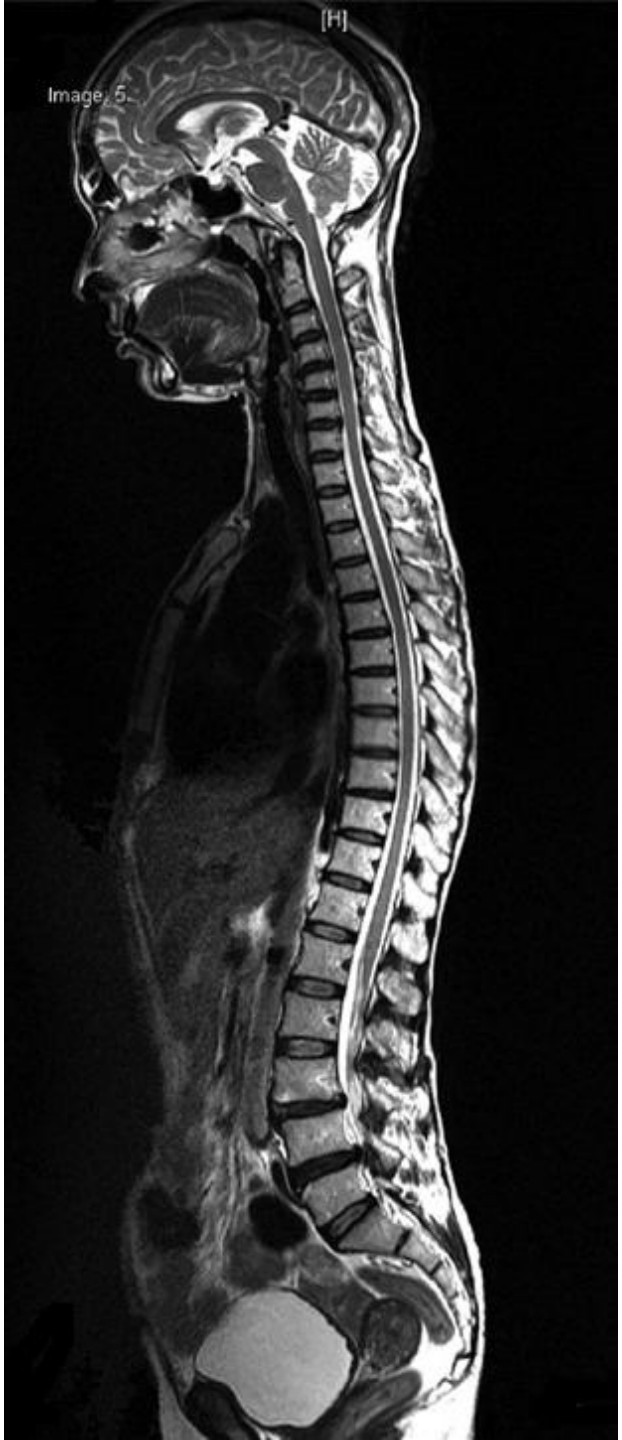

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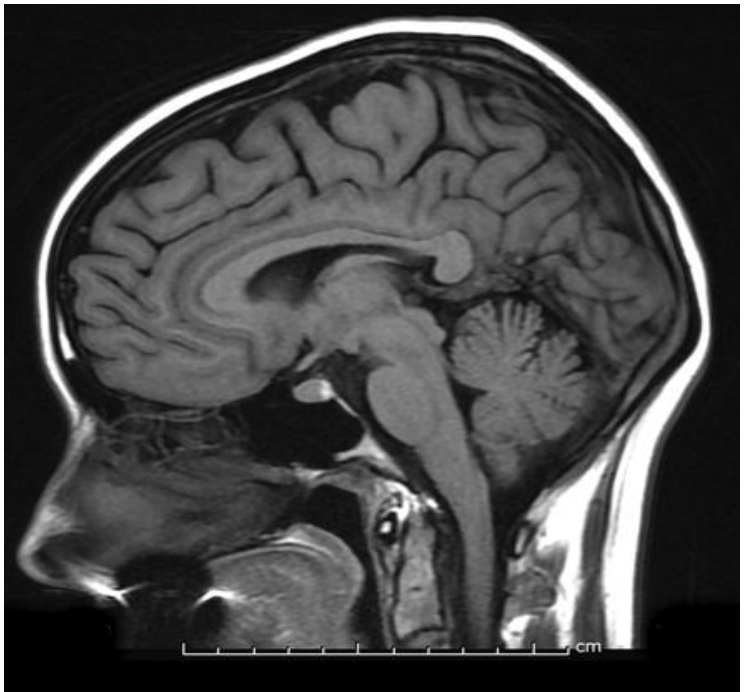
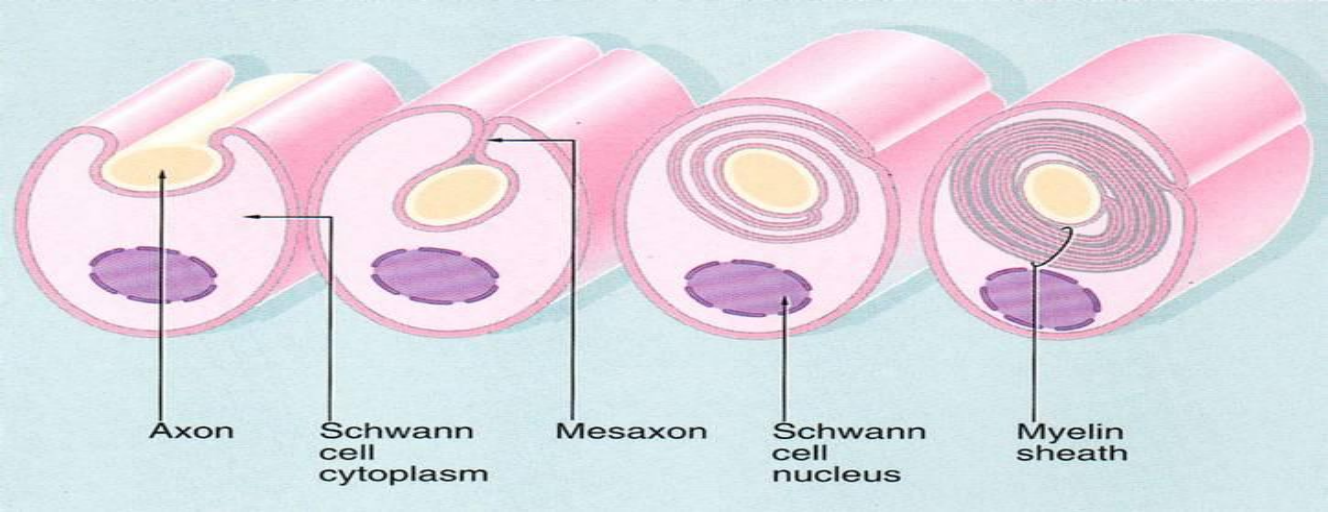
Image: 5

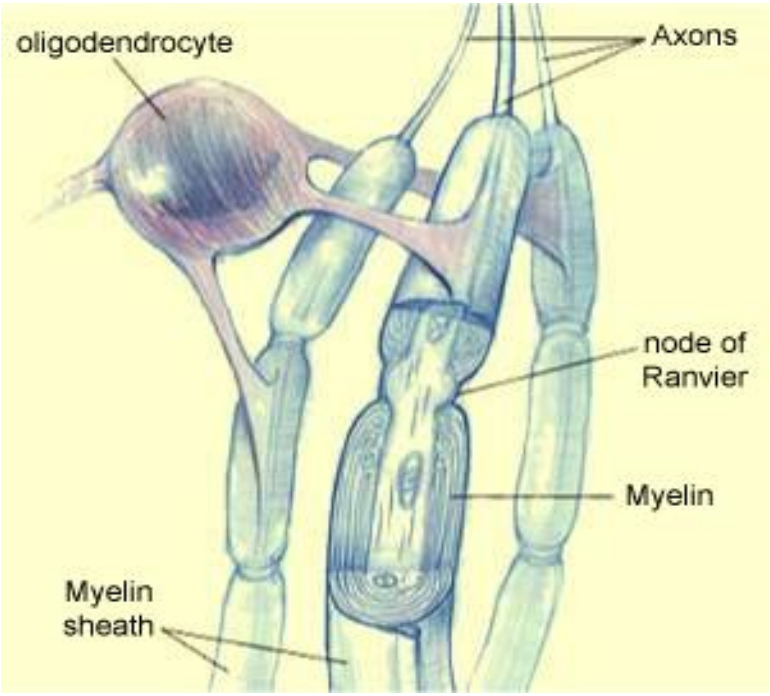

cm

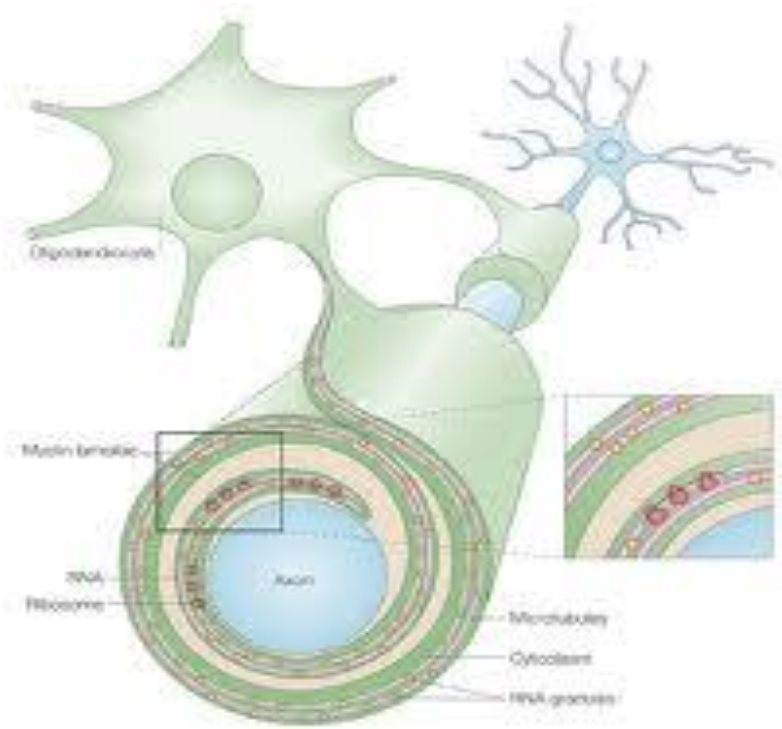
Myelin

- The myelin sheath is a greatly extended and modified plasma membrane wrapped around the nerve axon in a spiral fashion
- The myelin membranes originate from and are a part of the **Schwann cells** in the peripheral nervous system (PNS) and the **oligodendroglial cells** in the central nervous system (CNS)



Peripheral nervous system myelination



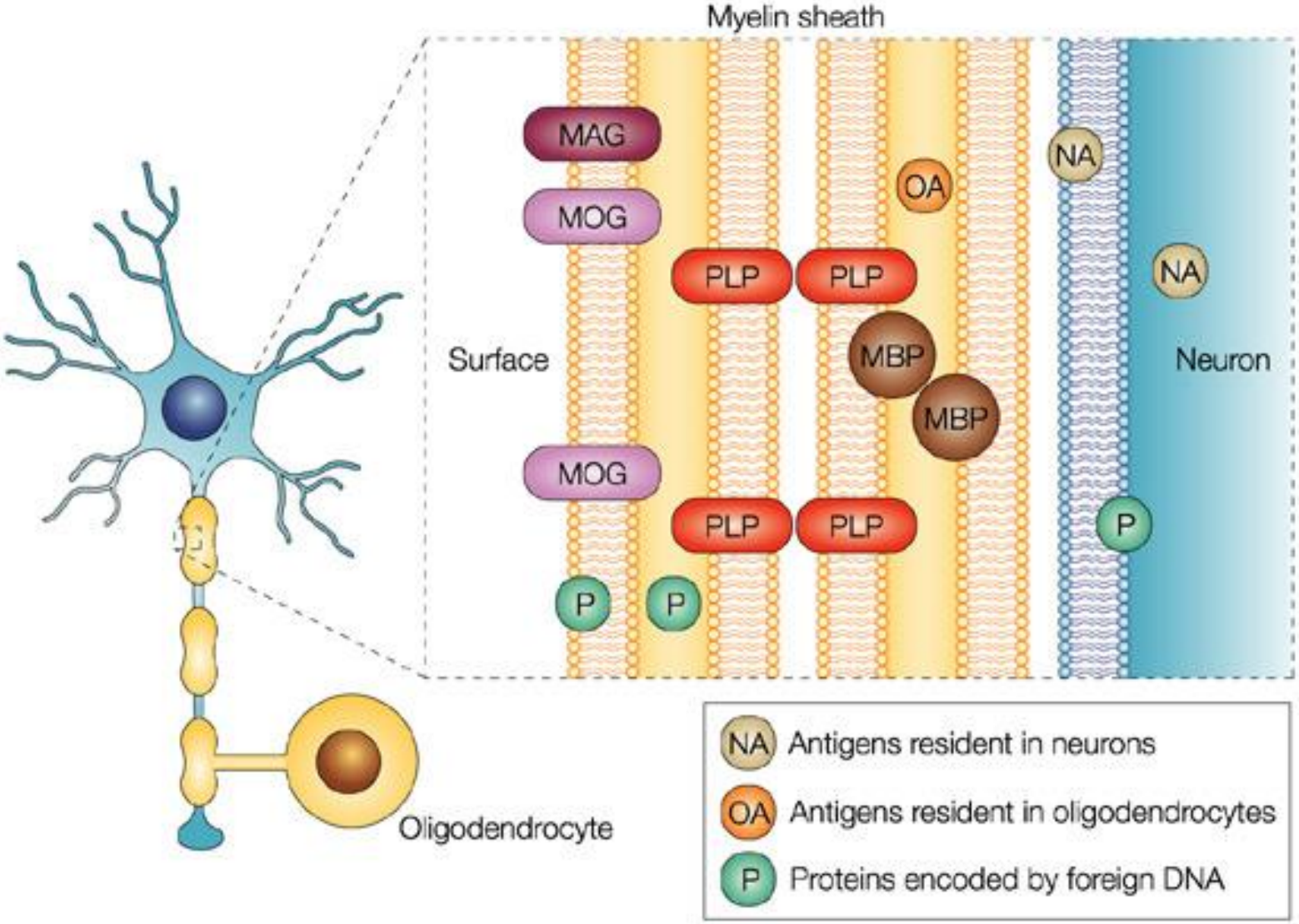


Central nervous system myelination

Content of myelin:

- Water 40%
- Lipid (70 to 85% of dry mass)
- Protein (15 to 30% of dry mass)

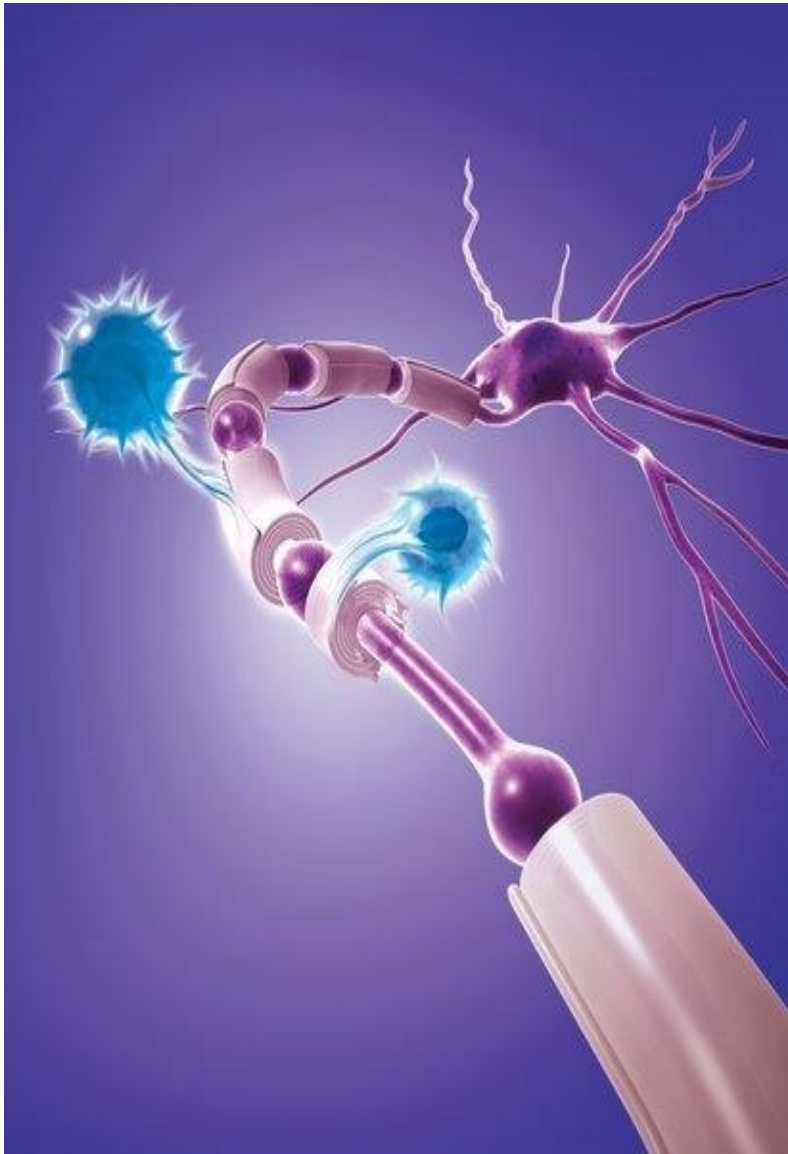
- Cerebroside, also known as galactosylceramide, is the most typical lipid of myelin
- Myelin/Oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP) ,myelin associated glycoprotein (MAG) and proteolipid proteins (PLP) are most important myelin proteins. Antigenic targets.


Myelin sheath
MAG
MOG
PLP
PLP
OA
NA
NA
MBP
MBP
Surface
Neuron
MOG
PLP
PLP
P
P
P
Oligodendrocyte
NA Antigens resident in neurons
OA Antigens resident in oligodendrocytes
P Proteins encoded by foreign DNA

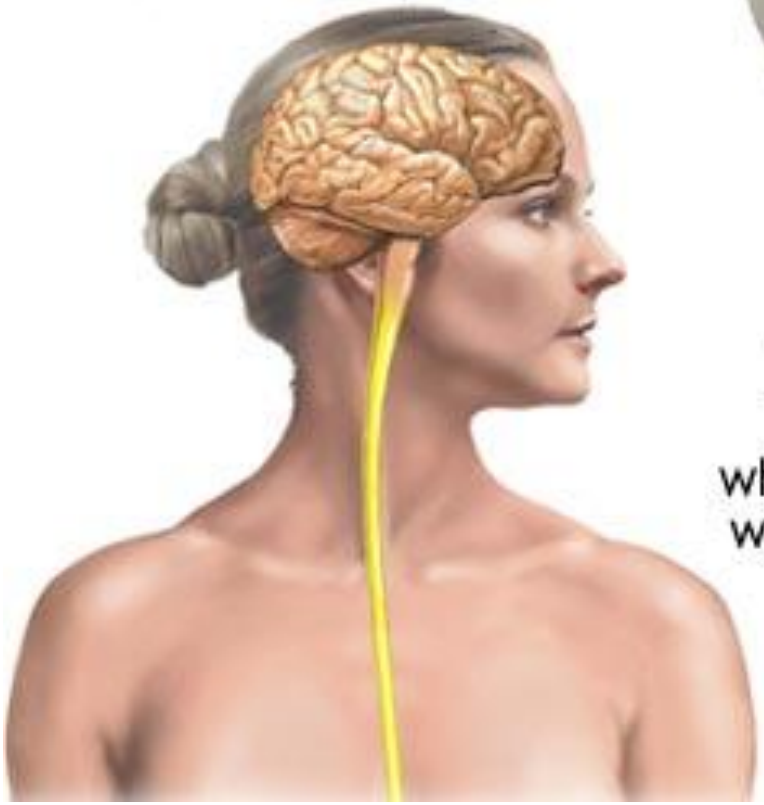
Myelin Function

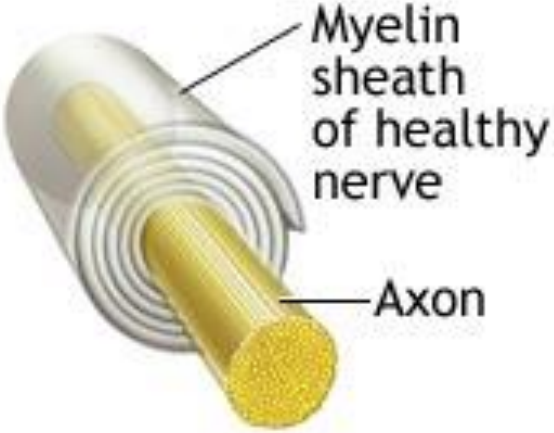
Myelin;

- Increases the conduction of impulses
- Protects axons from injury
- Contains growth factors for axonal survive



Central nervous system
(brain and spinal cord)

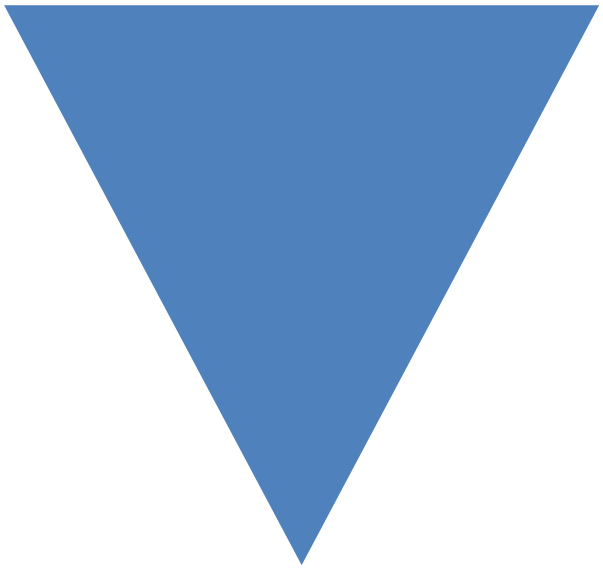




In multiple sclerosis
the myelin sheath,
which is a covering that
wraps around the axon,
is destroyed with
inflammation
and scarring

Multiple Sclerosis: Pathology

Inflammation
and
Eudema



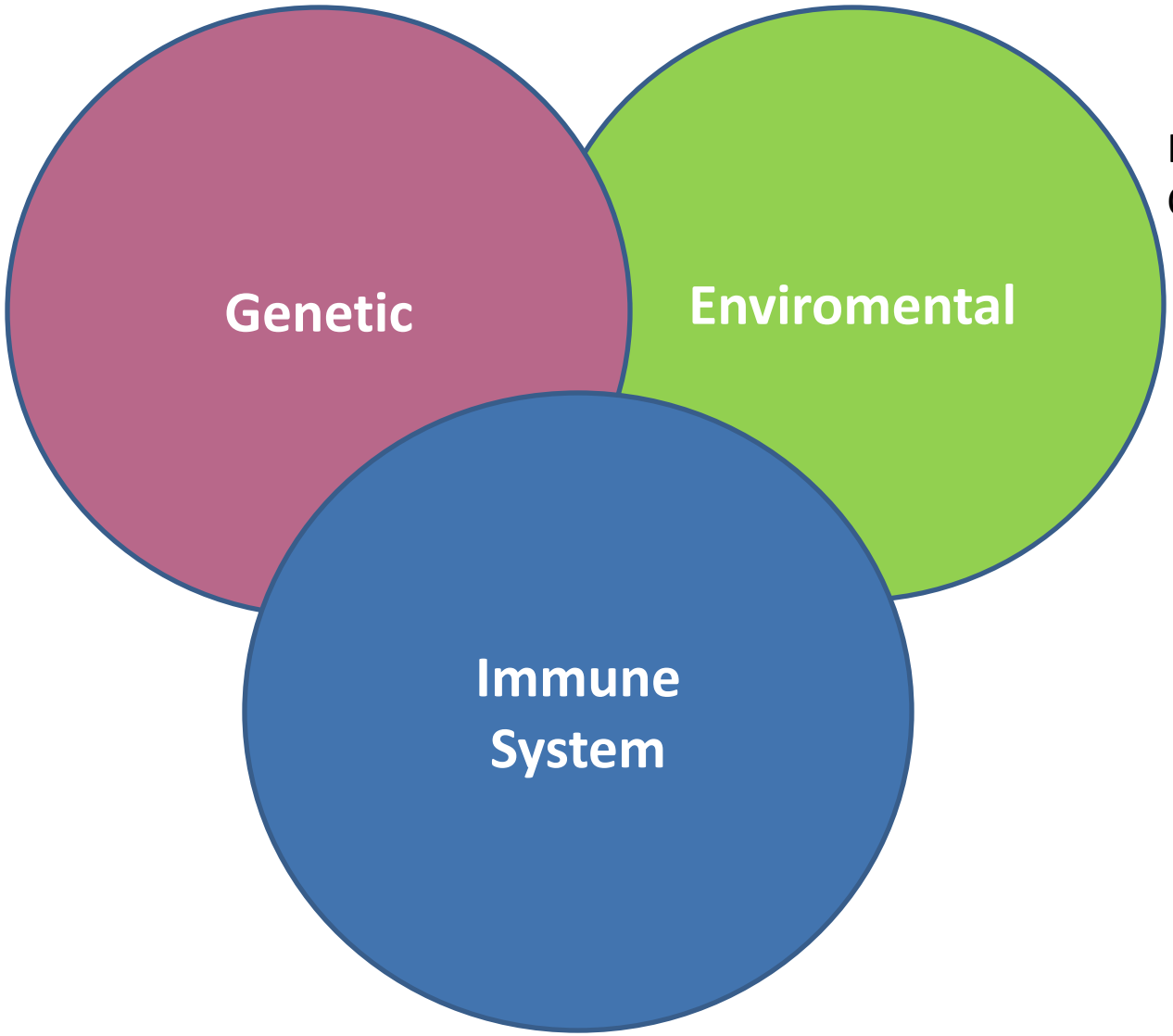
Demyelination
and
Remyelination

Axonal Loss / Neurodegeneration

Multiple means its influence multiple areas in CNS and **sclerosis** means scarring

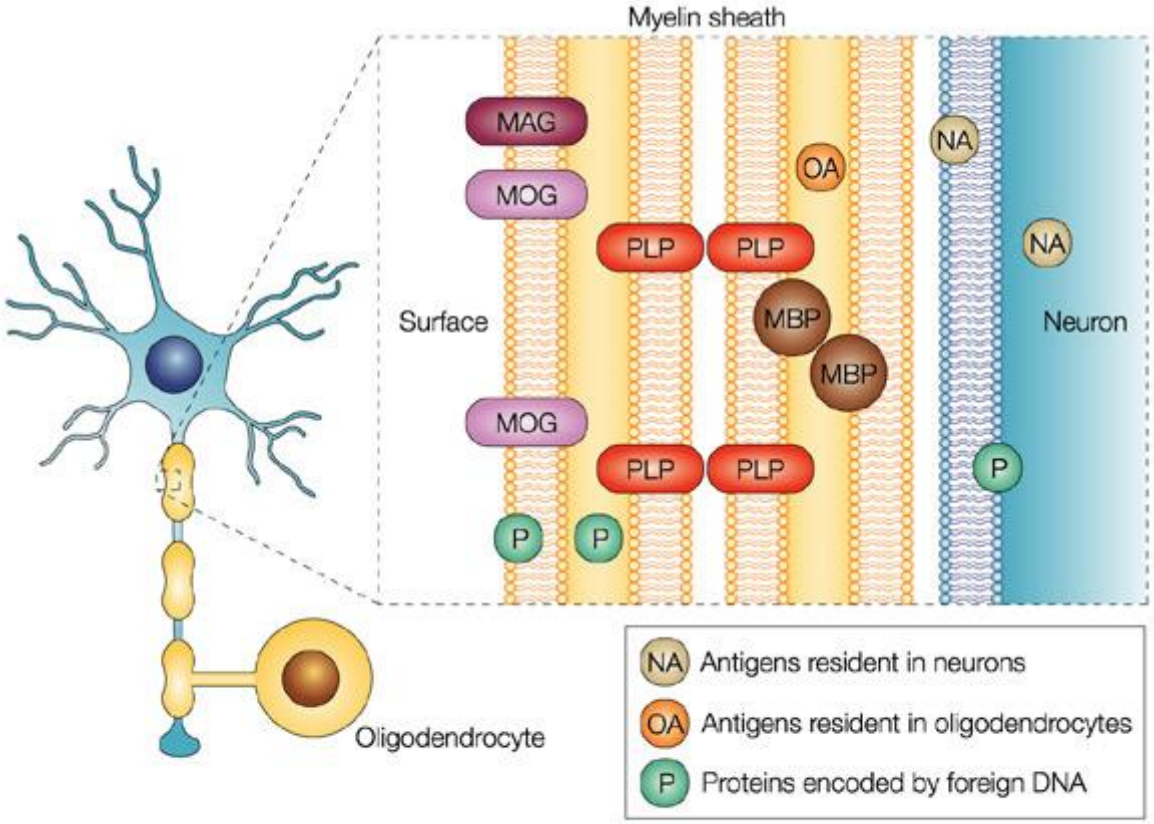
Pathogenesis

HLA DR2 allel

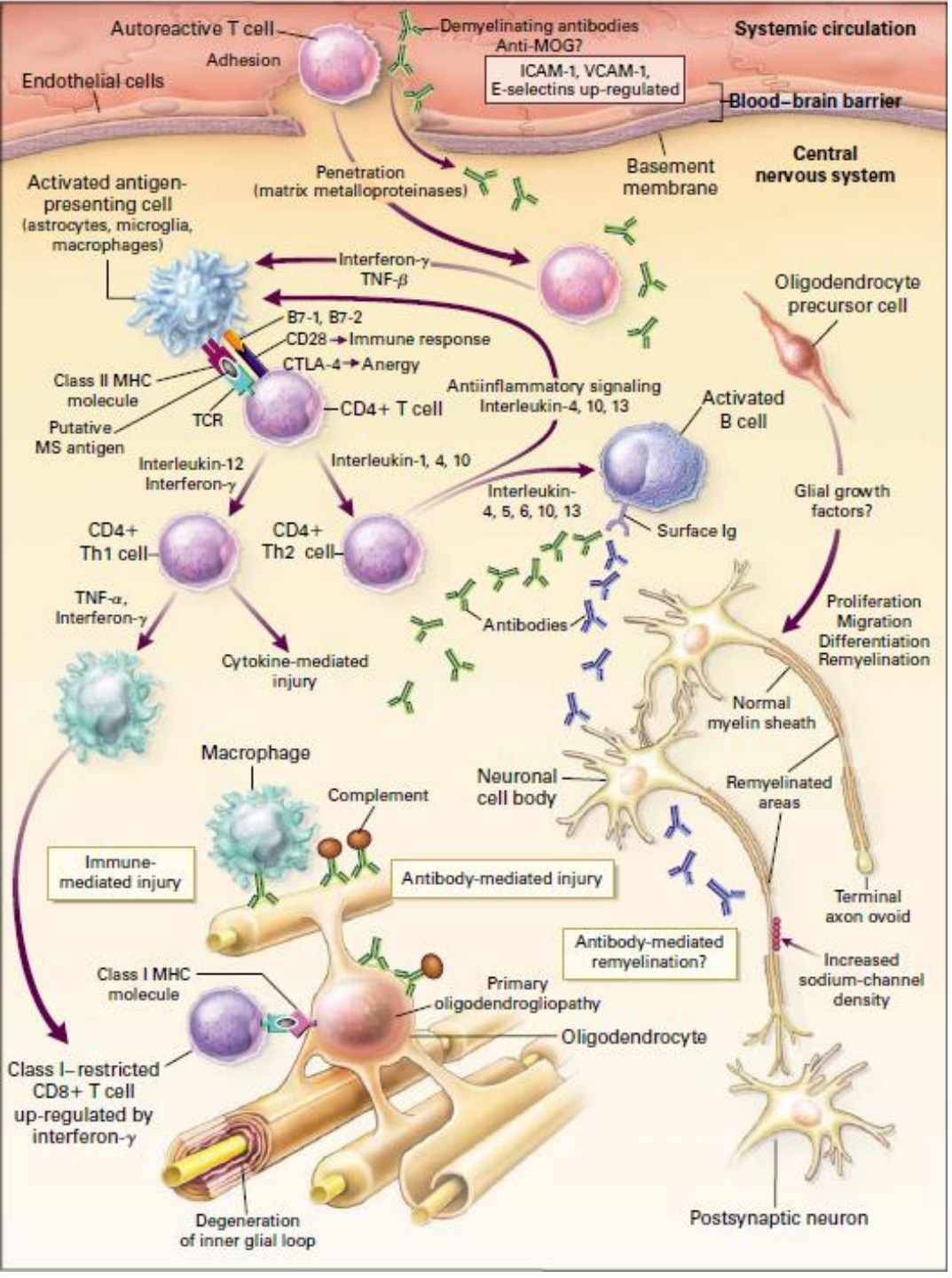


HHV 6
C. Pneumonia

Immun Myelin Damage Mechanism in Multiple Sclerosis



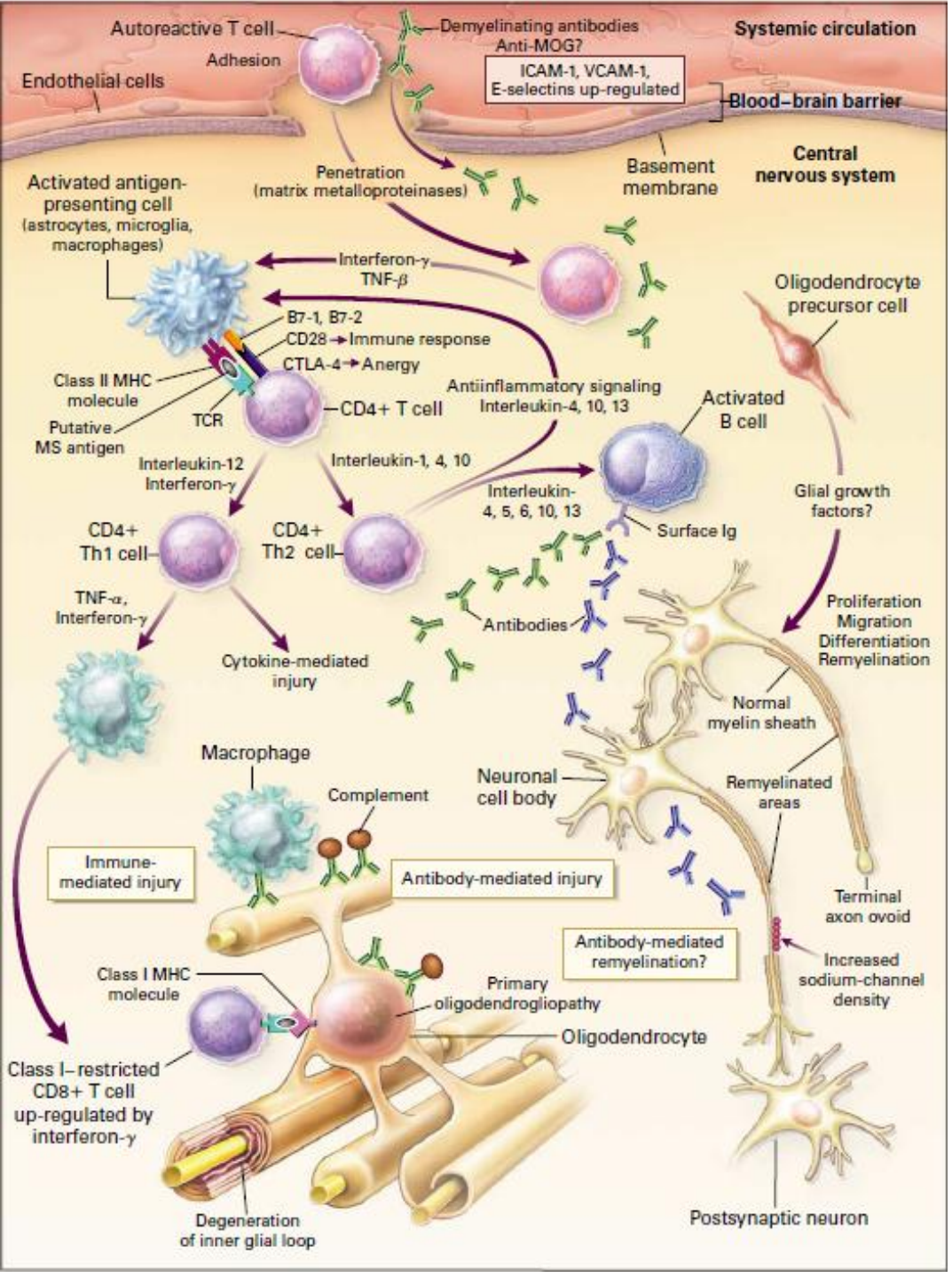
➢Proteins of the myelin sheath, oligodendrocytes and neurons are possible targets of the immune response in multiple sclerosis.



Genetic and environmental factors may facilitate autoreactive T cells

Also up-regulate the expression of endothelial adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1 (VCAM-1), and E-selectin

MMP's help penetration of T cells into the central nervous system.

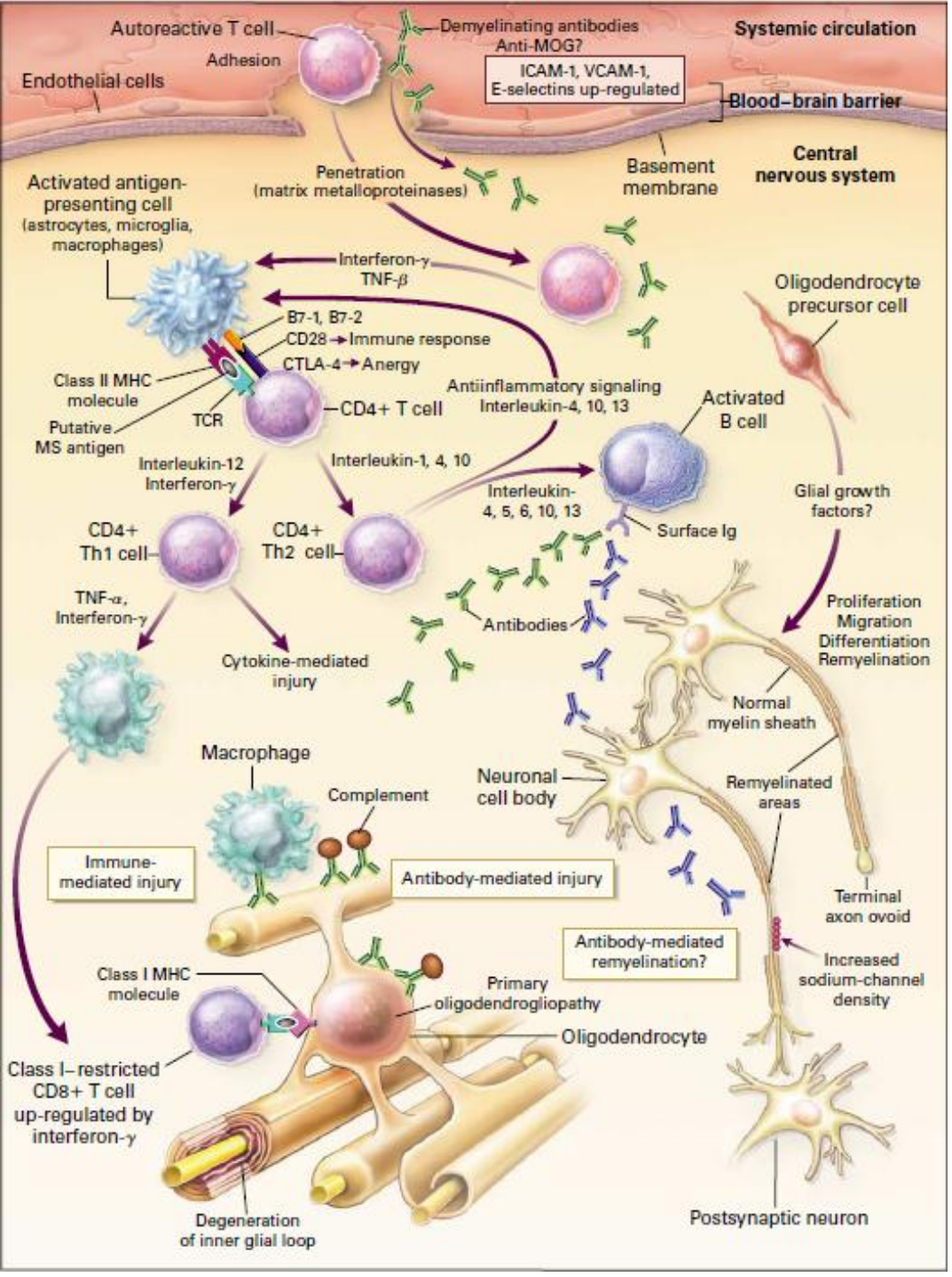


Proinflammatory cytokines such as Interferon *γ* and tumor necrosis factor *β* (TNF *β)* released by activated T cells

This cytokines up-regulate the expression of cell-surface molecules on neighboring lymphocytes and antigen-presenting cells.

Antigen-presenting cells make complexes with antigens (myelin proteins, MOG, MBP, MAG) and T cell receptor

Enhanced cytokine response -> *Cytokine mediated injury*

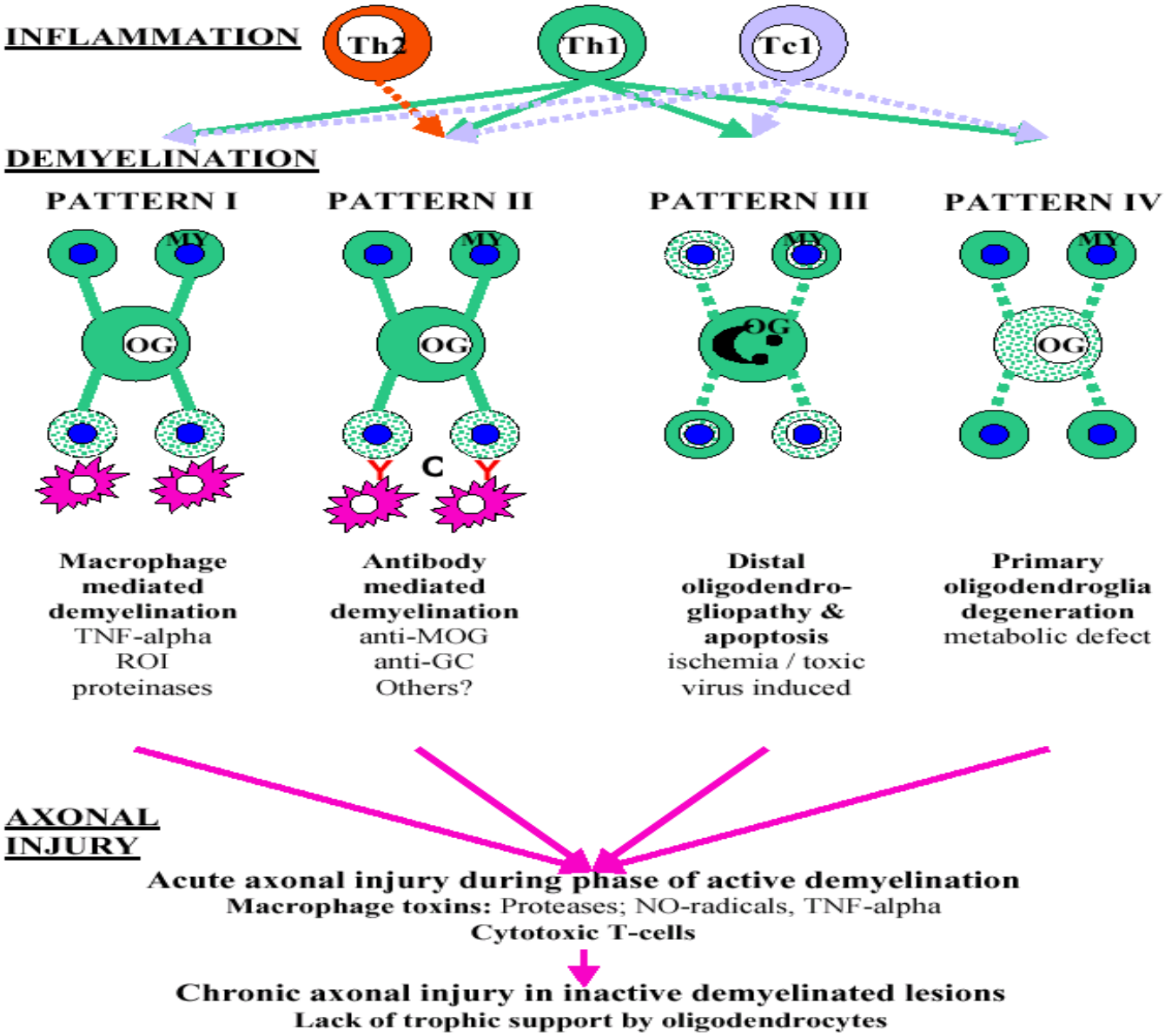


Cytokines from T cells activate B cell response and antibody syntesis

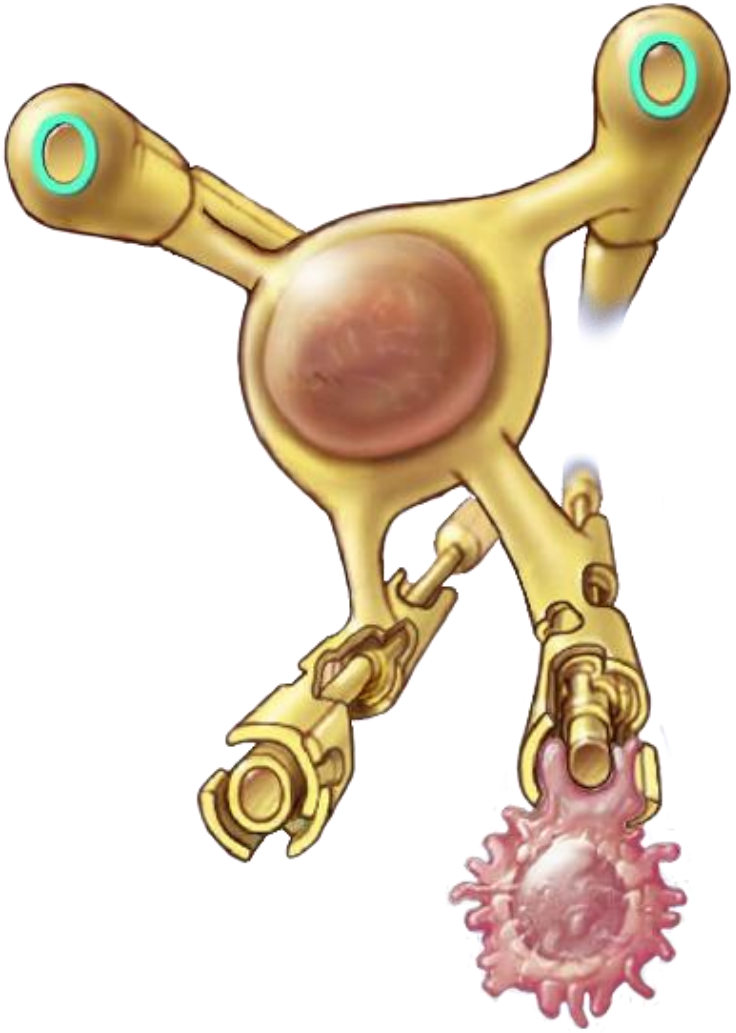
Antibody mediated injury;
digestion of surface myelin antigens by macrophages, including binding of antibodies against myelin and oligodendrocytes (complement-mediated injury)

Direct injury of oligodendrocytes
by CD4+ and CD8+ T cells

PATHOLOGY OF MULTIPLE SCLEROSIS



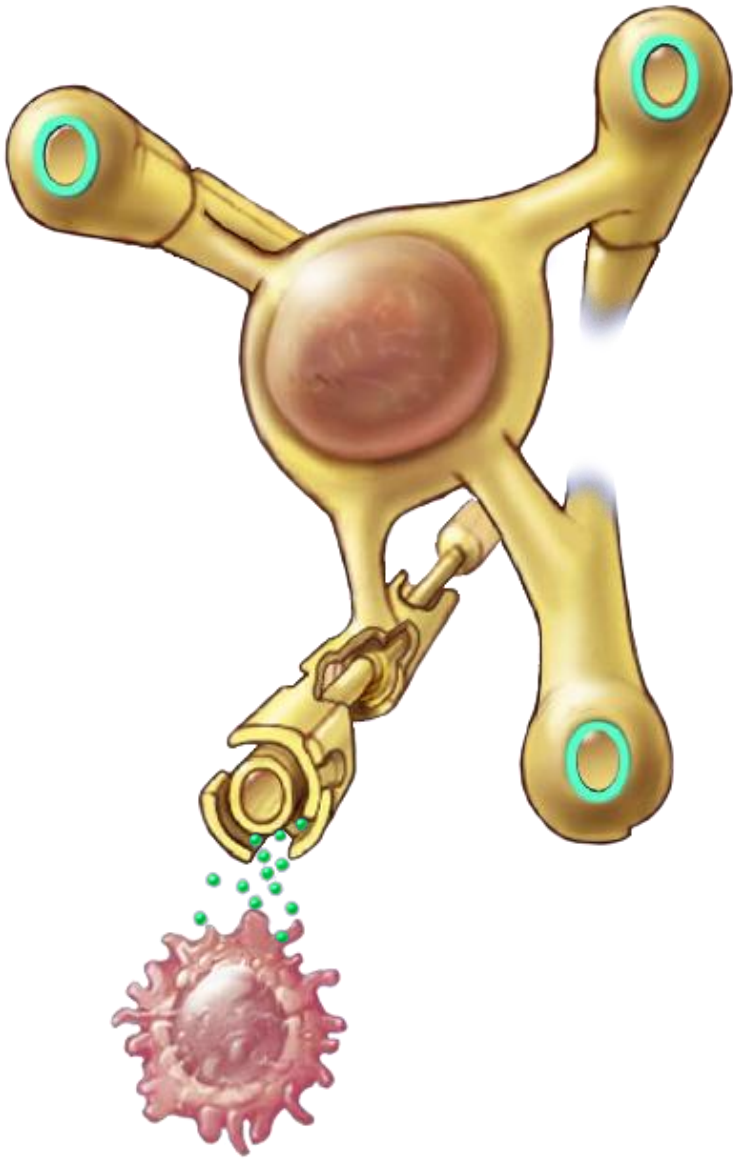
Pattern I Demyelination



T-cells
CD4-Th_1
CD4-Th_2
CD8

Macrophage mediated

Pattern II Demyelination



T-cells
CD4-Th_1
CD4-Th_2
CD8

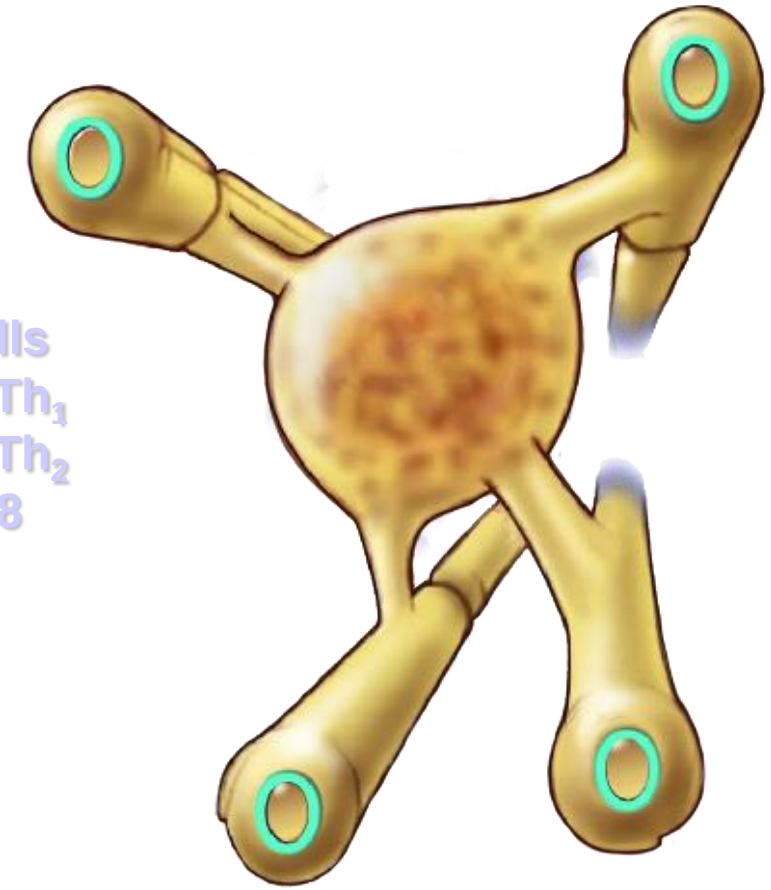
Antibody mediated

Pattern III Demyelination

T-cells
CD4-Th_1
CD4-Th_2
CD8

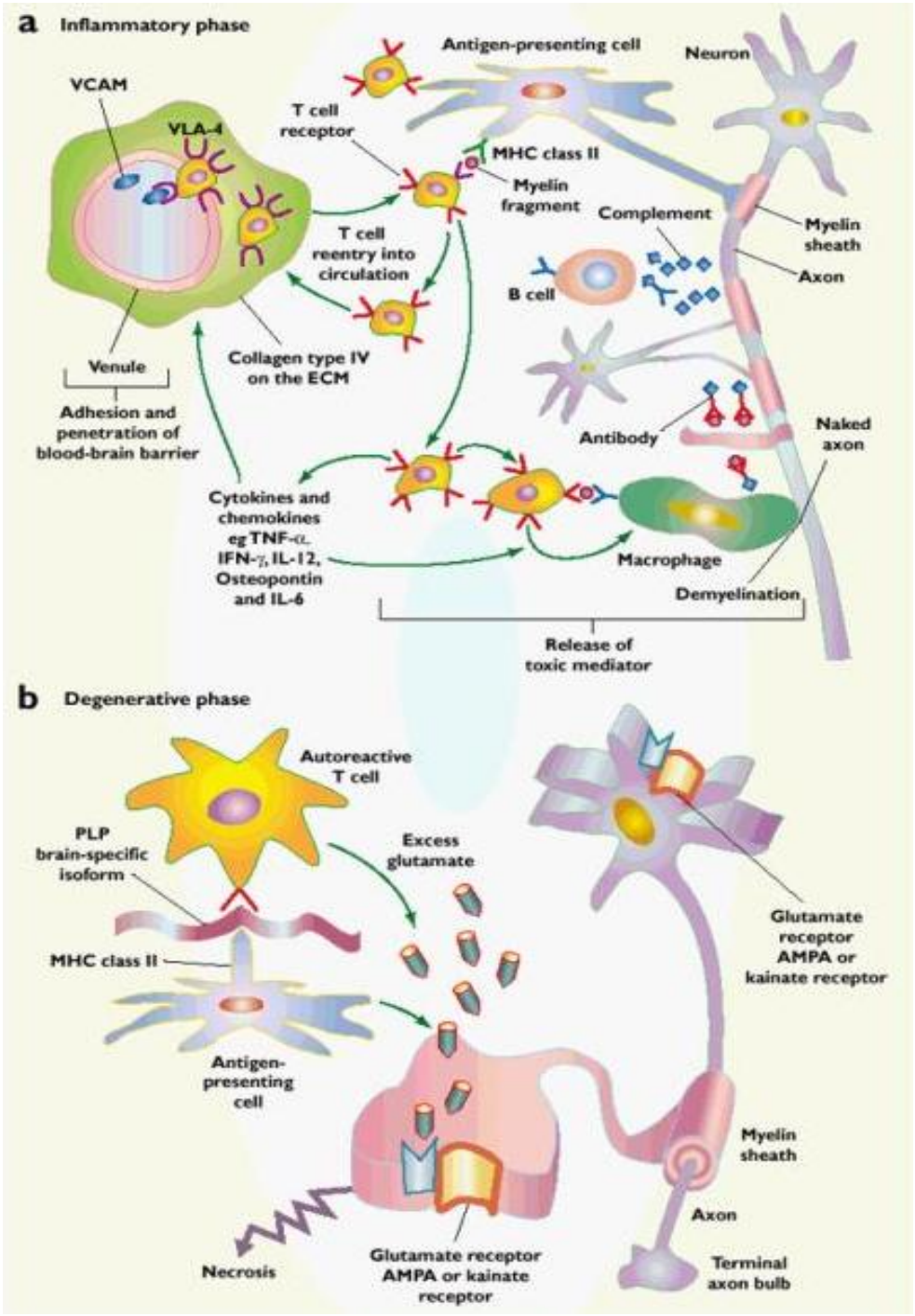
Distal oligodendrogliopathy & apoptosis

Pattern IV Demyelination



T-cells
CD4-Th_1
CD4-Th_2
CD8

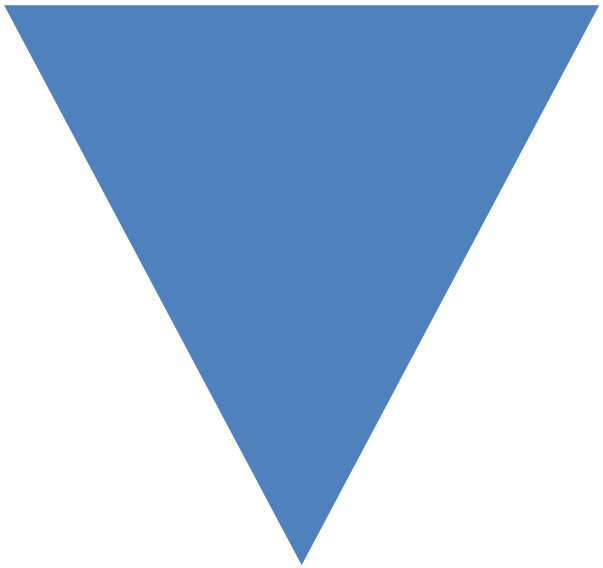
Primary oligodendrogliopathy degeneration



Multiple sclerosis: a two-stage disease

Multiple Sclerosis: Pathology

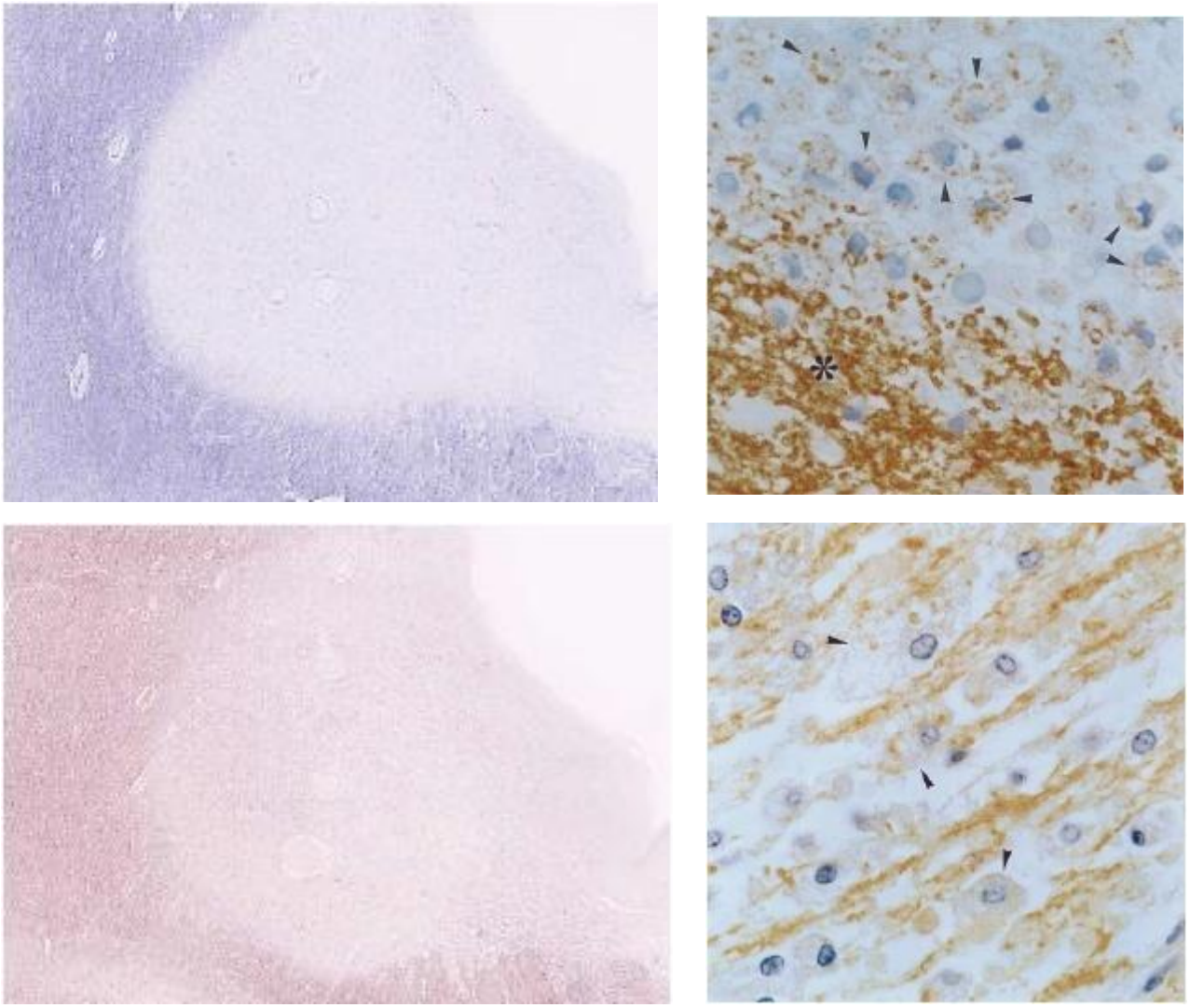
Inflammation
and
Eudema



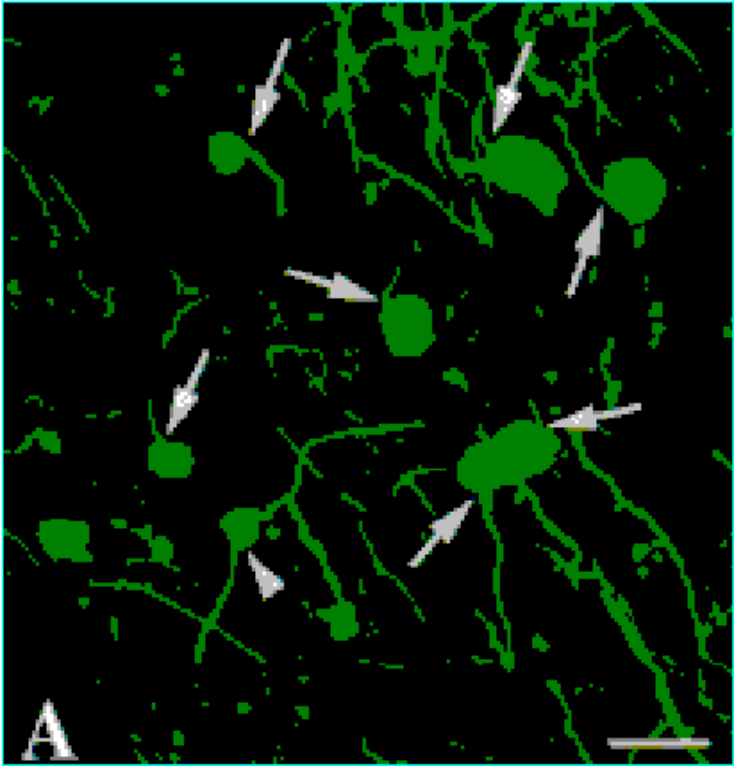
Demyelination
and
Remyelination

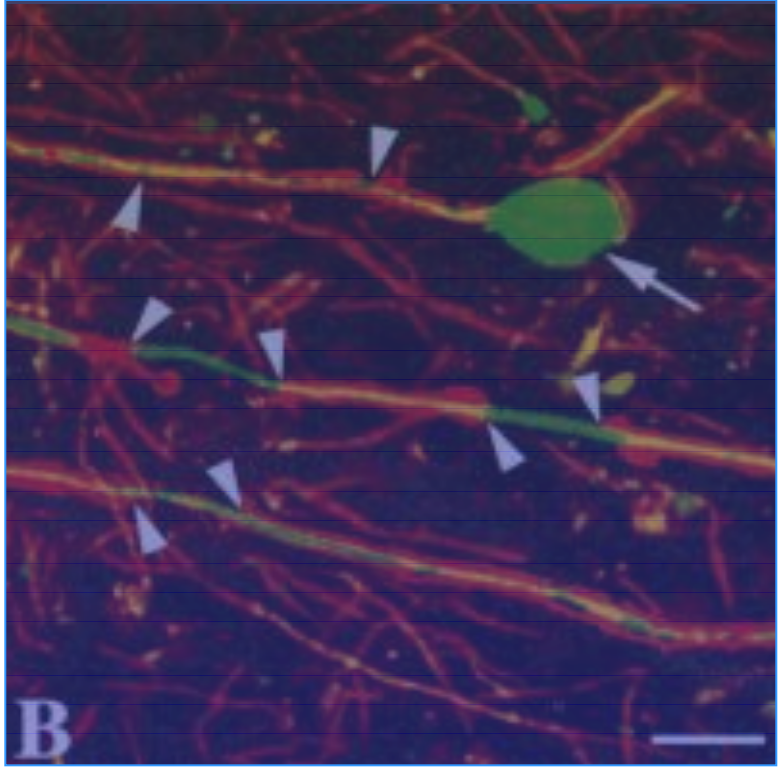
Axonal Loss / Neurodegeneration

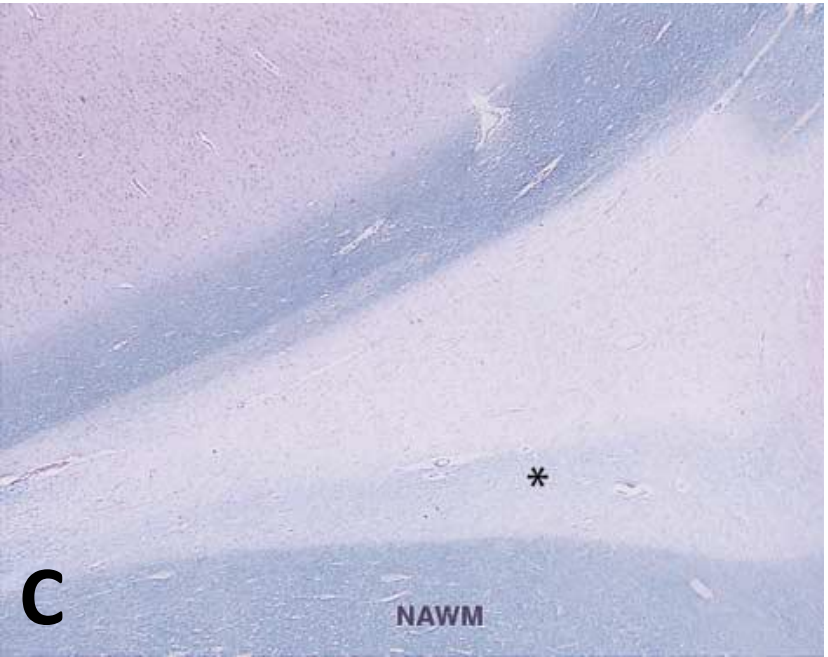
Multiple Sclerosis: Pathology



Inflammatory cells and myelin loss in plaques





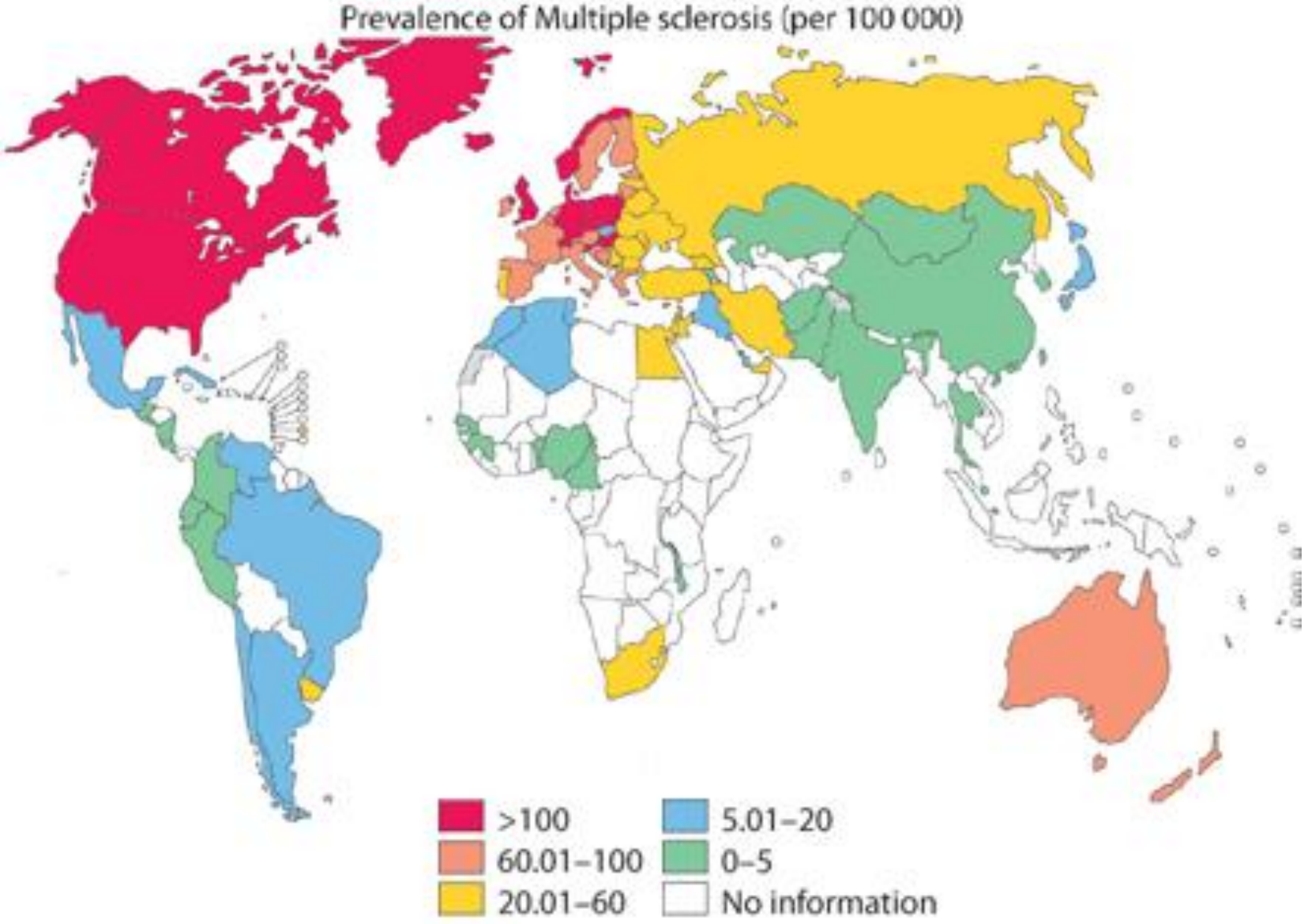


A-B: Axonal damage

C: Remyelination

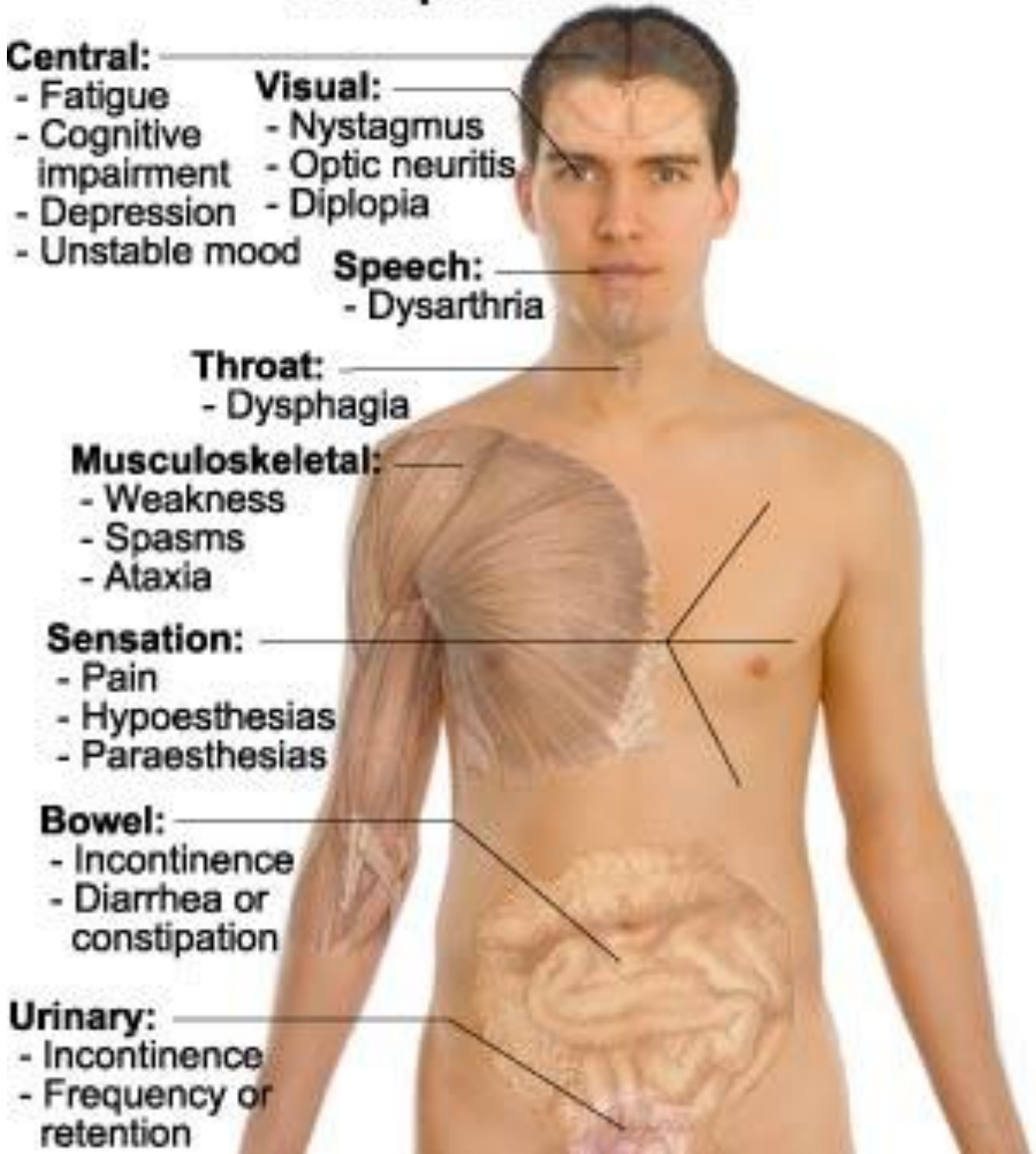
Epidemiology

- Common between 15-45 ages
- Symptom initiation age;
  - 70% between 20-40 yo
  - 10% <20y, 20% >40y
- F:M = 2:1
- The prevalence of multiple sclerosis varies considerably around the world
  - Common in Northern countries

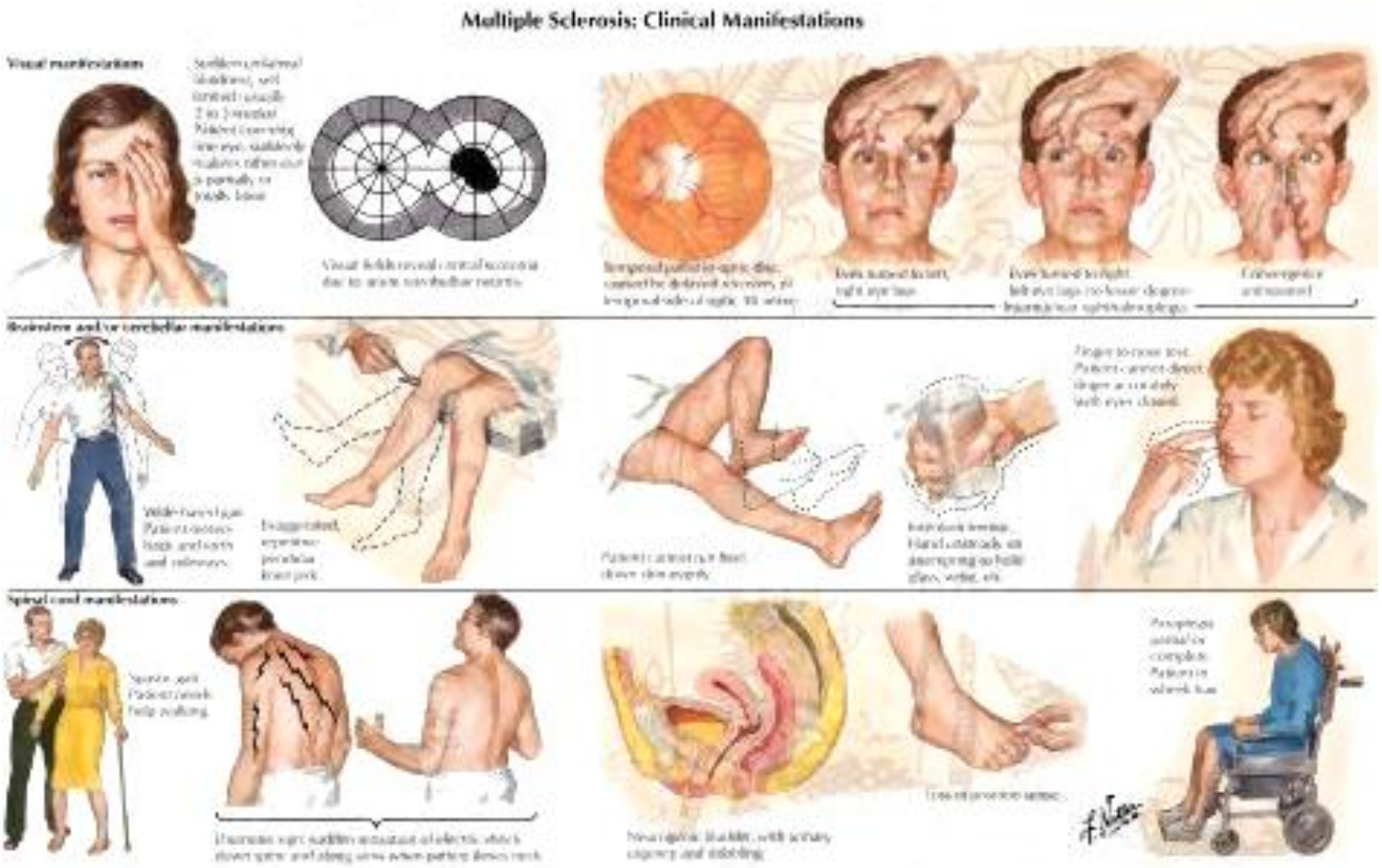

Prevalence of Multiple sclerosis (per 100 000)
>100
60.01–100
20.01–60
5.01–20
0–5
No information

Main symptoms of

Multiple sclerosis



Symptoms and Clinical Findings



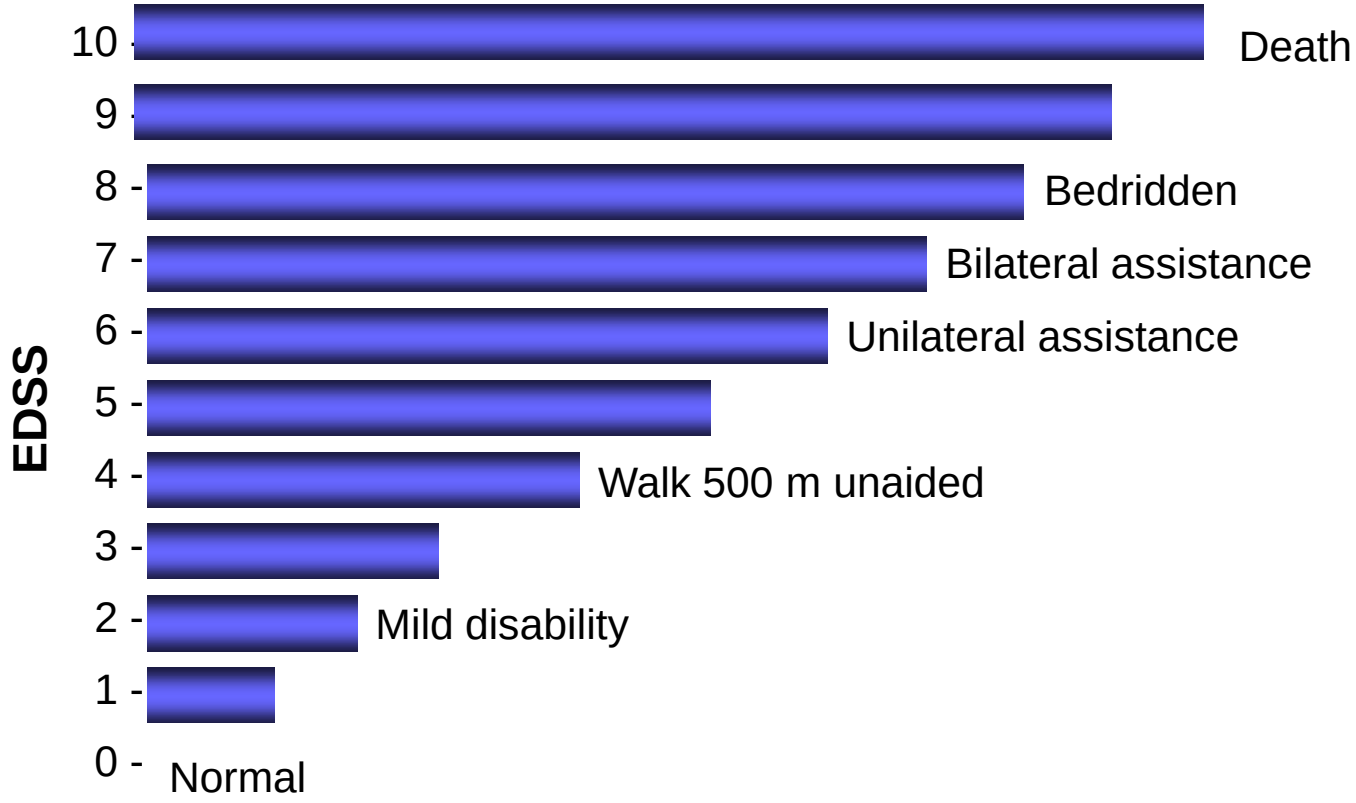
Sign and Symptoms

- **Lhermitte's sign**: Trunk and limb paresthesias evoked by neck flexion

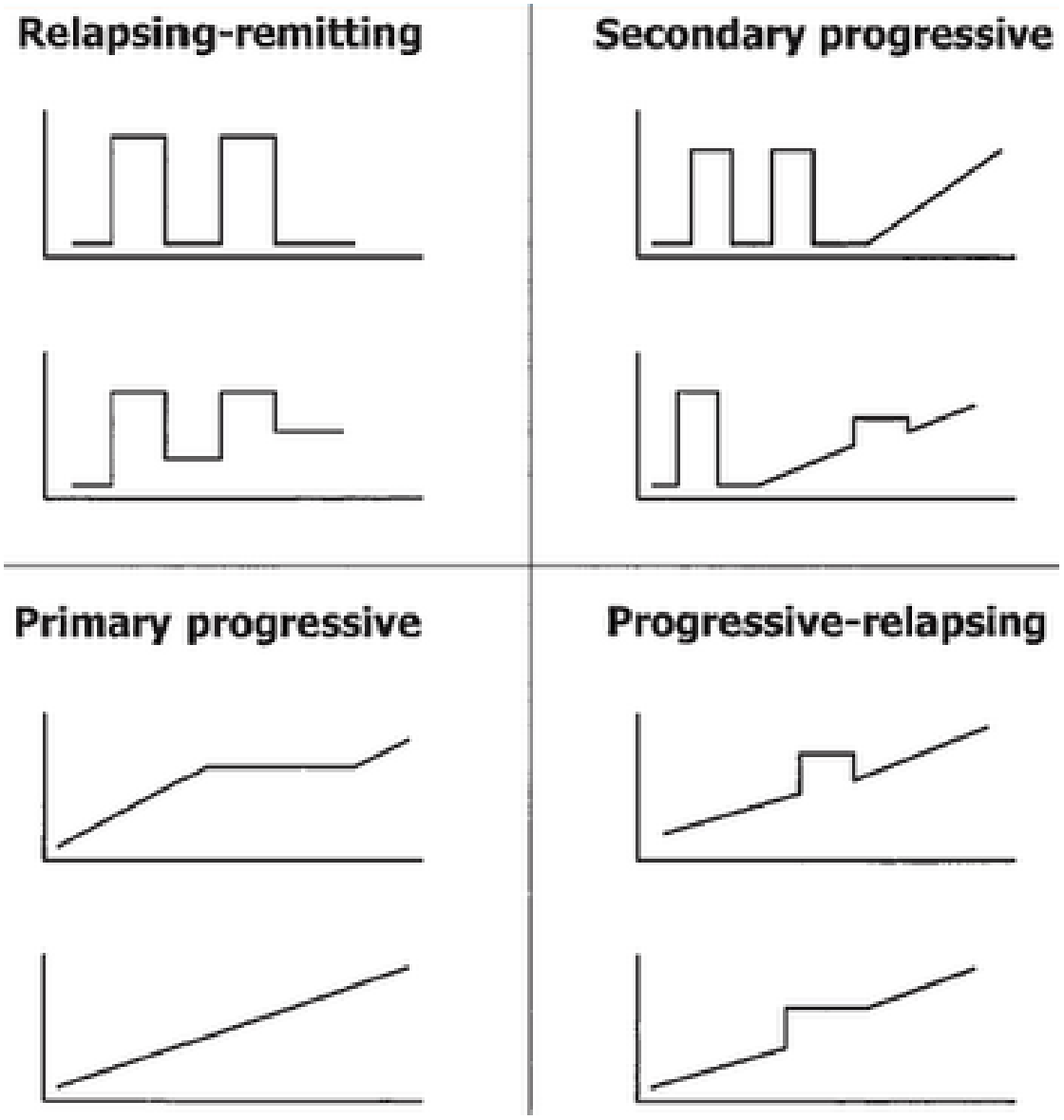
- **Uhthoff 's phenomenon** : Worsening with increases in body temperature

Expanded Disability Status Scale (EDSS)

The EDSS measures the physical, especially the ambulatory, disability of patients with MS, and is the most frequently used disability scale in MS



Disease course



Relapsing-Remitting MS

- 80- 85% of patients have RRMS type course initially
- Complete/nearly complete recovery after acute attact
- No progression between attacts
- Progression to SPMS ; %25 in 10, %90 in 25 years

Primary Progressive MS

- 10- 15% of patients
- Progression from onset

Other Forms

Benign Form

20% of patients

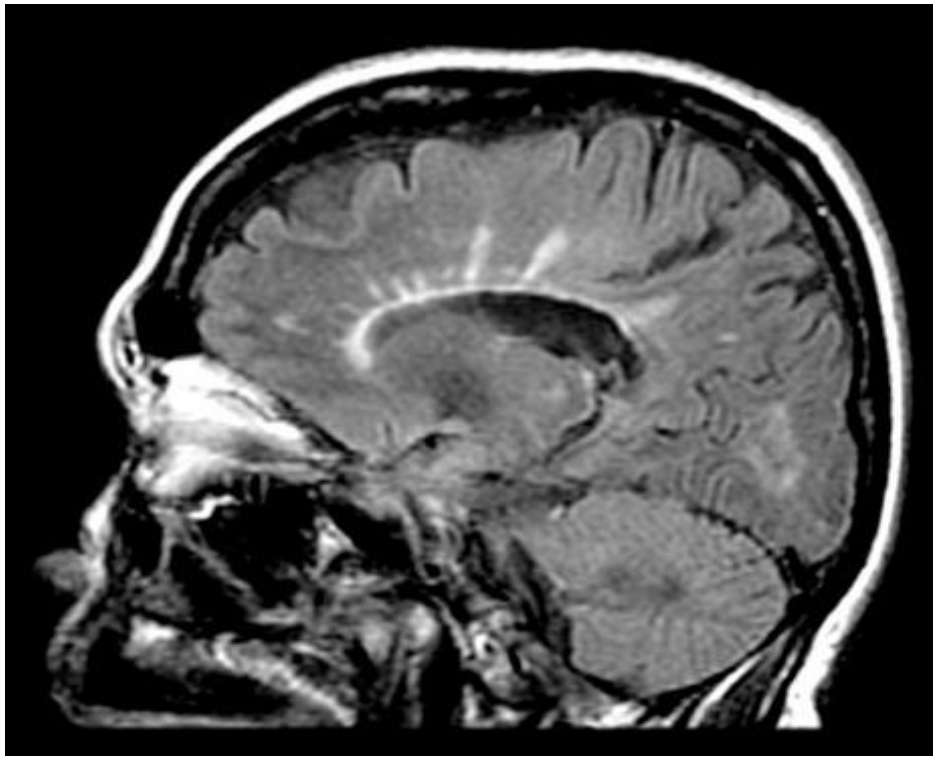
Subtype of RRMS

Minor disability (EDSS≤3)after 10 years from onset

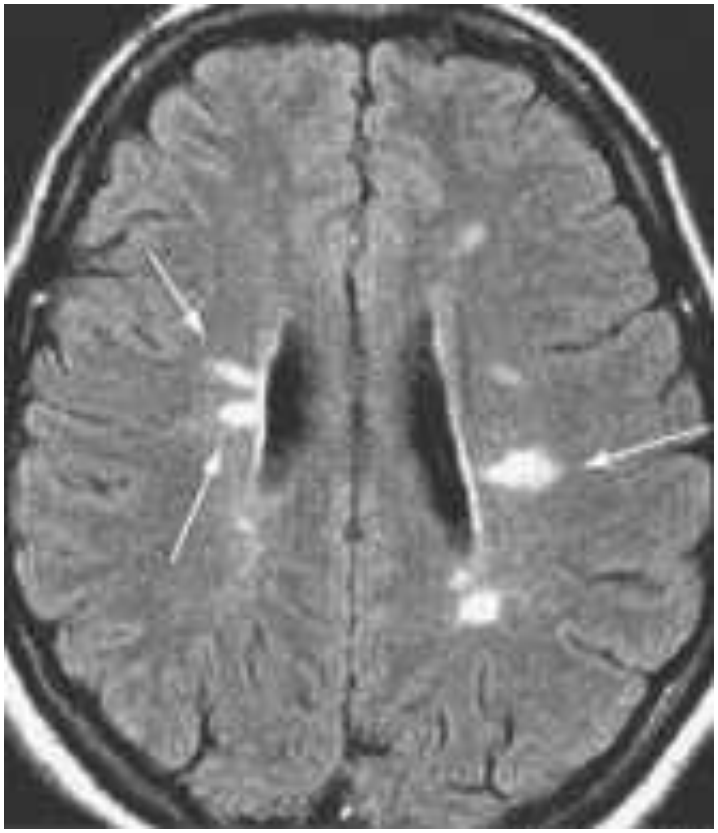
Malignant/Fulminant MS

Progression to severe disability or death within few months from onset.

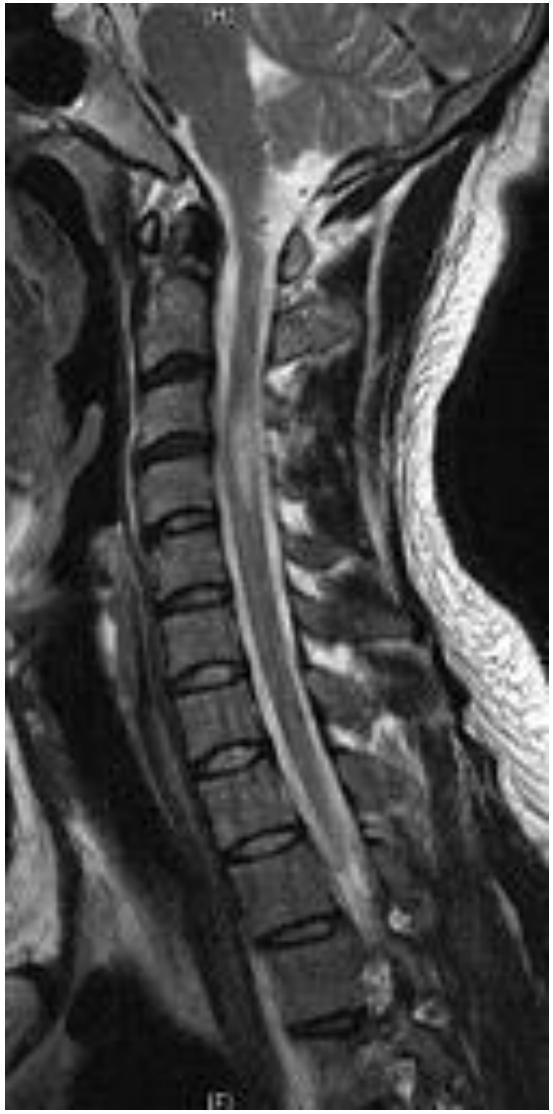
Magnetic Resonans Imaging



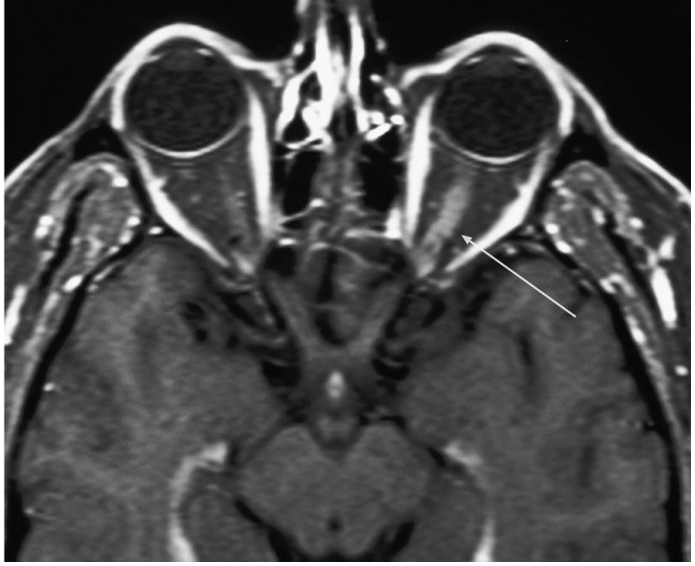
Dawson's Fingers



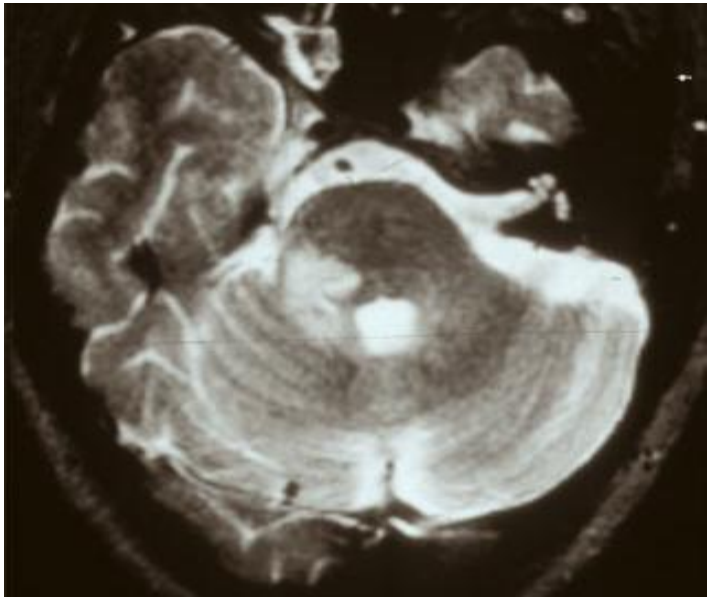
- Perivenulear inflammation



Spinal plaque



Optic neuritis



Cerebellar plaque

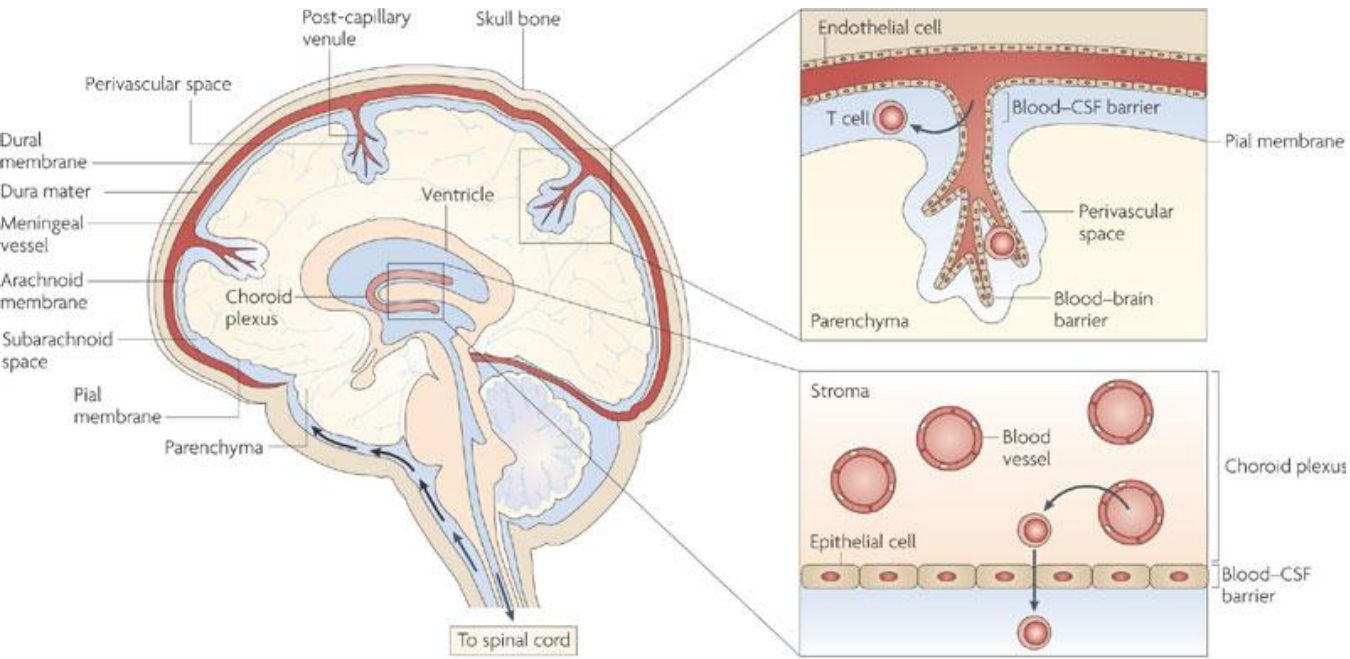
Immune Sytem and CNS

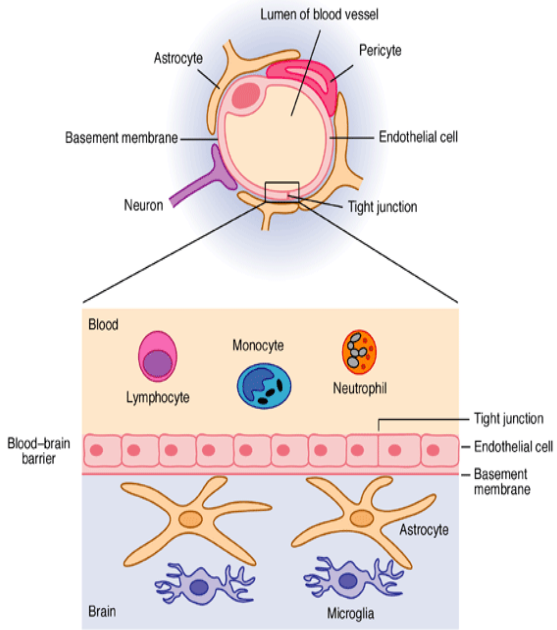
Gates to the CNS

1- Blood → **BBB** → Paranchima

Perivascular space

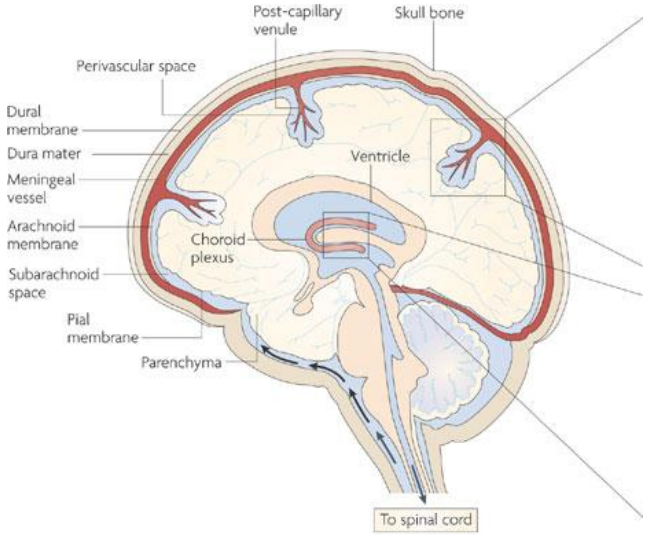
2- Blood → **choroid plexus** → CSF

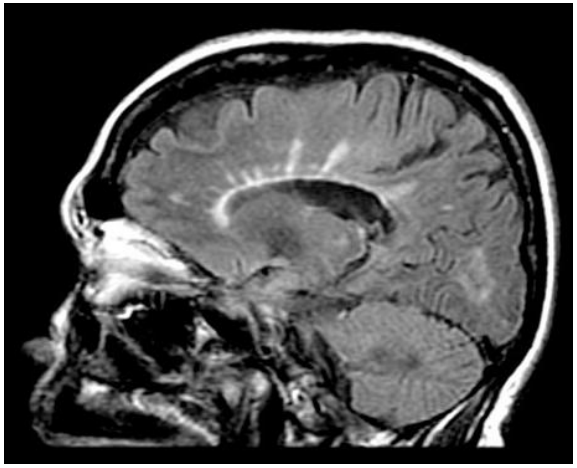


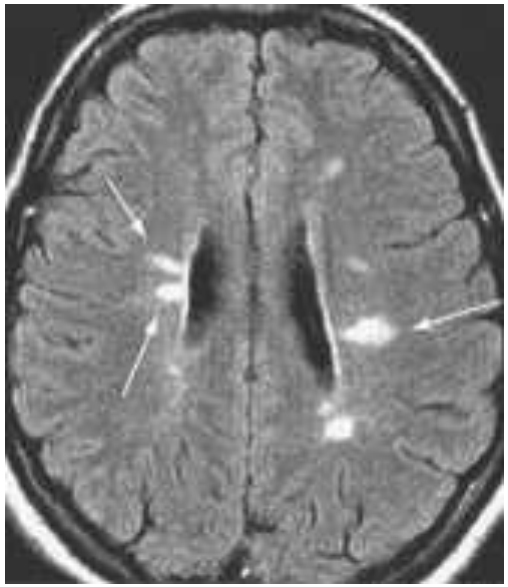


The blood–brain barrier (BBB)

- Initial lesions arise around small veins. This is reflected by the perivenous orientation of demyelinated lesions in ***multiple sclerosis***.

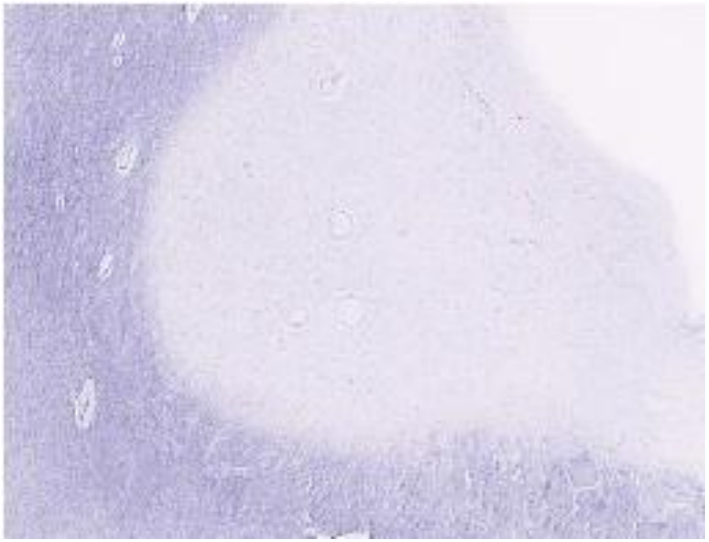


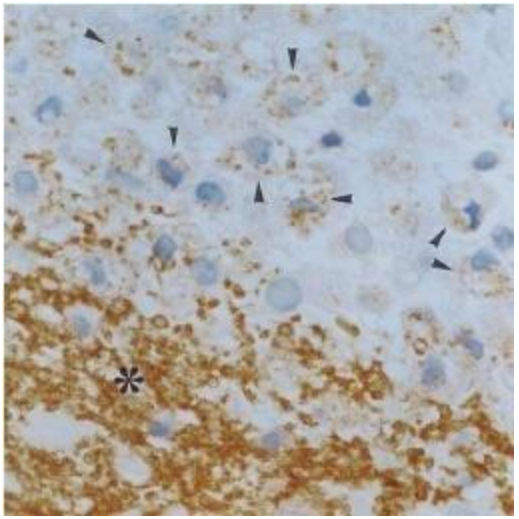


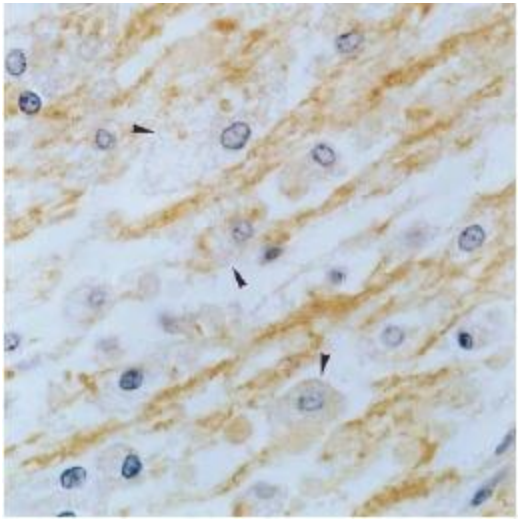


- Common lesion areas : Lateral ve 4. ventricle neighborhood, corpus callosum, optic nerve,, corticomedullary junction, brain stem subpial part , spinal cord dorsal column

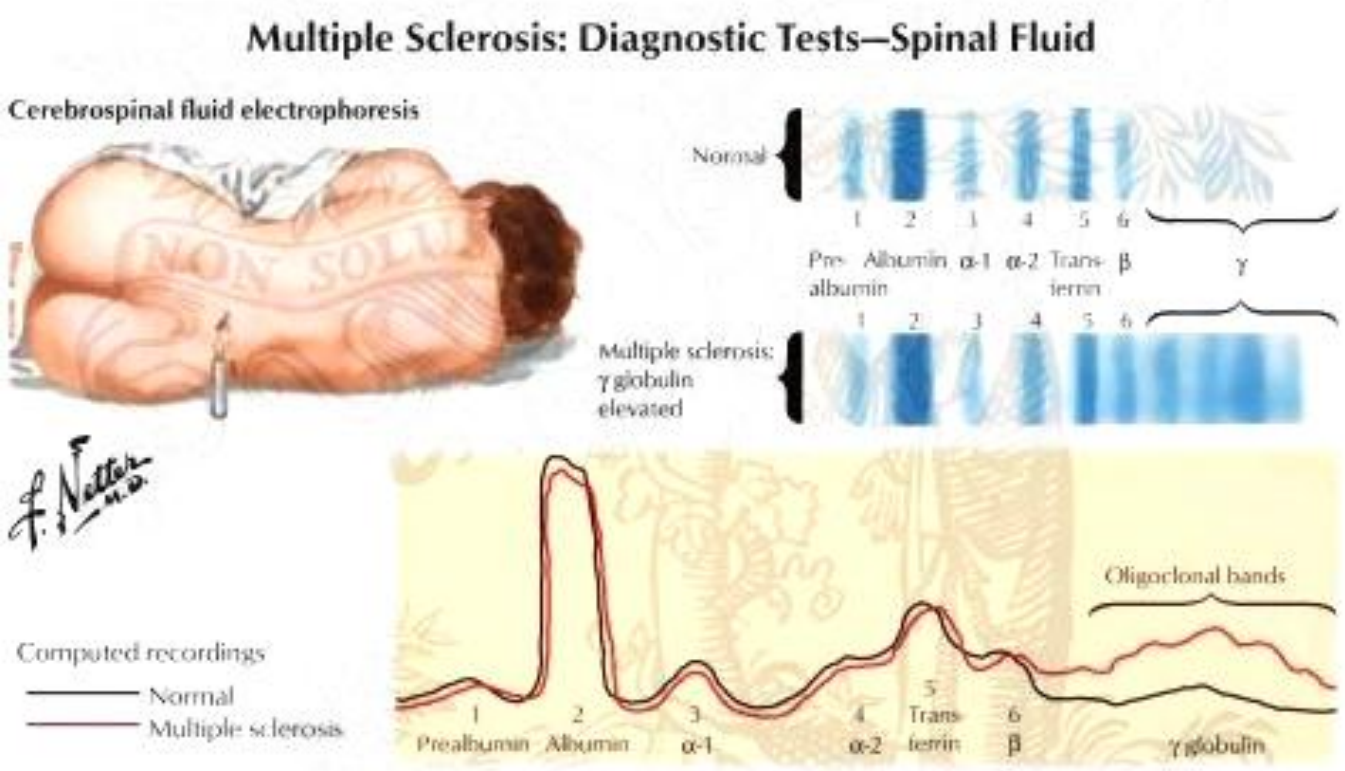
Plaque

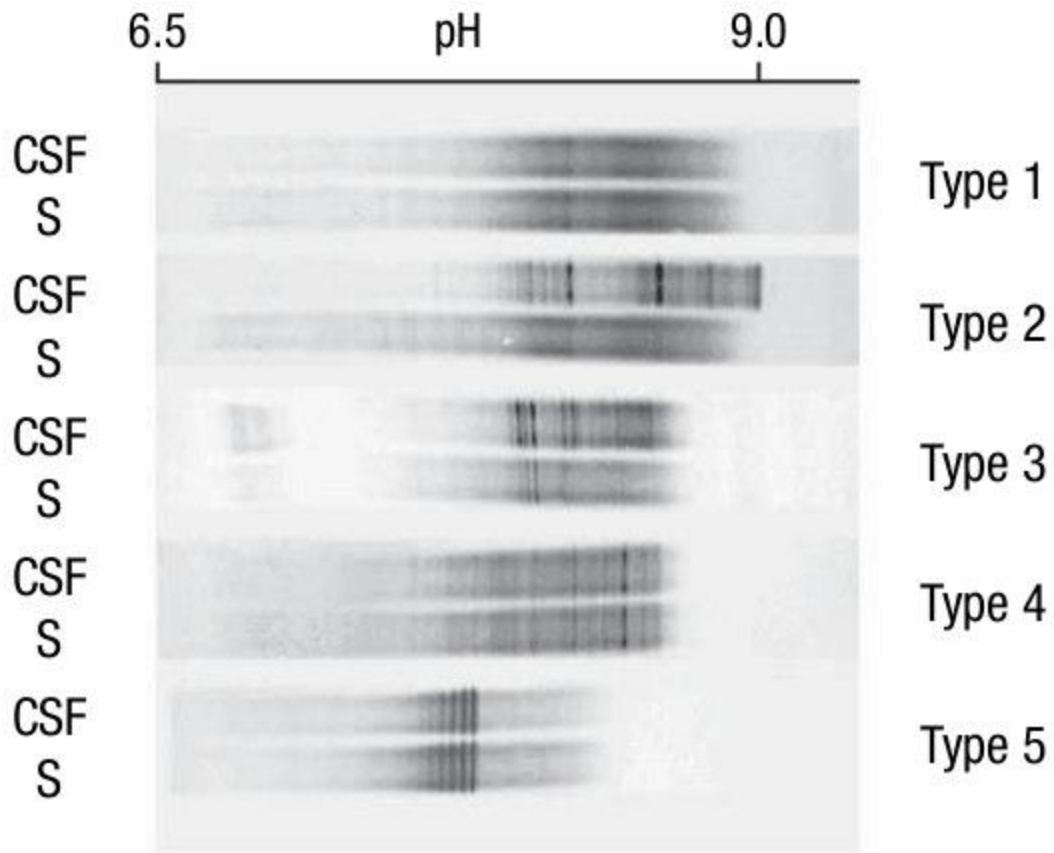






Evaluation


Multiple Sclerosis: Diagnostic Tests—Spinal Fluid
Cerebrospinal fluid electrophoresis
Normal
1 2 3 4 5 6
Pre-albumin
Albumin
α-1
α-2
Trans-ferrin
β
γ
Multiple sclerosis: γ globulin elevated
Oligoclonal bands
Computed recordings
Normal
Multiple sclerosis
1 Prealbumin
2 Albumin
3 α-1
4 α-2
5 Trans-ferrin
6 β
γ globulin


6.5
pH
9.0
CSF
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2010 Revised McDonald Diagnostic Criteria for MS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of ***dissemination of lesions in space and time***

CLINICAL (ATTACKS)	LESIONS	ADDITIONAL CRITERIA TO MAKE DX
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by ➢ ≥ 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratorial, spinal cord); **OR** ➢ Await further clinical attack implicating a different CNS site

2010 Revised McDonald Diagnostic Criteria for MS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of ***dissemination of lesions in space and time***

1	Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by ➢ Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time ; **OR** ➢ A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; **OR** ➢ Await a second clinical attack
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by ➢ ≥ 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); **OR** ➢ Await further clinical attack implicating a different CNS site **AND** Dissemination in time, demonstrated by ➢ Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; **OR** ➢ A new T2 and/or contrast-enhancing lesions(s) on follow-up MIR, irrespective of its timing; **OR** ➢ Await a second clinical attack

2010 Revised McDonald Diagnostic Criteria for MS

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of ***dissemination of lesions in space and time***

0 (progression from onset)		One year of disease progression (retrospective or prospective) **AND** at least 2 out of 3 criteria: ➢ Dissemination in space in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; ➢ Dissemination in space in the spinal cord based on ≥2 T2 lesions; **OR** ➢ Positive CSF

Further Information on Diagnosing MS

What Is An Attack?

- Neurological disturbance of kind seen in MS
- Subjective report or objective observation
- At least 24 hours duration in absence of fever or infection
- Excludes pseudoattacks, single paroxysmal symptoms (multiple episodes of paroxysmal symptoms occurring over 24 hours or more are acceptable as evidence)
- Some historical events with symptoms and pattern typical for MS can provide reasonable evidence of previous demyelinating event(s), even in the absence of objective findings

Determining Time Between Attacks

- 30 days between onset of event 1 and onset of event 2

Further Information on Diagnosing MS

What Provides Evidence for Dissemination in Space?[2]

≥ 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord

- Gadolinium enhancement of lesions is not required for DIS
- If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count

What Provides MRI Evidence of Dissemination in Time?[3]

- A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI **OR**
- Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

What is Positive CSF?

Oligoclonal IgG bands in CSF (and not serum) *or* elevated IgG index

Good and Bad Prognostic Features

+	-
*Low lesion number in MRI * Long first remission period * Predominantly sensory symptoms and optic neuritis	*Progressive course from the onset *Short period between first two attact *Frequent relapses in the first two years * Presenting with motor or cerebellar findings *Spinal cord involvement *Male sex

Table 1. Differential Diagnosis of Multiple Sclerosis.

Metabolic disorders

Disorders of B_{12} metabolism*
Leukodystrophies

Autoimmune diseases

Sjögren's syndrome, systemic lupus erythematosus, Behçet's disease, sarcoidosis, chronic inflammatory demyelinating polyradiculopathy associated with central nervous system demyelination, antiphospholipid-antibody syndrome

Infections†

HIV-associated myelopathy* and HTLV-1–associated myelopathy,* Lyme disease, meningovascular syphilis, Eales' disease

Vascular disorders

Spinal dural arteriovenous fistula*
Cavernous hemangiomata
Central nervous system vasculitis, including reticulocochlear cerebral vasculitis
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Genetic syndromes

Hereditary ataxias and hereditary paraplegias*
Leber's optic atrophy and other mitochondrial cytopathies

Lesions of the posterior fossa and spinal cord

Arnold–Chiari malformation, nonhereditary ataxias
Spondylotic and other myelopathies*

Psychiatric disorders

Conversion reaction, malingering

Neoplastic diseases

Spinal cord tumors,* central nervous system lymphoma
Paraneoplastic disorders

Variants of multiple sclerosis‡

Optic neuritis; isolated brain-stem syndromes; transverse myelitis; acute disseminated encephalomyelitis, Marburg disease; neuromyelitis optica

Treatment

- Acute attact treatment
  - Steroids
    - Administered intravenously on a daily basis for 3 to 5 days at a dose of 1 g
  - Plasmapheresis
- Disease-modifying treatments
  - Immunomodulatory treatments
  - Immunosuppressive treatments

Targets: Blood-brain barrier, myelin proteins, inflamatory cytokins, T and B cells

TABLE 2. CURRENT TREATMENTS FOR MULTIPLE SCLEROSIS.

TYPE OF MULTIPLE SCLEROSIS OR RELAPSE	AGENT	DOSE	KNOWN OR POSSIBLE BENEFITS OF TREATMENT	UNKNOWN EFFECTS OR ASPECTS OF TREATMENT
Relapsing–remitting	Interferon beta-1b (Betaseron)	8 million IU subcutaneously every other day	Reduces rate of clinical relapse Reduces the development of new lesions on MRI Delays the increase in the volume of lesions on MRI	Ability to delay progression of disability Duration and clinical significance of benefit Mechanism of action Most effective dose and route of administration Frequency and clinical significance of the formation of neutralizing antibodies
	Interferon beta-1a (Avonex)	30 μg intramuscularly once weekly	Reduces rate of clinical relapse May delay progression of disability Reduces the development of new lesions on MRI Delays the increase in the volume of lesions on MRI	Whether the effect on disability is clinically meaningful and sustained Duration and clinical significance of benefit Mechanisms of action Most effective dose and route of administration Frequency and clinical significance of the formation of neutralizing antibodies
	High-dose interferon beta-1a (Rebif)*	22 or 44 μg subcutaneously every other day	Possible dose-related benefit in patients with more severe disabilities	
	Glatiramer acetate (Copaxone)	20 μg subcutaneously daily	Reduces rate of clinical relapse Moderately reduces the development of new lesions on MRI	Effect on the progression of disability Duration and clinical significance of benefit Mechanism of action Most effective dose and route of administration
	Immune globulin	0.15–0.2 g/kg of body weight intravenously monthly for 2 yr	Reduces rate of clinical relapse May delay progression of disability	Whether progression of disability is actually delayed, as measured by a second evaluation in 3 mo Effect on the number and volume of lesions, as assessed by MRI Duration and clinical significance of benefit Mechanism of action Most effective dose and route of administration

TABLE 2. CURRENT TREATMENTS FOR MULTIPLE SCLEROSIS.

Secondary progressive	Interferon beta-1b (Betaferon)	8 million IU subcutaneously every other day	Reduces rate of clinical relapse May reduce progression of disability regardless of relapse status (recent or current)† Delays the increase in the volume of lesions on MRI	Whether progression of disability is actually delayed, and if so, for how long and to what effect Mechanism of action Most effective dose and route of administration Frequency and clinical significance of the formation of neutralizing antibodies
	Mitoxantrone hydrochloride	5 or 12 mg/m² of body-surface area intravenously every 3 mo for 2 yr	Reduces rate of clinical relapse Delays progression of disability Reduces activity evident on MRI	Duration of benefit Most effective dose Dose-dependent risk of cardiac toxicity

Natalizumab	Humanized monoclonal antibody that is specific for alpha-4 integrin, an adhesion molecule expressed on activated T lymphocytes and other immune cells.	Progressive multifocal leukoencephaolpathy (PML) due to an CNS infection with JC virus

Cyclophosphamide

Rituximab

TABLE 2. CURRENT TREATMENTS FOR MULTIPLE SCLEROSIS.

Primary progressive	Azathioprine			
Acute relapses	Corticosteroids	Various doses (see text)	Hastens clinical recovery Transiently restores blood–brain barrier on MRI	Duration and clinical significance of benefit Effect on progression of disability Mechanism of action Most effective agent, dose, and route of administration Why responsiveness to corticosteroids declines over time
	Plasma exchange	Seven exchanges of one plasma volume on alternate days	Enhances recovery of relapse-related neurologic deficits in patients with no response to high-dose corticosteroids	Effect on recurrent disease Duration of effect Mechanism of action

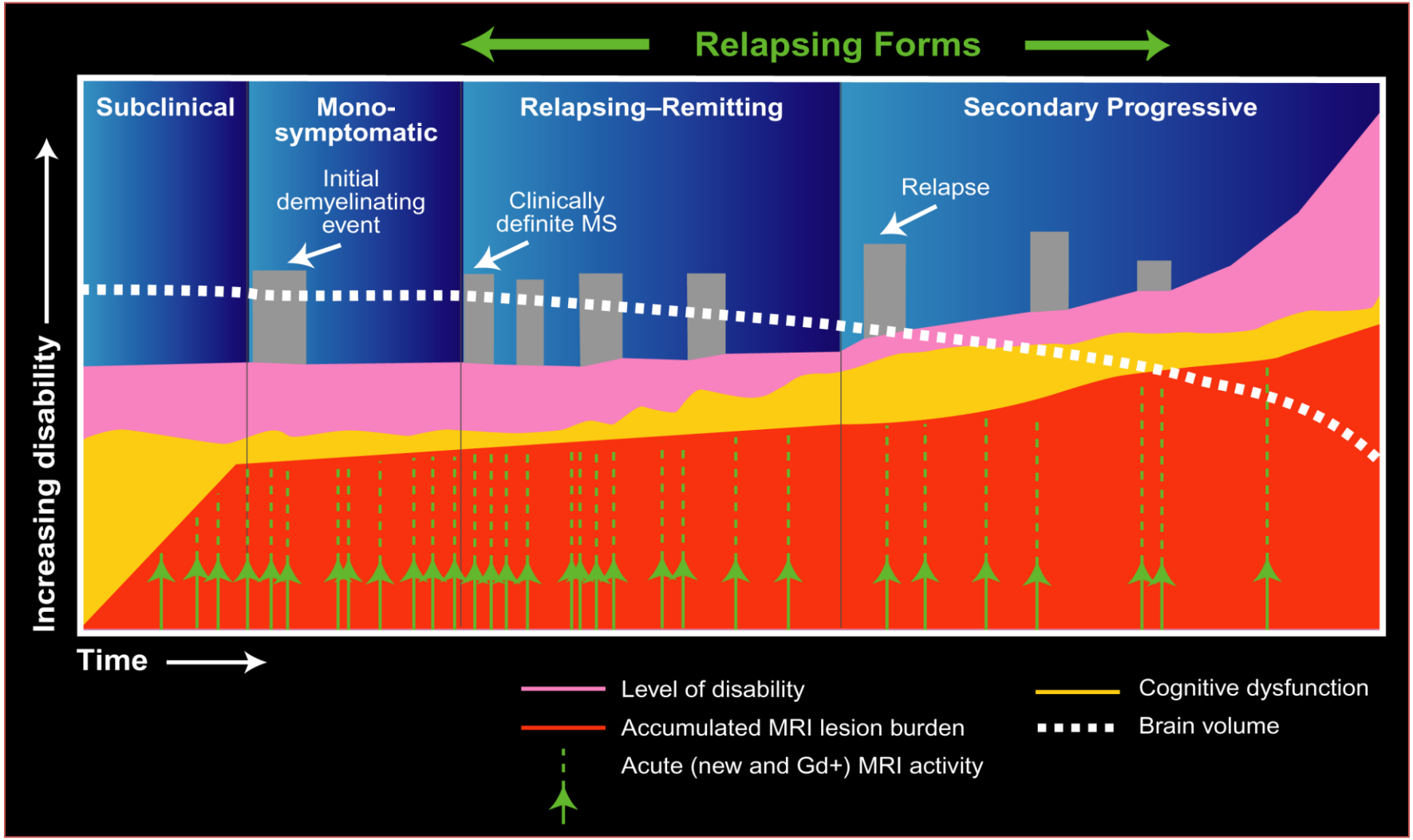
New treatments & Investigations

- Humanized monoclonal antibodies
  - Alemtuzumab
  - Daclizumab
- Oral agents
  - Fingolimod
  - Cladribine
  - Laquinimod
  - Fumarate
  - Teriflunamid

Treatment of Complications

- **Fatigue** ;amantadine and energy-conservation strategies.
- **Spasticity**; Baclofen, Tizanidine
- **Paroxysmal events**; Carbamazepine and phenytoin, acetazolamide, gabapentin, and pergolide.
- **Tremor**; Medical , surgical treament
- **Neurogenic bladder** and **bowel disturbances**
- **Depression , mood and sleep disorders**
- Problems with **gait, speech and swallowing** disorders;multidisciplinary approach with specialists in physical medicine and rehabilitation.

Natural Progression of MS



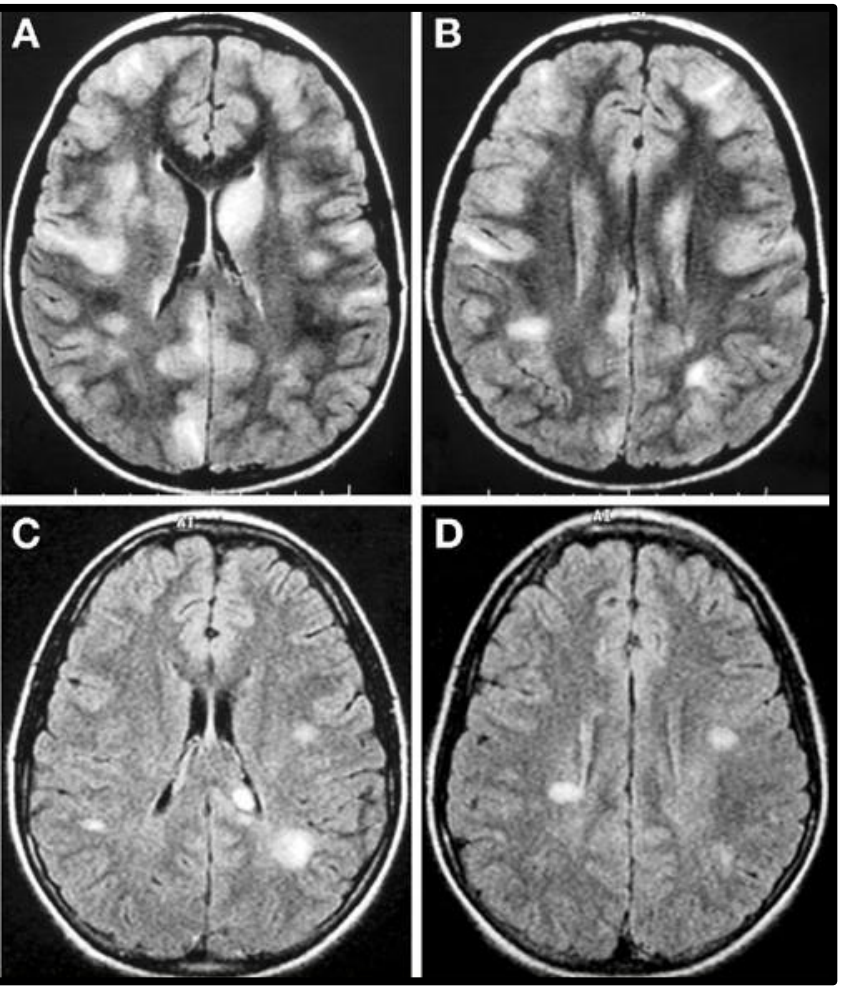
Other Demyelinating Disorders

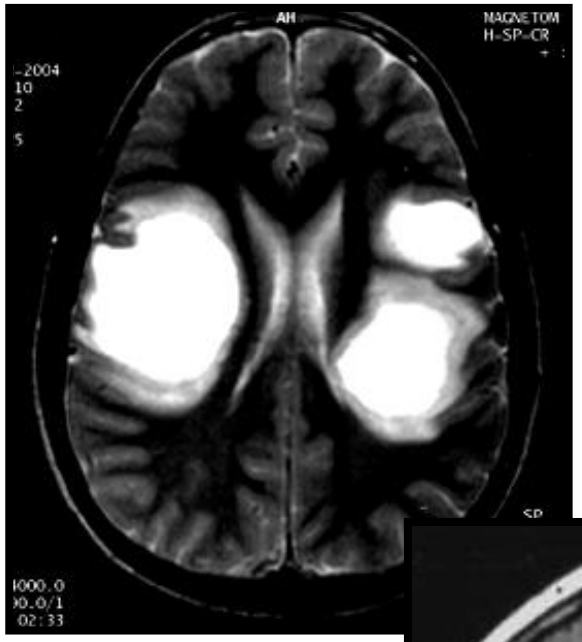
- Acute Disseminated Encephalomyelitis (ADEM)
- Neuromyelitis Optica (Devic’s Disease)
- Marchiafava-Bignami Disease
- Central Pontine Myelinolysis
- Balo's Concentric Sclerosis
- Demyelinisation in Connective Tissue Diseases (SLE, Sjogren Disease, Neurobehcet Disease)
- Ischemic demyelination
- Progressive multifocal leukoencephalopathy (PML)
- Leukodystrophies

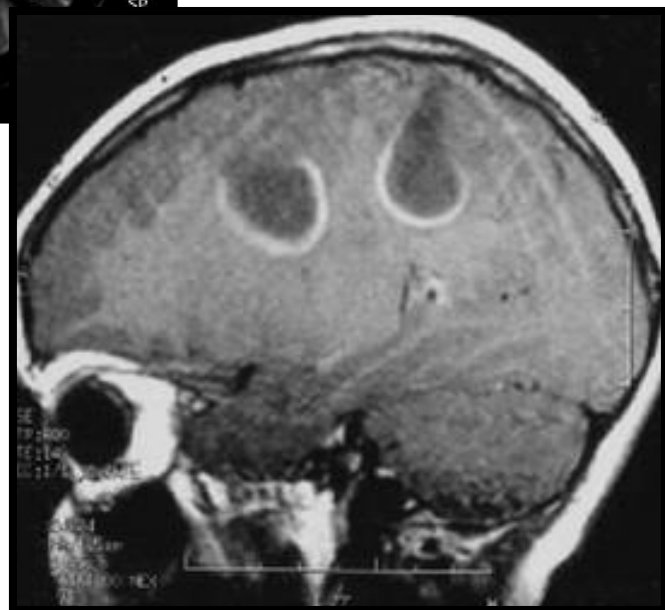
Acute Disseminated Encephalomyelitis (ADEM)

- Nonvasculitic inflammatory demyelinating condition
- Usually occurs following a viral infection but may appear following vaccination or other infections. Within 6 days-6 weeks.
- Typically a monophasic disease of prepubertal children. Also observed in adults.
- Multiple inflammatory lesions in the brain and spinal cord, particularly in the white matter.
- Because of cross reaction of infectious antigens and myelin antigens.

Acute Disseminated Encephalomyelitis (ADEM)







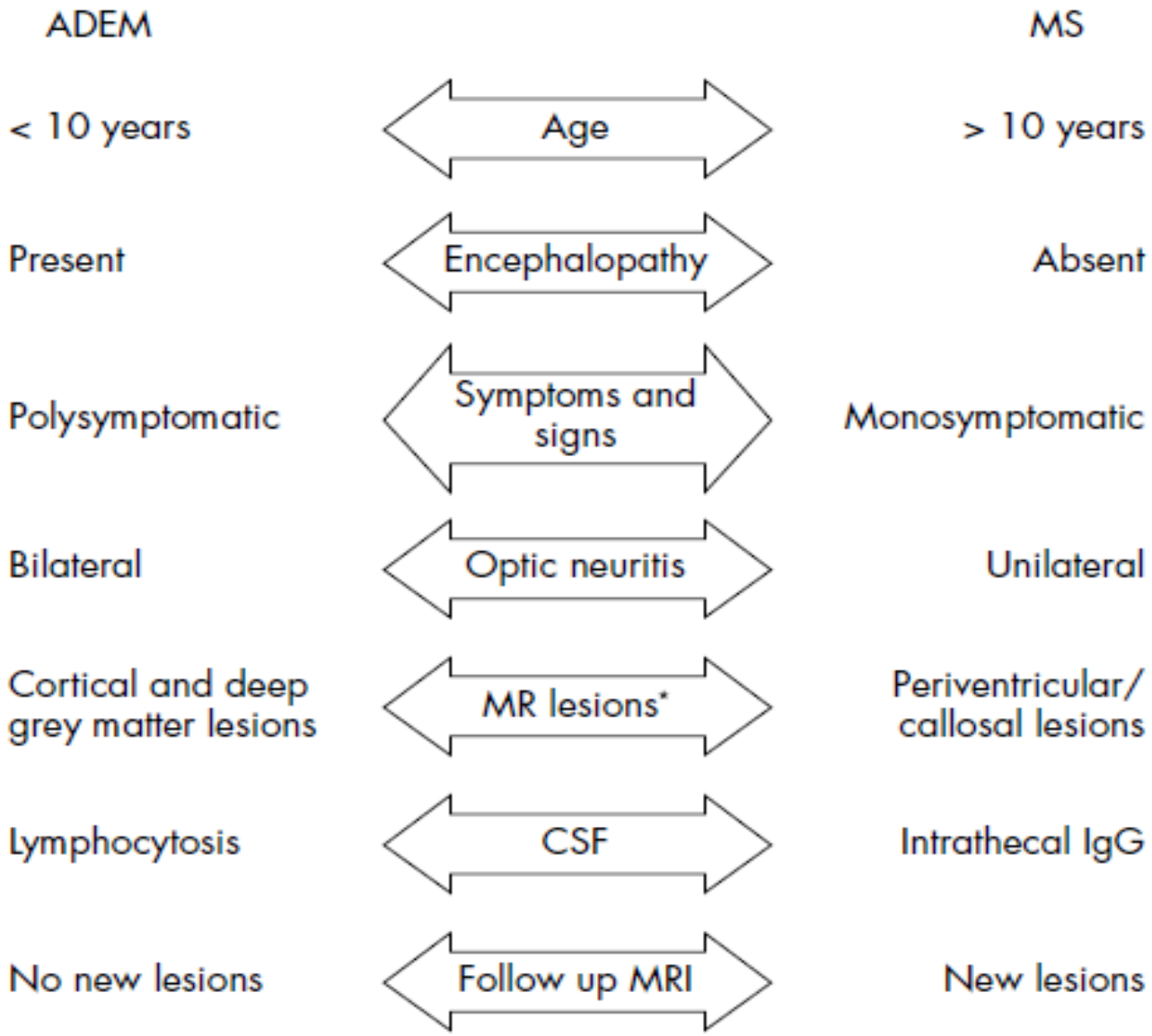
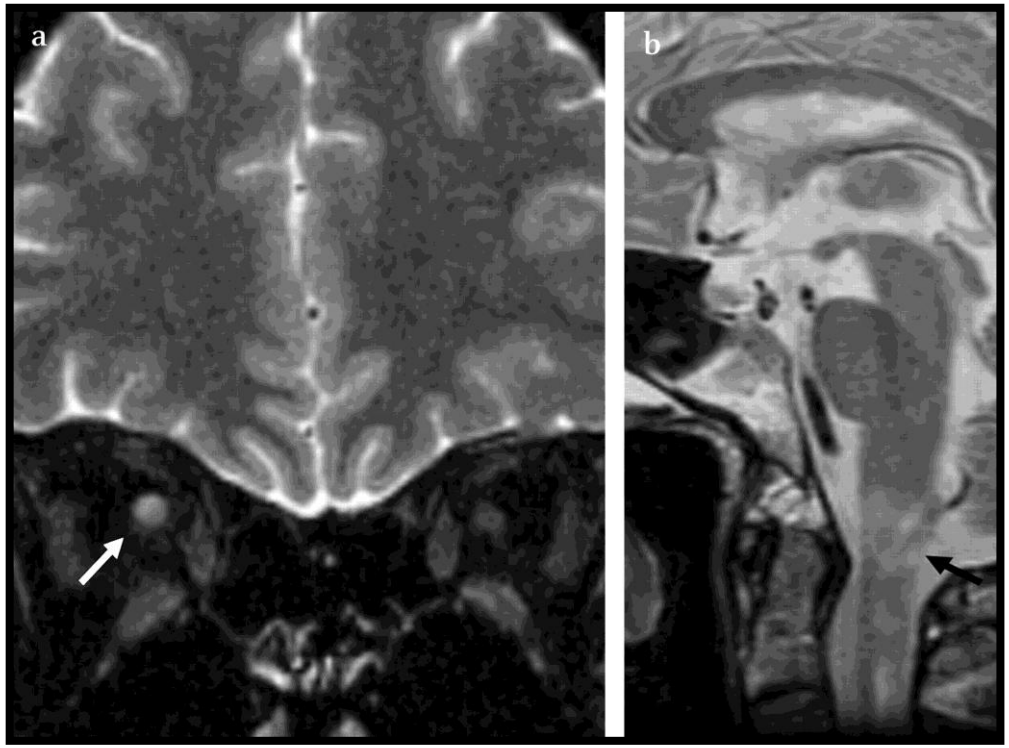
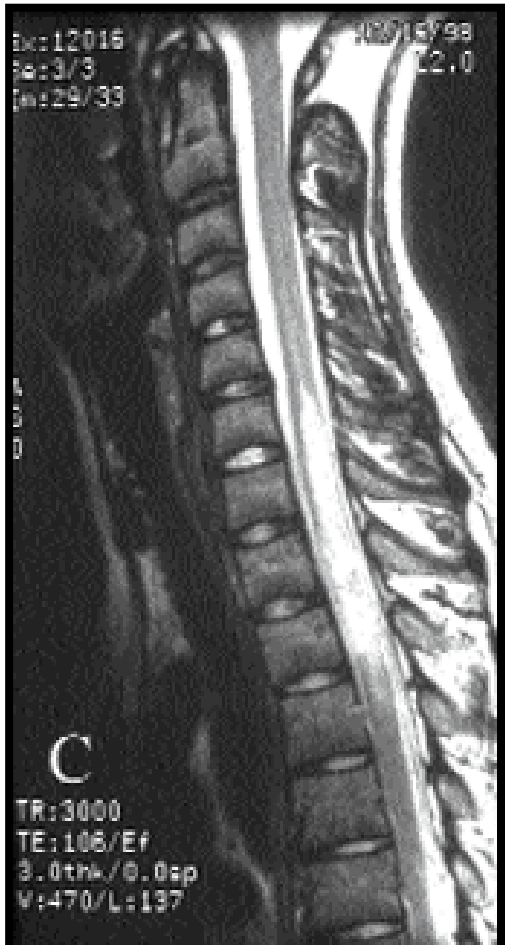


Figure 3 Clinical and investigation differences between ADEM and MS (trends only). *MR lesions other than white matter.

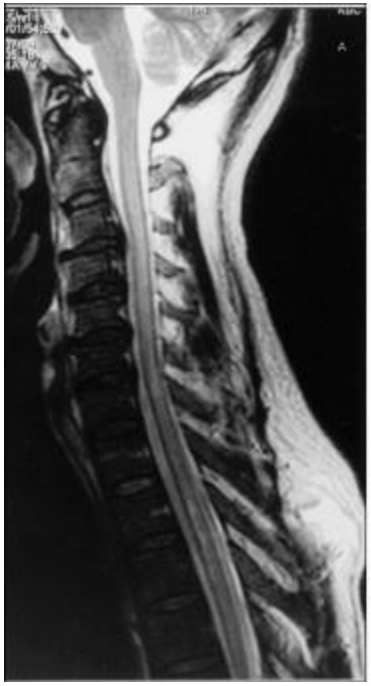
Neuromyelitis Optica (Devic's Disease)

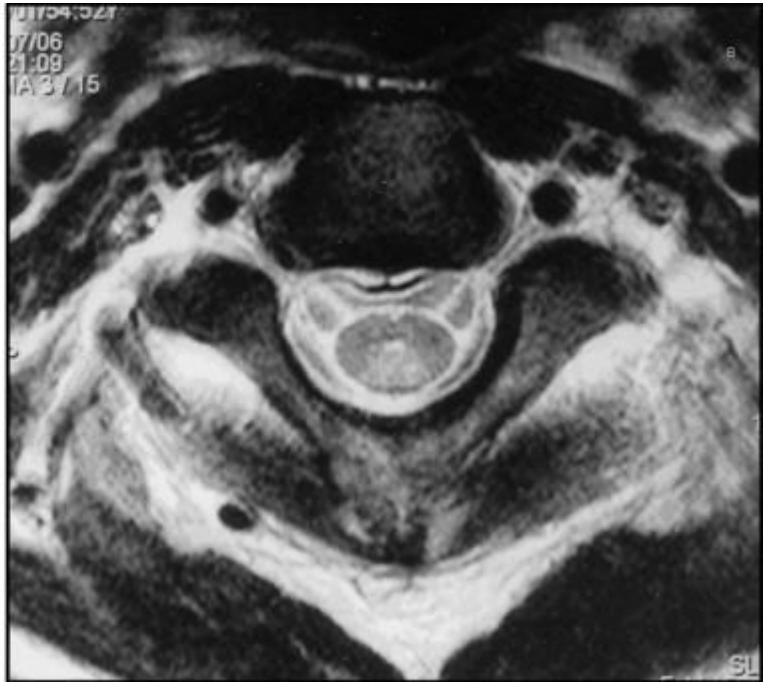
- Optic nerves and spinal cord inflammation
- AQP4 antibodies in %60

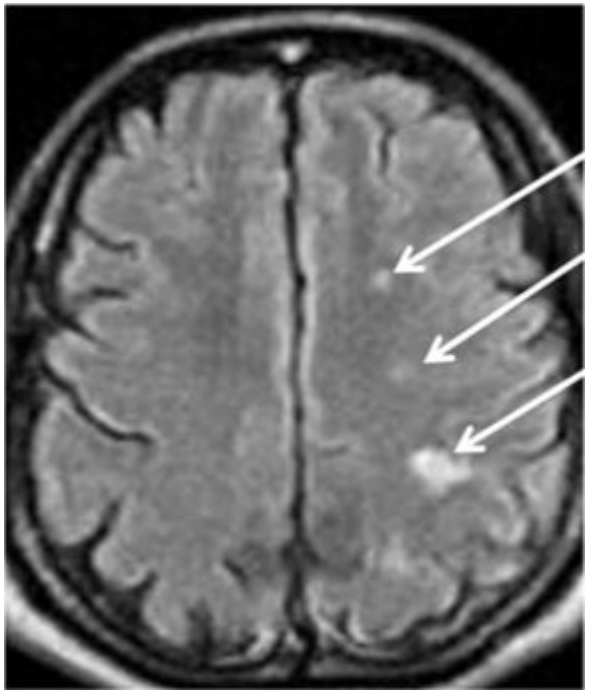




Demyelinisation in Connective Tissue Diseases

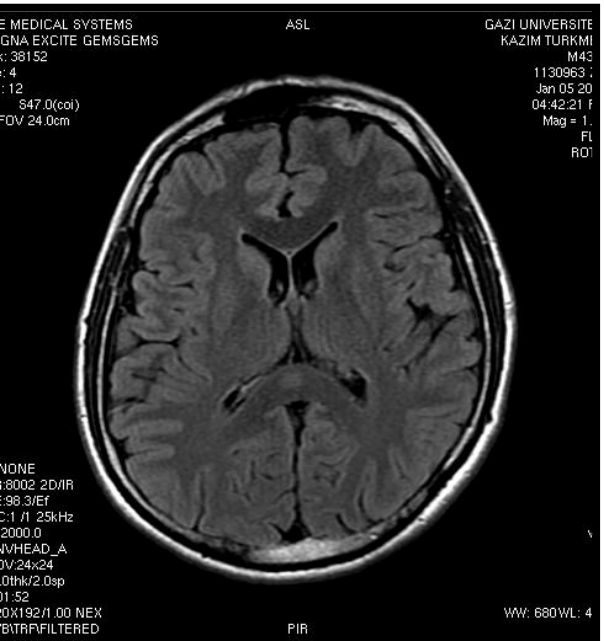


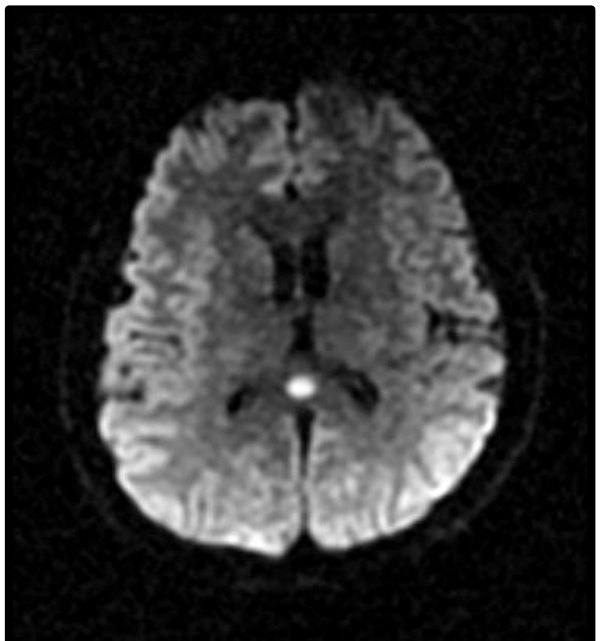


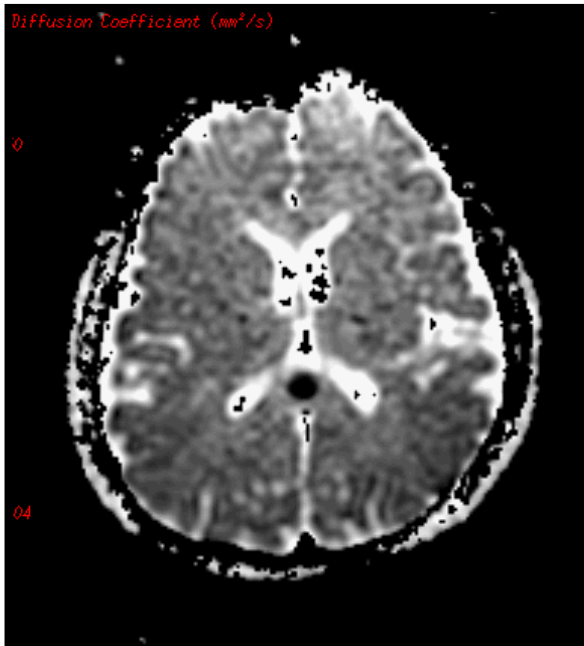


Marchiafava-Bignami Disease

- Cental focal demyelination of corpus callosum
- Usually observed in vitamin B complex deficiencies

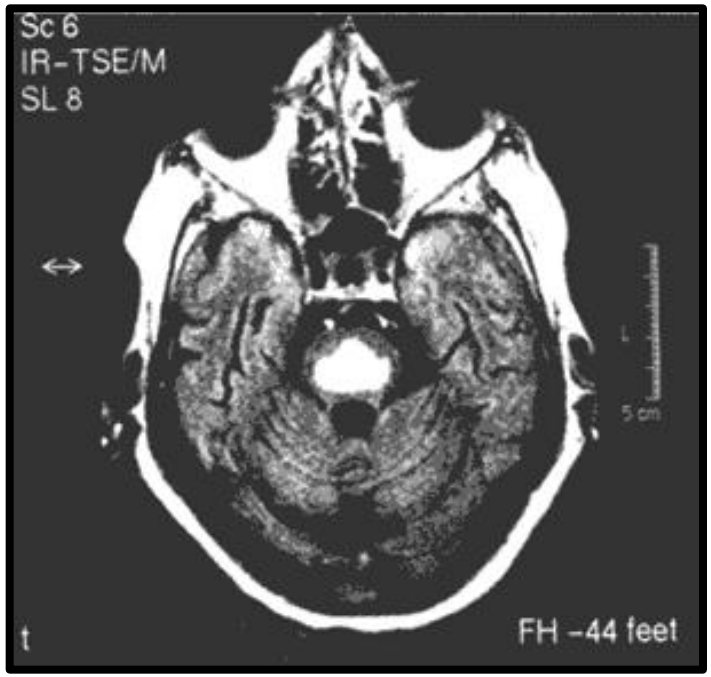


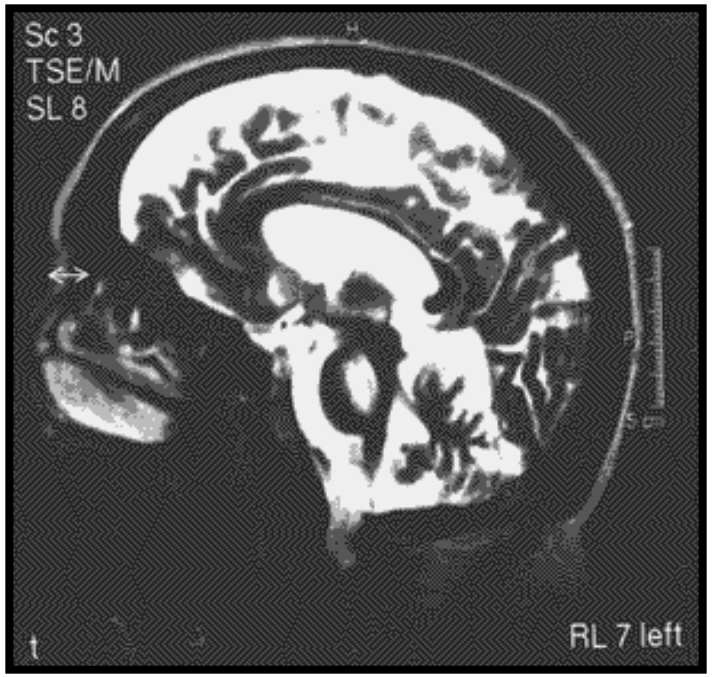




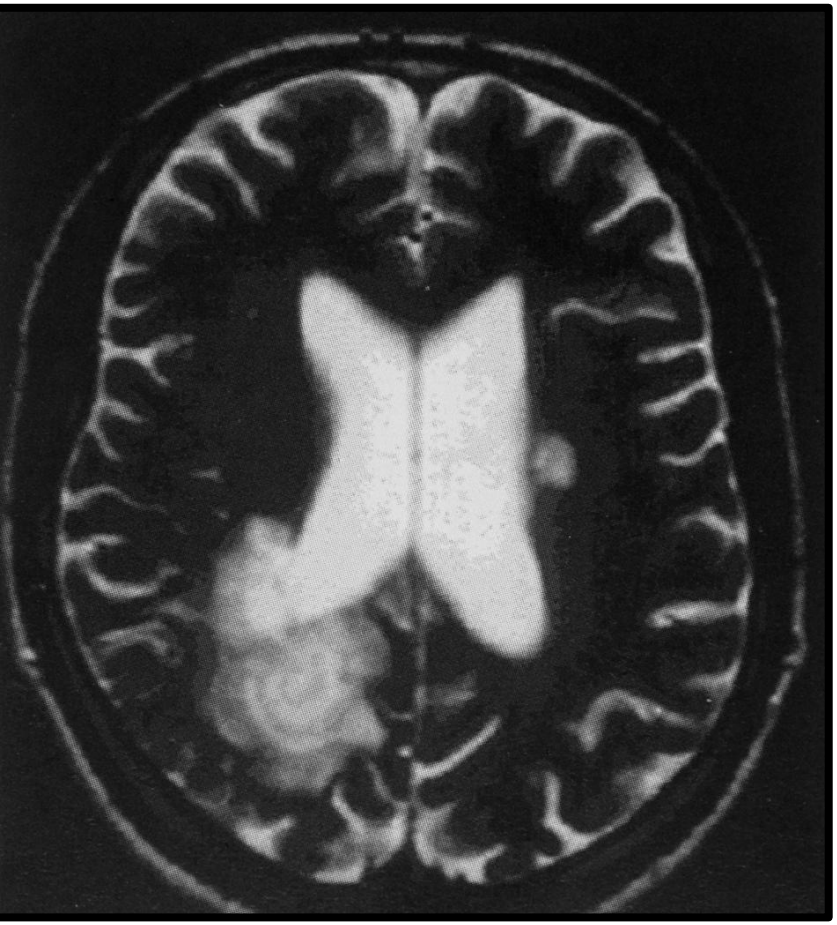
Central Pontine Myelinolysis

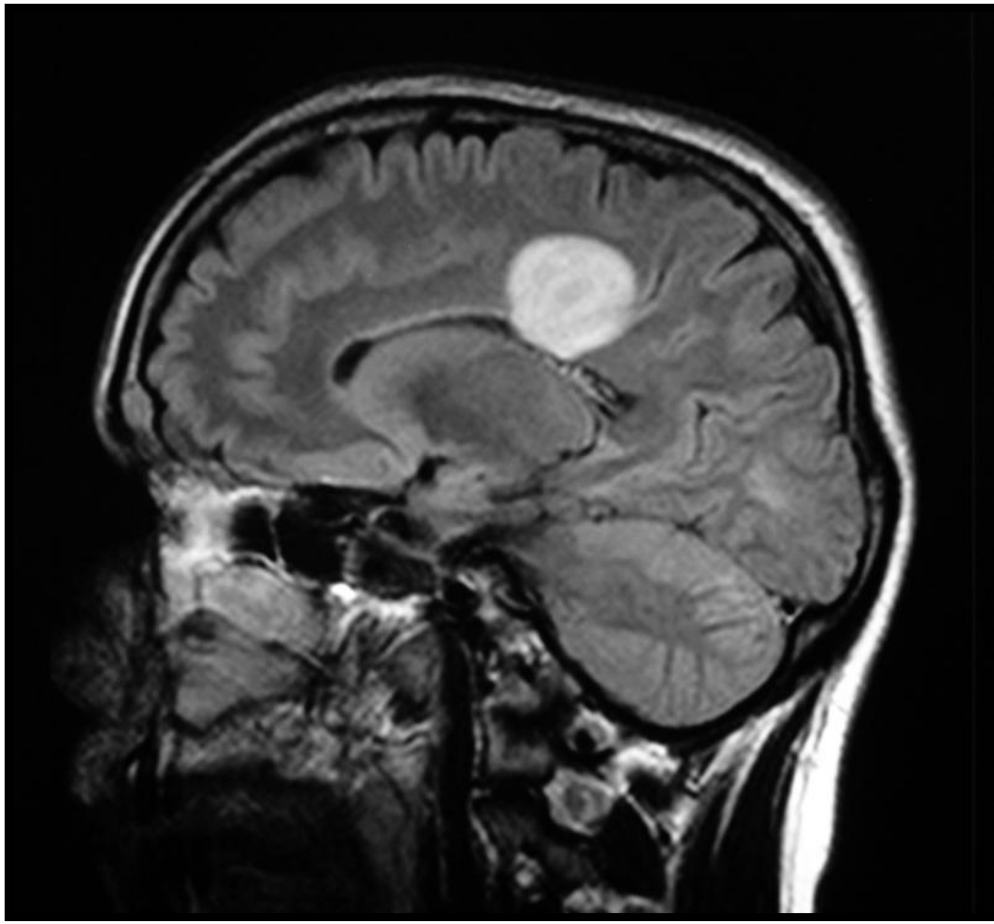
- Common mecanism is fast correction of hyponatremia /hypernatremia





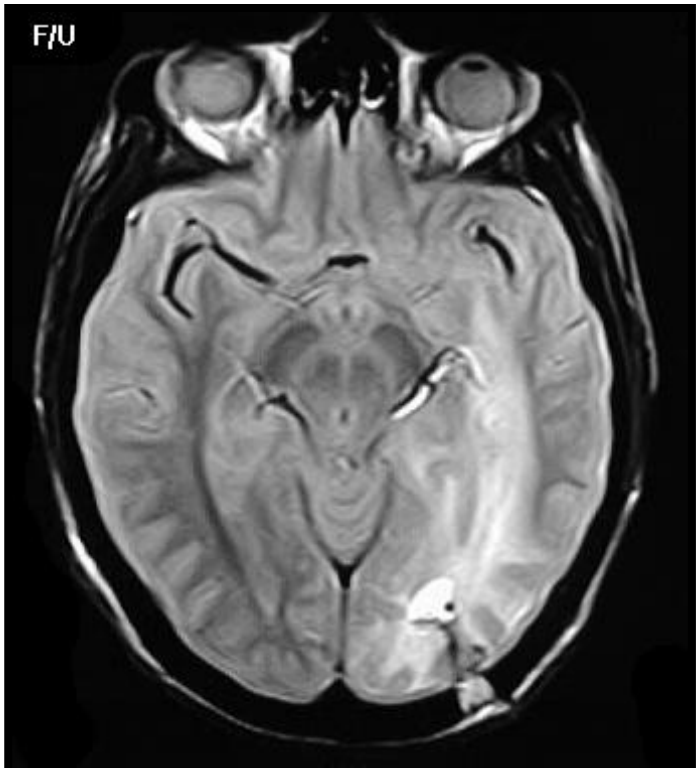
Balo's Concentric Sclerosis

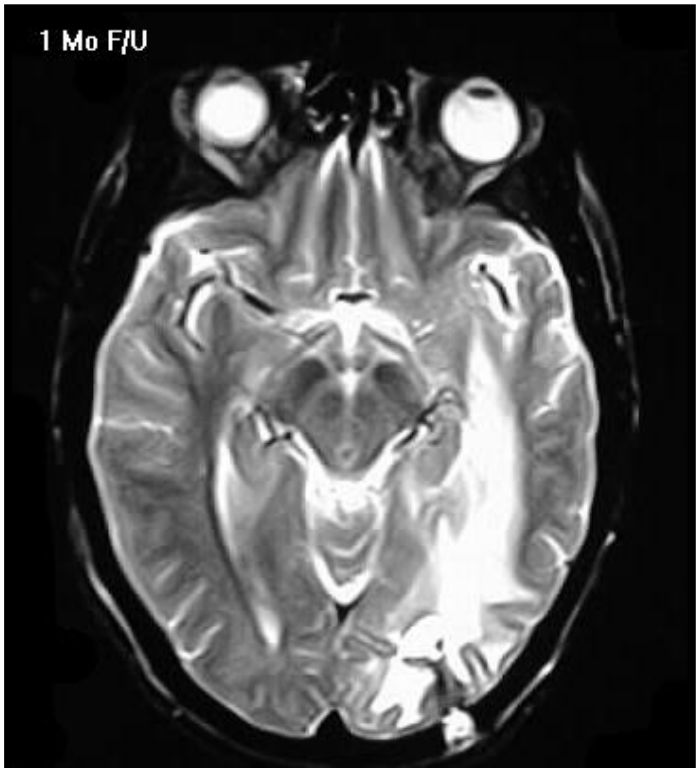




Progressive multifocal leukoencephalopathy (PML)

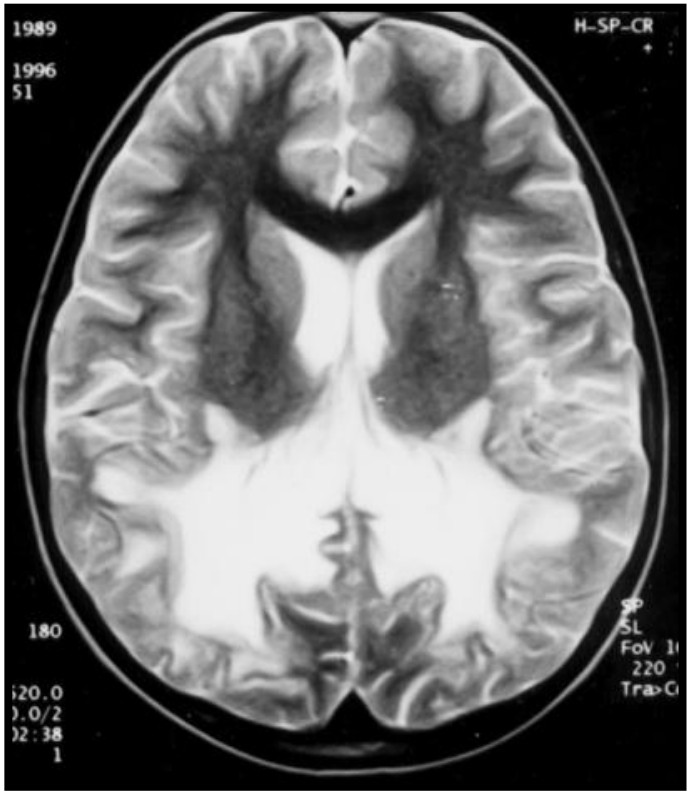
- Obseved in immunosuppressive patients
- Human papilloma virus JC virus infects oligodendrocytes and causes demyelination

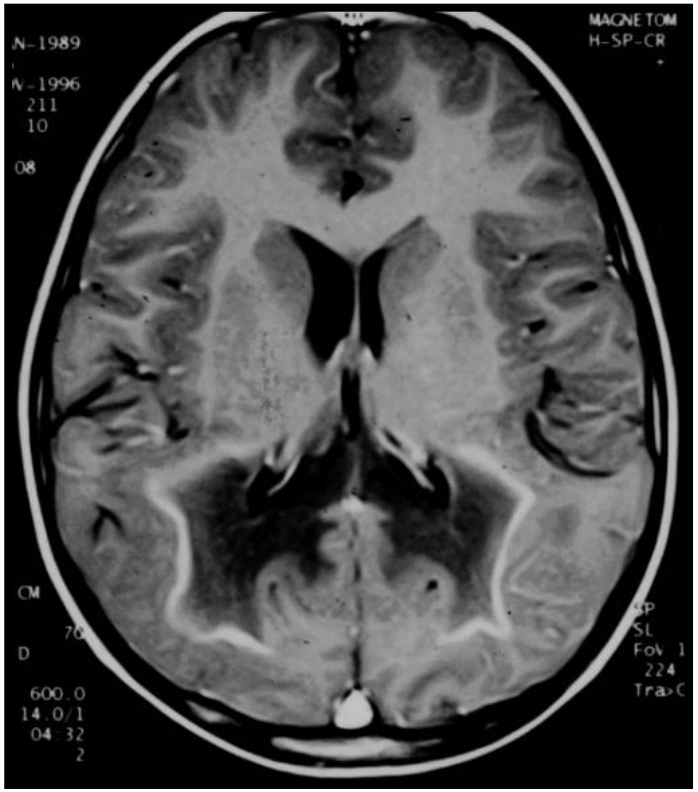


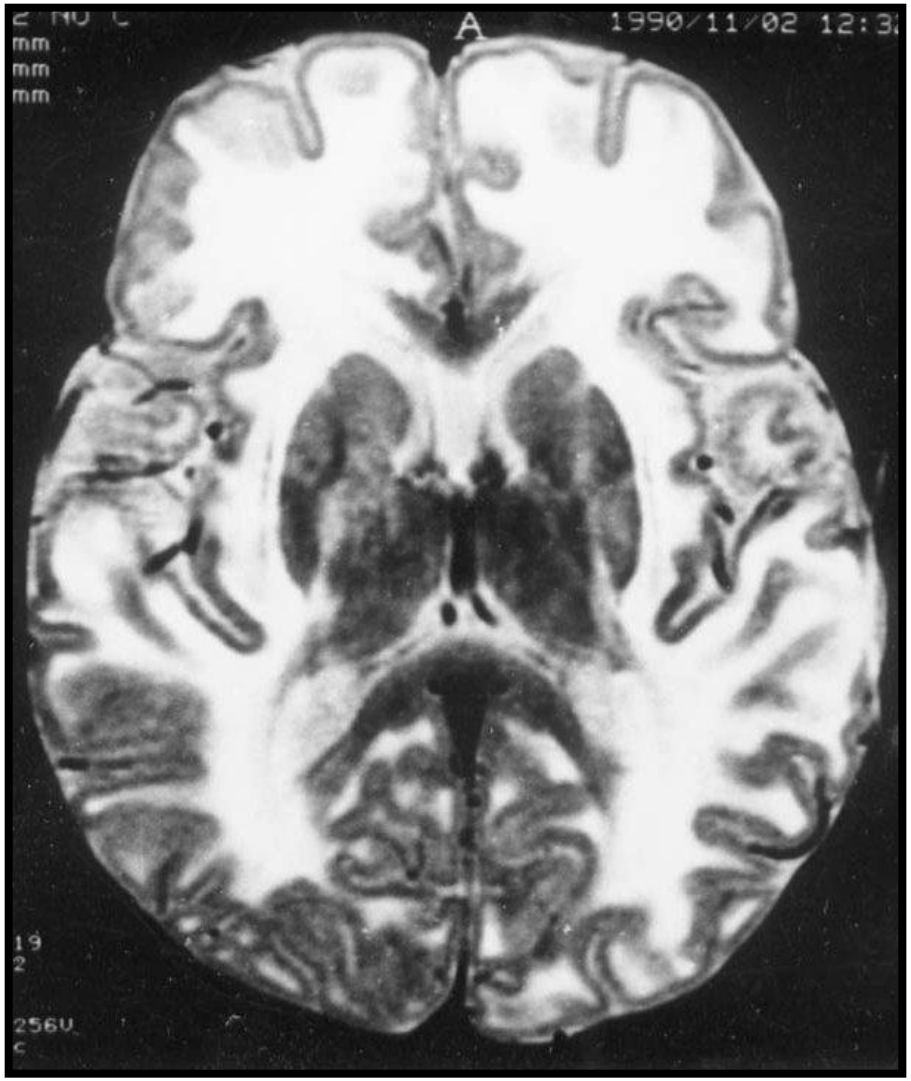


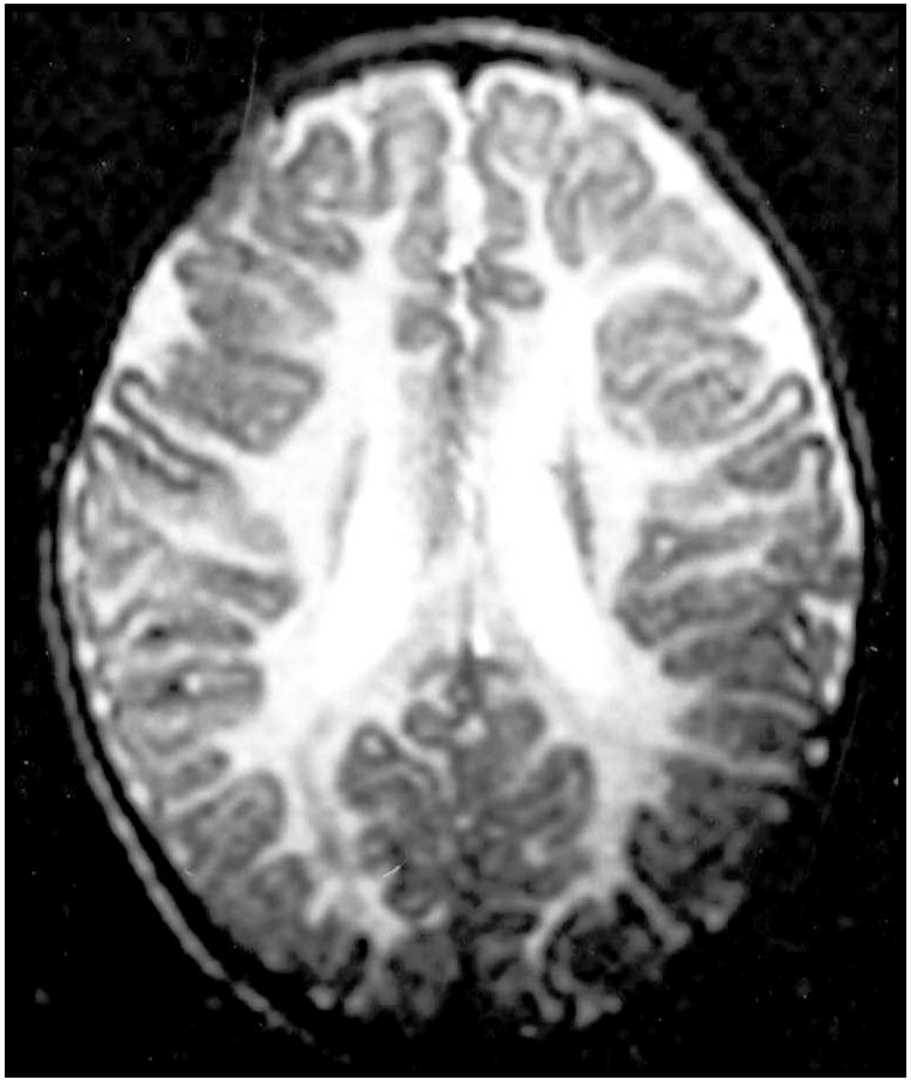
Leukodystrophies

Adrenoleukodystrophy









Canavan Disease

Pelizaeus-Merzbacher