Immun System and Demyelinating Disorders of Central Nervous System

Amber Eker, MD
Assistant Professor
Near East University
Department of Neurology

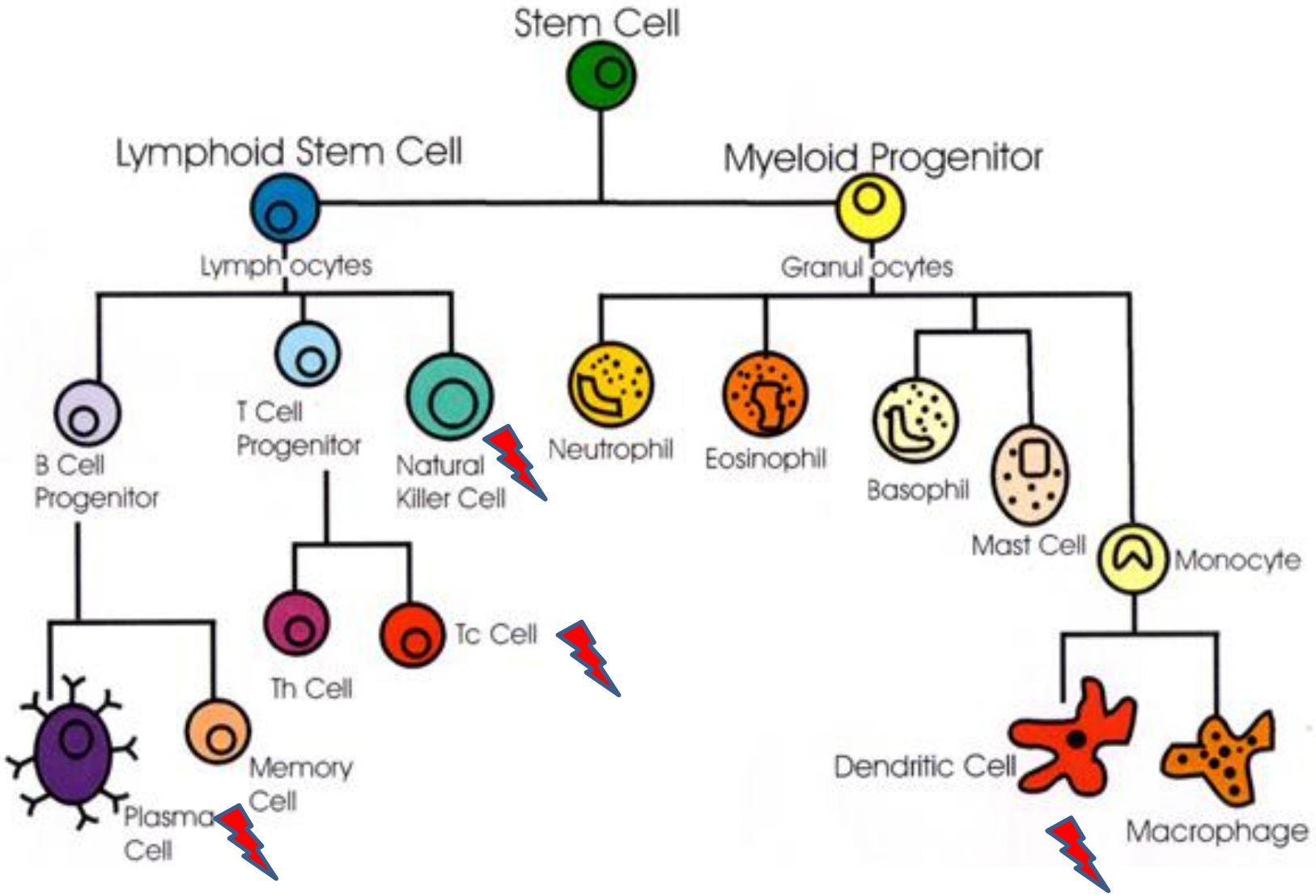
Immune System

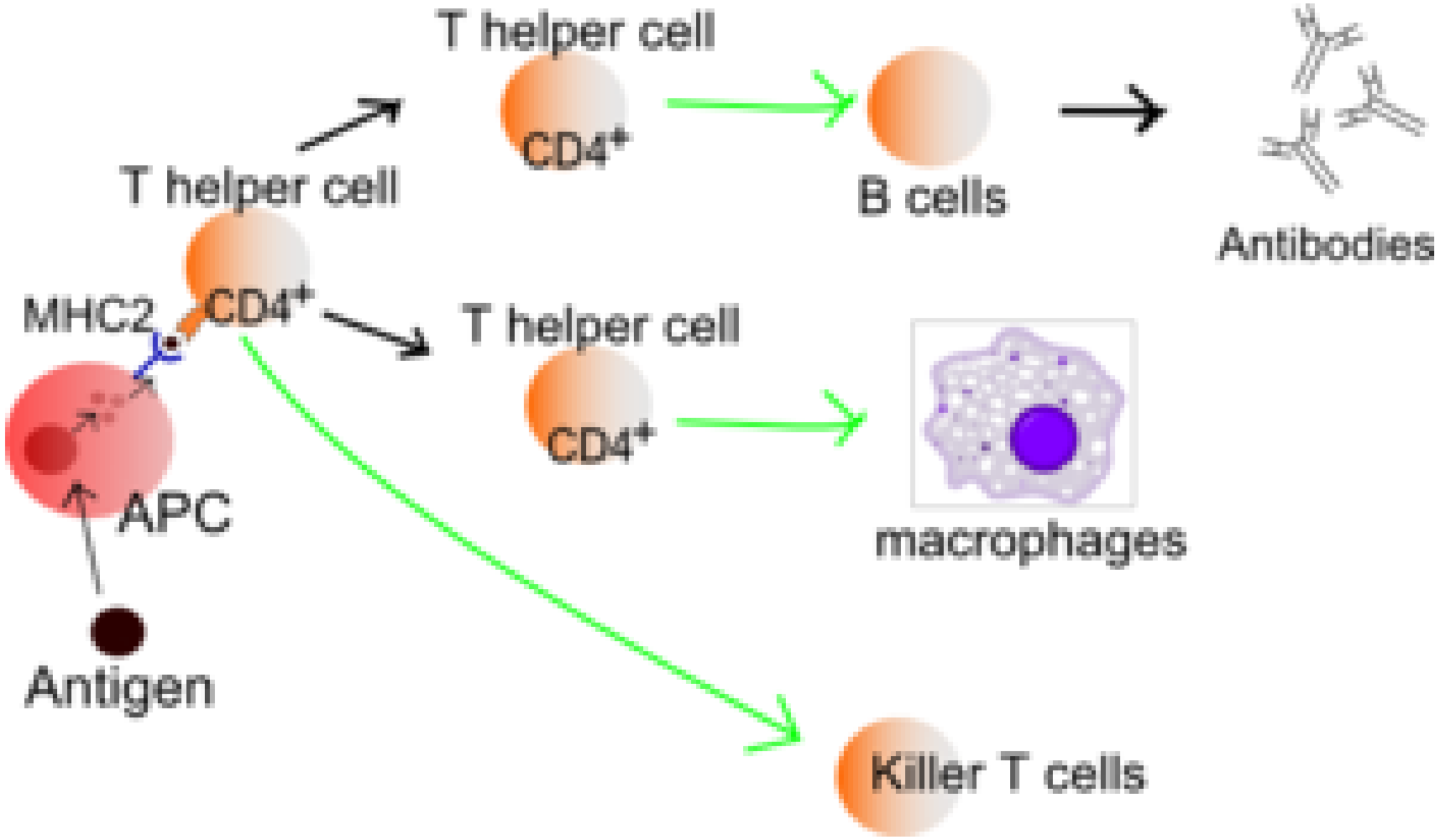
- An **immune system** is a system of biological structures and processes within an organism that protects against disease.
- In order to function properly, an immune system must detect a wide variety of agents and distinguish them from the organism's own healthy tissue.
- Immune system fighting mechanisms include phagocytosis, antimicrobial peptides (antibodies), and the complement system

Immune System

- More sophisticated defense mechanisms, including the ability to adapt over time to recognize specific pathogens more efficiently.
- Adaptive (or acquired) immunity creates **immunological memory** after an initial response to a specific pathogen, leading to an enhanced response. This process of acquired immunity is the basis of vaccination.

Cells of the Immune System




T helper cell
CD4+
B cells
Antibodies
T helper cell
MHC2
CD4+
T helper cell
CD4+
macrophages
APC
Antigen
Killer T cells


INFLAMMATION
HEAT
REDNESS
SWELLING
PAIN
LOSS OF FUNCTION

The Two Sides of Inflammation

Proinflammatory and neurotoxic factors

TH1 cytokines
TNF
IL-1
osteopontin
leukotrienes
MMP
plasminogen activators
nitric oxide
reactive oxygen species
glutamate
antibody + complement
cell-mediated cytotoxicity
neurotrophins via $p75^{NTR}$?

Antiinflammatory and neuroprotective factors

TH2 cytokines
TGF
TNF ?
soluble TNF receptor
soluble IL-1 receptor
IL-1 receptor antagonist
some prostaglandins
lipoxins
TIMP
antithrombin

BDNF
NGF
NT3
NT4/5
GDNF
LIF
} neurotrophic factors

Destruction

Protection

Immune System

- Disorders of the immune system can result in **autoimmune diseases**, **inflammatory diseases** and **cancer**.
- Autoimmunity result from a hyperactive immune system attacking normal tissues.
- Common autoimmune diseases include Hashimoto's thyroiditis, rheumatoid arthritis, diabetes mellitus type 1, and systemic lupus erythematosus.

Immune System and CNS

- In the past, central nervous system was believed to be an immune privileged area.
- Immune privilege means an absent or limited response of the immune system to antigenic challenge.
- Recently, it is known that the CNS and PNS are not isolated from the immune system. They are in interaction with the peripheral immune system.
- CNS and PNS are accepted to be **‘immune specific area’**
- Both central and peripheric nervous system are isolated from peripheric immune circulation by barriers.

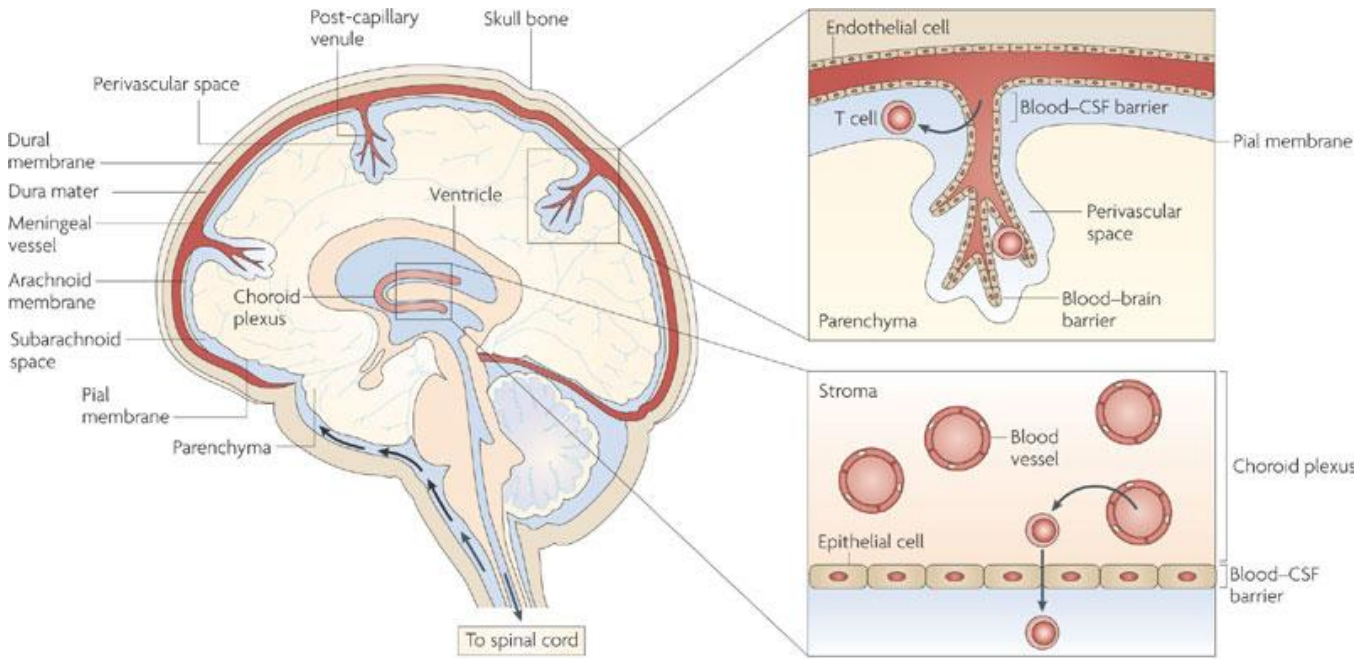
Immune Sytem and CNS

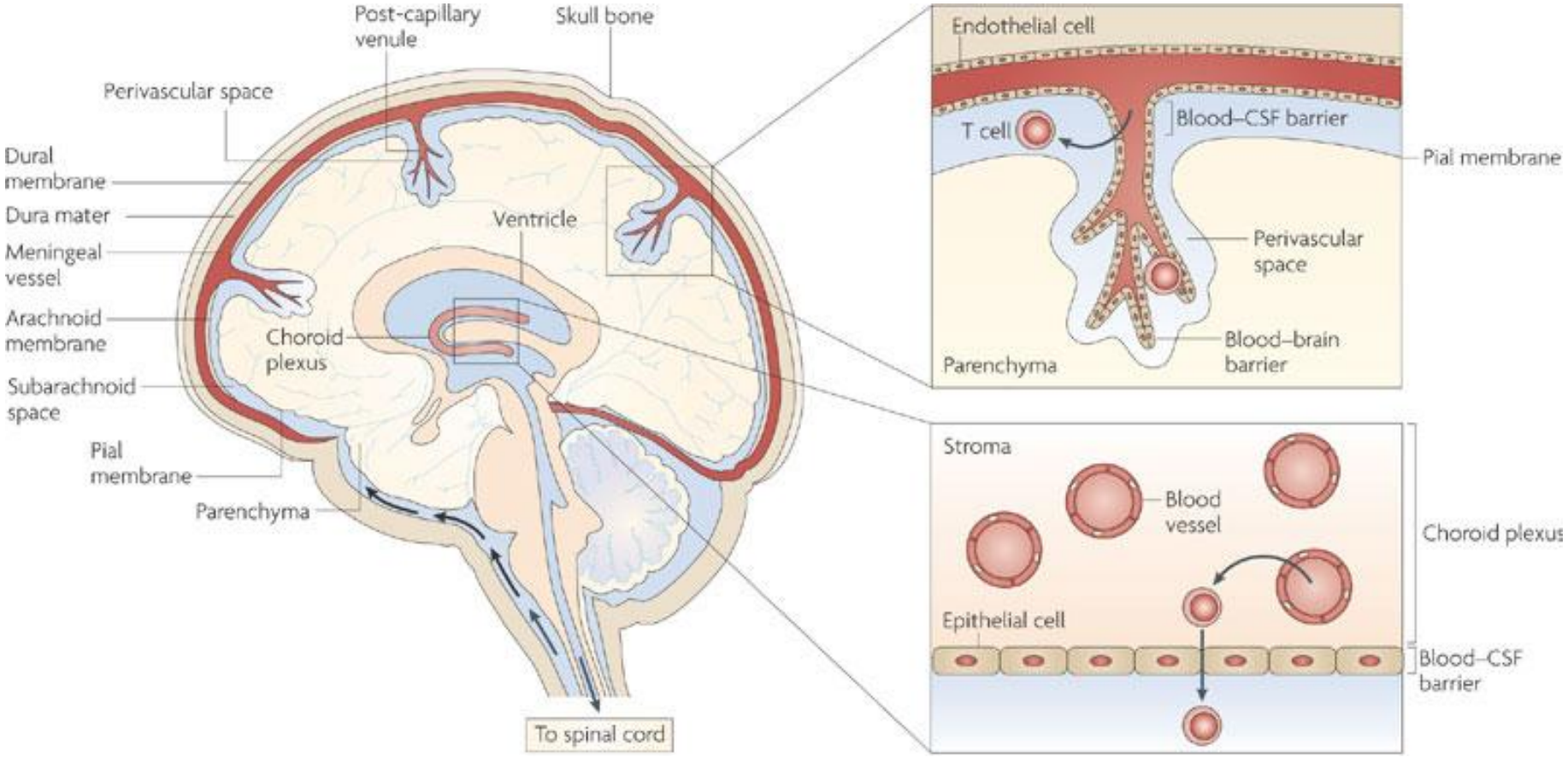
Gates to the CNS

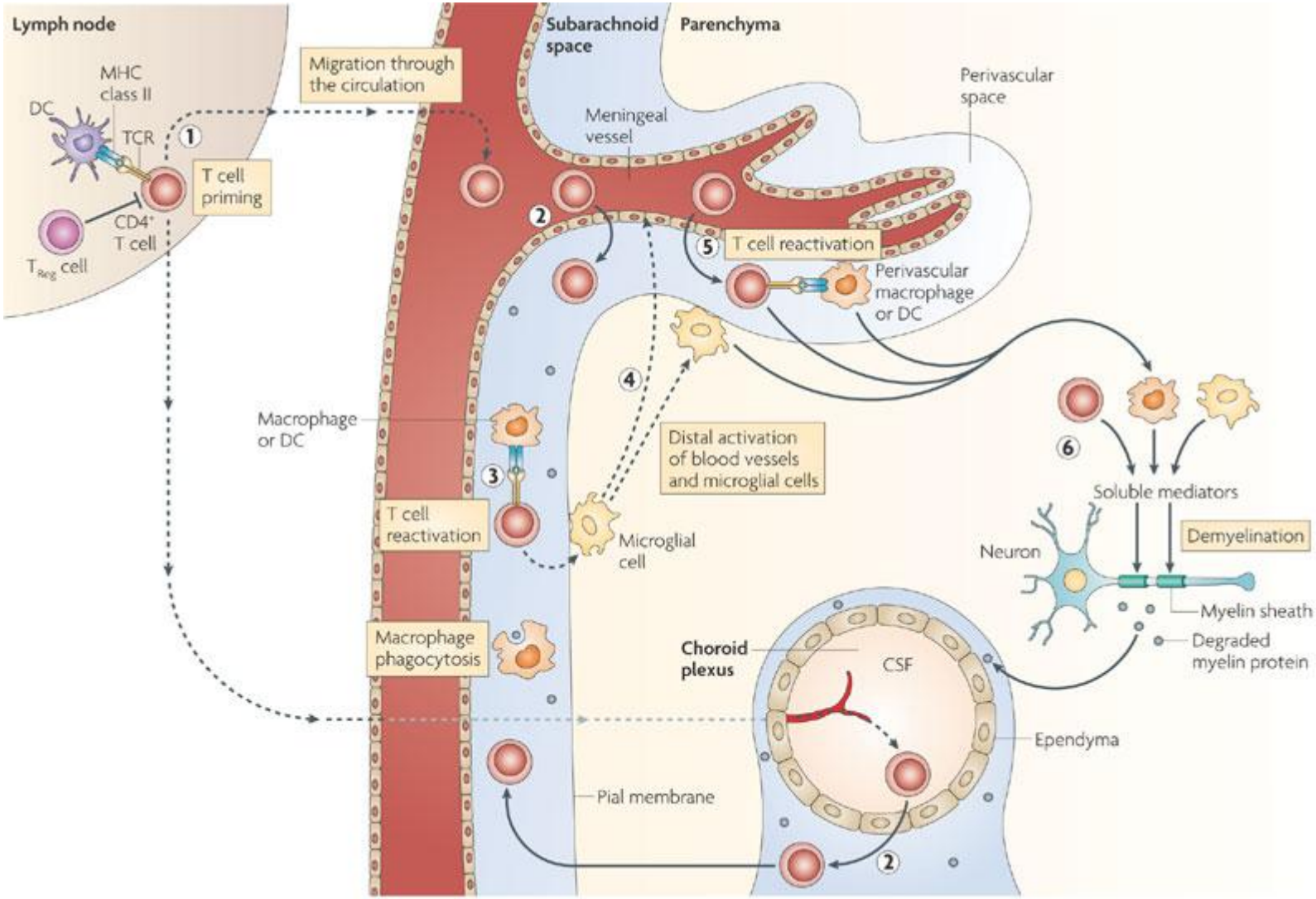
1- Blood → **BBB** → Paranchima

Perivascular space

2- Blood → **choroid plexus** → CSF



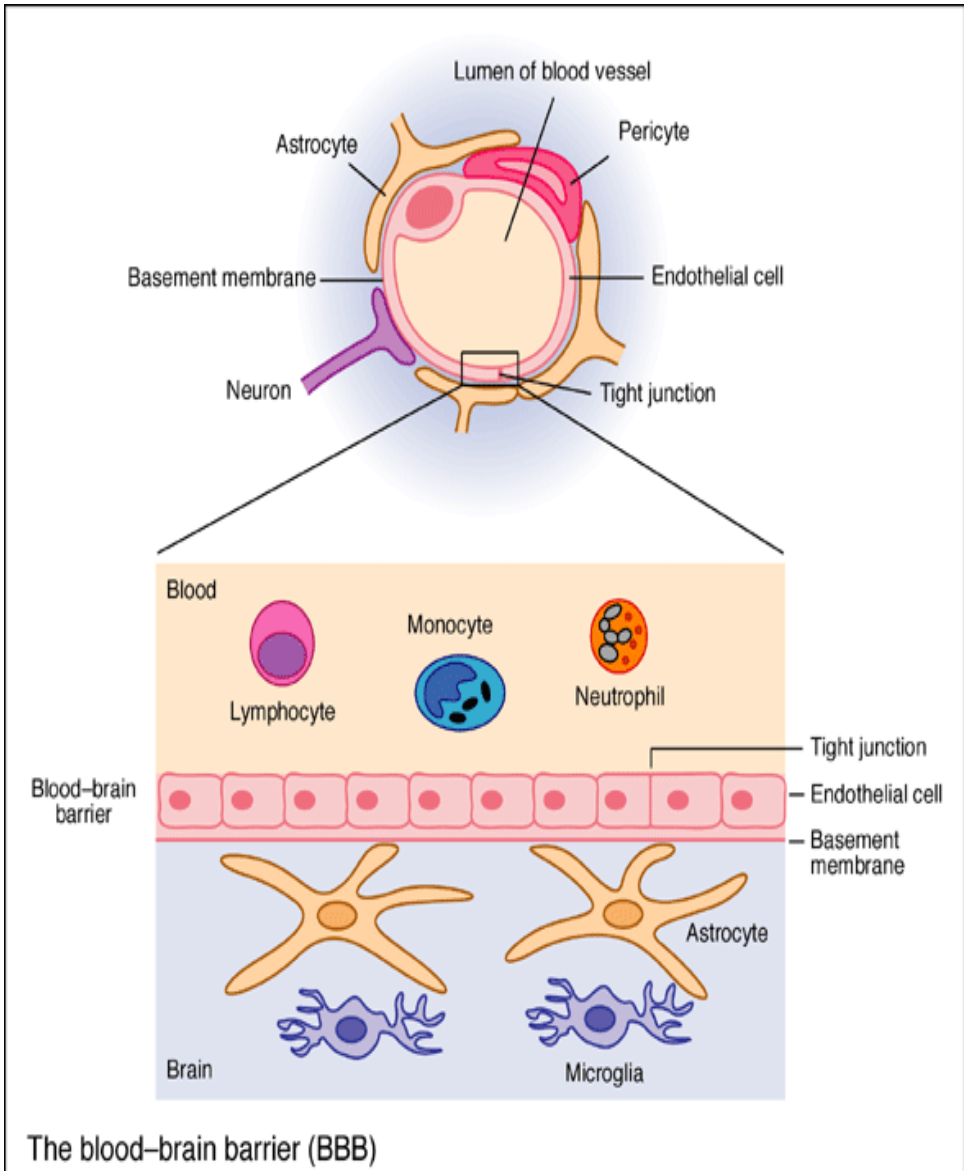

Post-capillary venule
Skull bone
Perivascular space
Dural membrane
Dura mater
Meningeal vessel
Arachnoid membrane
Subarachnoid space
Pial membrane
Parenchyma
Ventricle
Choroid plexus
To spinal cord
Endothelial cell
T cell
Blood–CSF barrier
Pial membrane
Perivascular space
Blood–brain barrier
Parenchyma
Stroma
Blood vessel
Choroid plexus
Epithelial cell
Blood–CSF barrier


Lymph node
MHC class II
DC
TCR
1
T cell priming
CD4+ T cell
TReg cell
Migration through the circulation
Subarachnoid space
Parenchyma
Perivascular space
Meningeal vessel
2
5
T cell reactivation
Perivascular macrophage or DC
4
Macrophage or DC
3
T cell reactivation
Distal activation of blood vessels and microglial cells
Microglial cell
6
Soluble mediators
Demyelination
Neuron
Myelin sheath
Degraded myelin protein
Macrophage phagocytosis
Choroid plexus
CSF
Ependyma
Pial membrane
2

Blood Brain Barrier

- The BBB is formed by highly specialized endothelial cells, which inhibit transcellular molecular traffic owing to its low pinocytotic activity

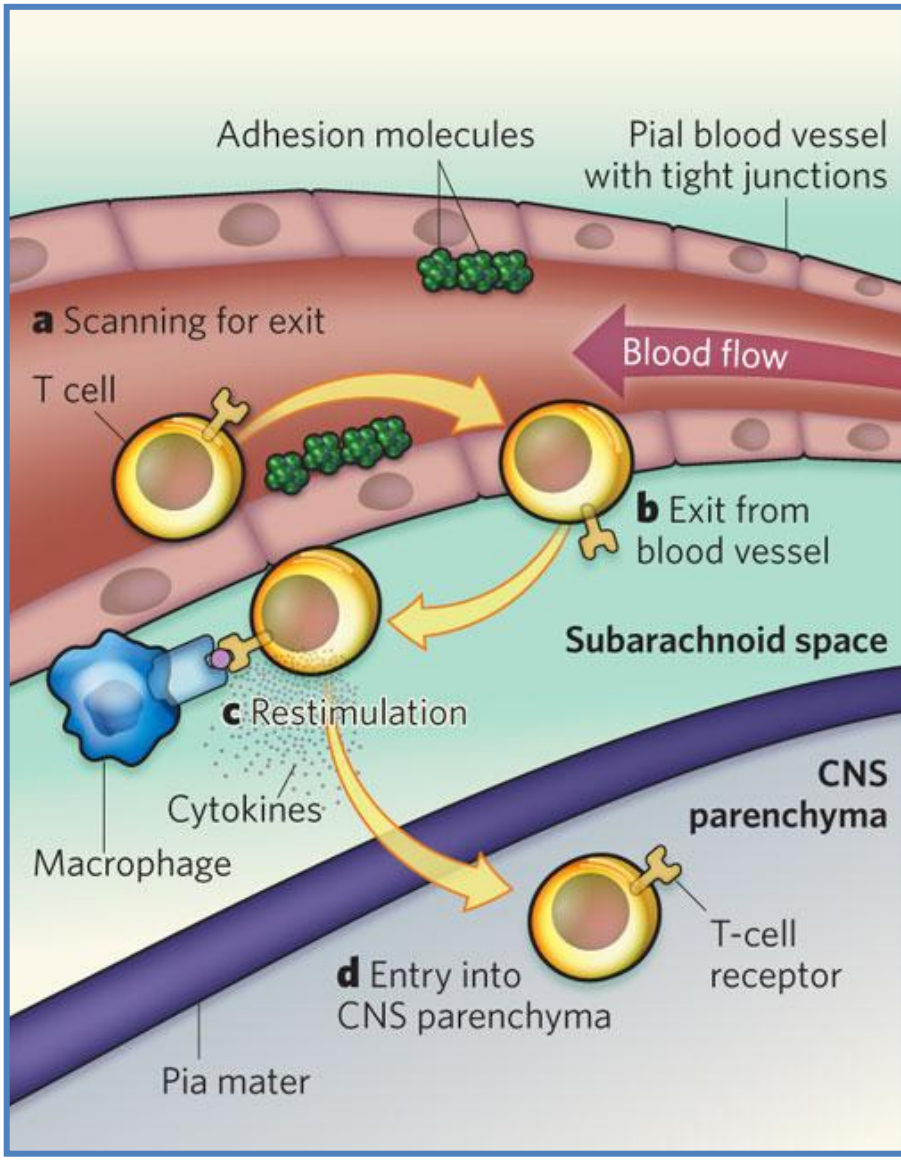
- The BBB restrict paracellular diffusion of hydrophilic molecules because of complex interendothelial tight junctions

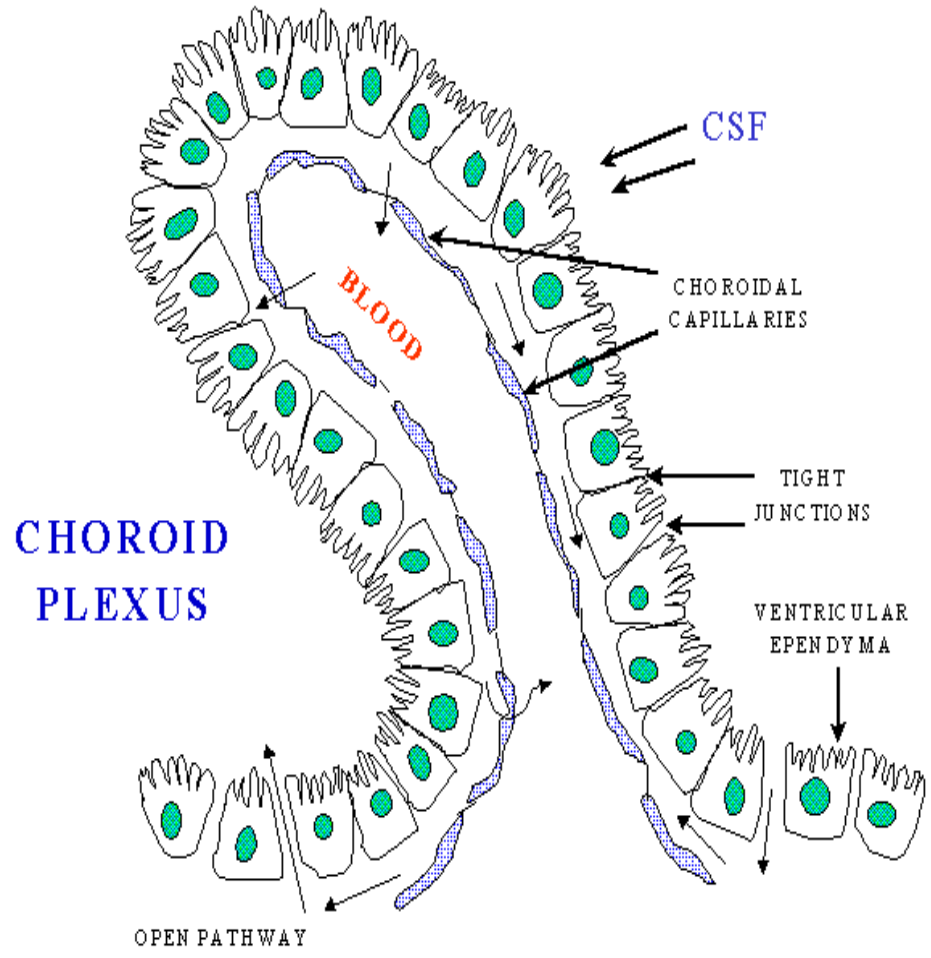


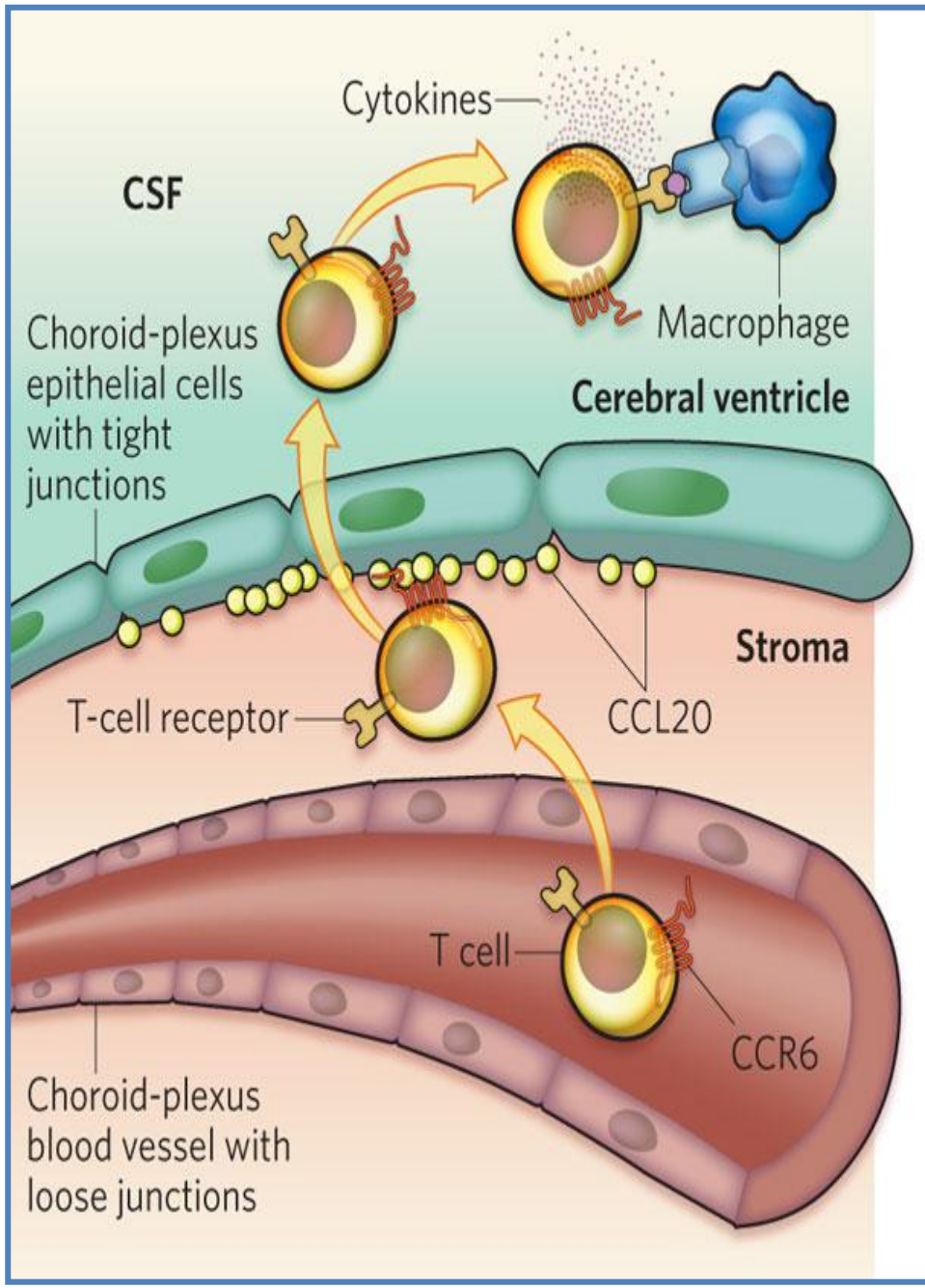
The blood–brain barrier (BBB)

- Leukocyte migration across the BBB is a multi-step process.

- An initial contact of the circulating leukocyte with the vascular endothelium, generally mediated by **adhesion molecules** of the **selectin** family.
- Lymphocytes can also roll via the interaction of **integrins** with their endothelial ligands VCAM-1 or MAdCAM-1.
- The rolling leukocyte perceive **chemotactic factors** from the endothelial surface.
- This process results in leukocyte diapedesis, through inter-endothelial cell junctions or directly through the endothelial cell.



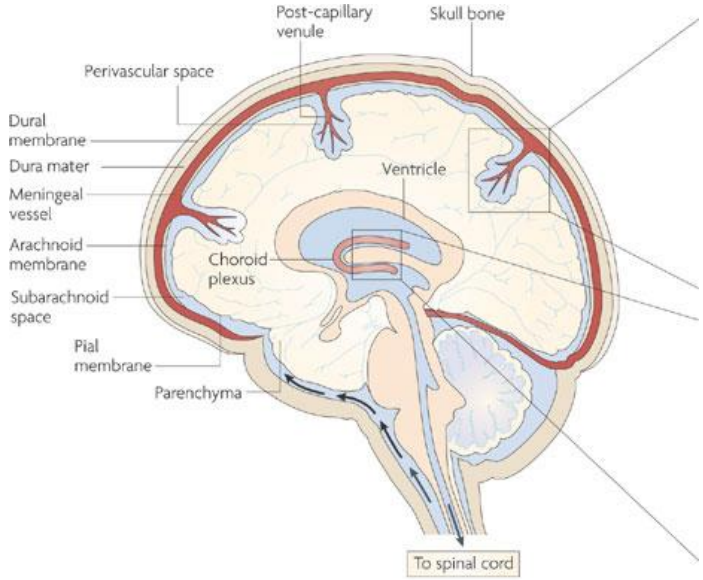

CSF
BLOOD
CHOROIDAL CAPILLARIES
TIGHT JUNCTIONS
CHOROID PLEXUS
VENTRICULAR EPENDYMA
OPEN PATHWAY

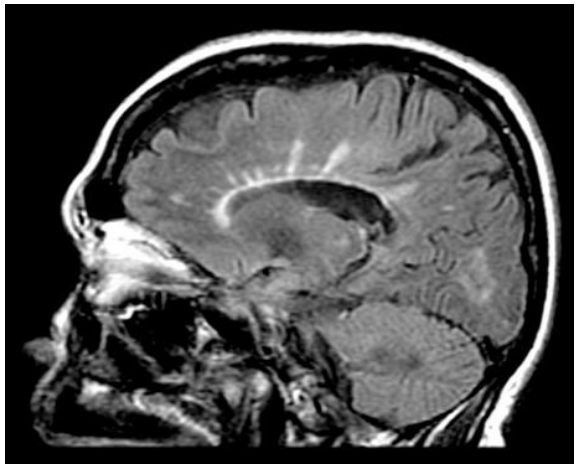

Cytokines
CSF
Macrophage
Choroid-plexus epithelial cells with tight junctions
Cerebral ventricle
Stroma
T-cell receptor
CCL20
T cell
CCR6
Choroid-plexus blood vessel with loose junctions

- In neuroimmunology area, leukocyte recruitment into the brain is an important topic.
- In inflammatory conditions of the CNS, the expression of adhesion molecules and chemokines is induced on BBB endothelium and the choroid plexus epithelium, providing additional traffic signals for circulating leukocytes.

- Inflammation and inflammatory mediators contribute to acute and chronic CNS disorders.
- It may neurologic and psychiatric disorder.
- Recent studies have demonstrated a strong link between neurodegeneration and ***chronic inflammation*** which has been reported in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis also depression.

- Acute ınflammation & BBB :
  - Initial lesions arise around small veins.
  - This is reflected by the perivenous orientation of demyelinated lesions in ***multiple sclerosis***.
  - It is mainly discuss as ***T cell mediated disease***.



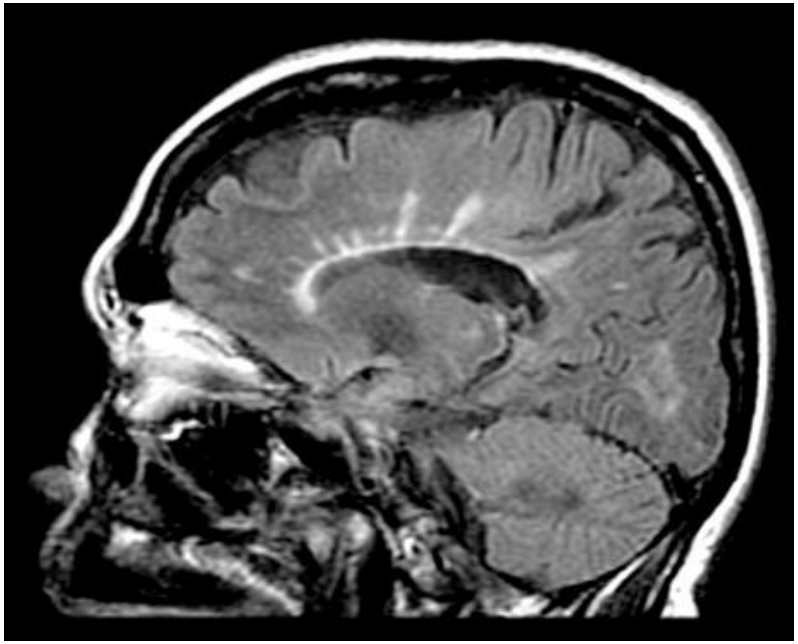


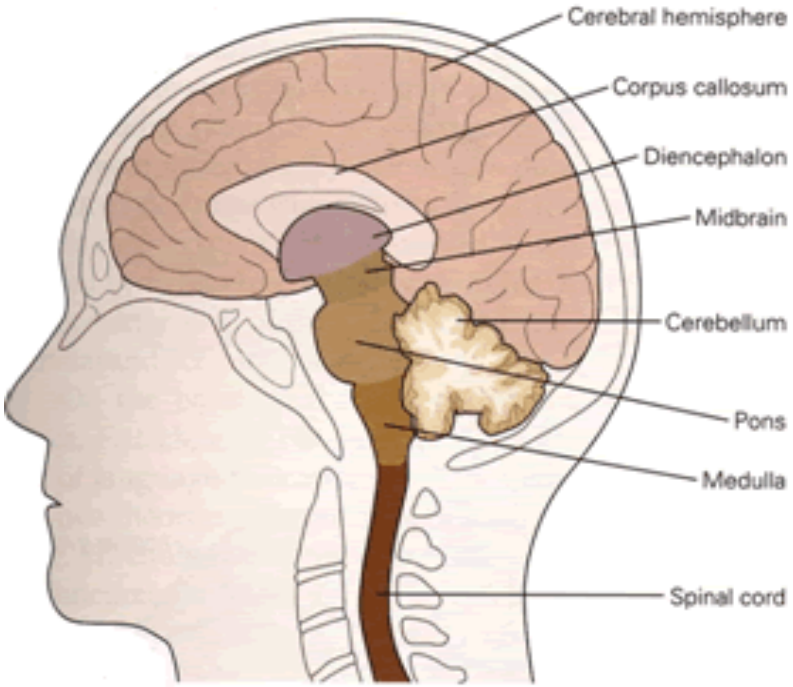
- There is also a evidence that ***B cells*** are involved in the pathophysiology of many neurological diseases, either in a causative or contributory role, via production of autoantibodies, cytokine secretion, or by acting as antigen-presenting cells triggering T cell activation.
- Antibody-mediated autoimmune diseases principally affect ***peripheral nerves and the neuromuscular junction. (eg.Myastenia Gravis)***

Demyelinating Disorders of Central Nervous System

What is multiple sclerosis?

- Chronic, immune mediated demyelinating disease of central nervous system



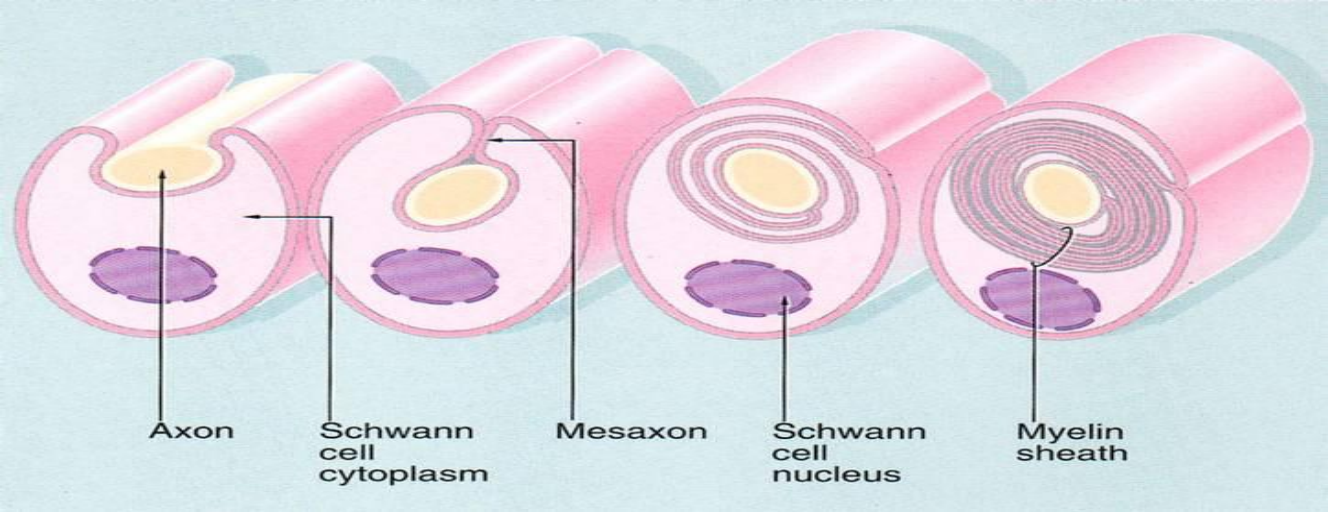

Cerebral hemisphere
Corpus callosum
Diencephalon
Midbrain
Cerebellum
Pons
Medulla
Spinal cord


[H]
Image: 5

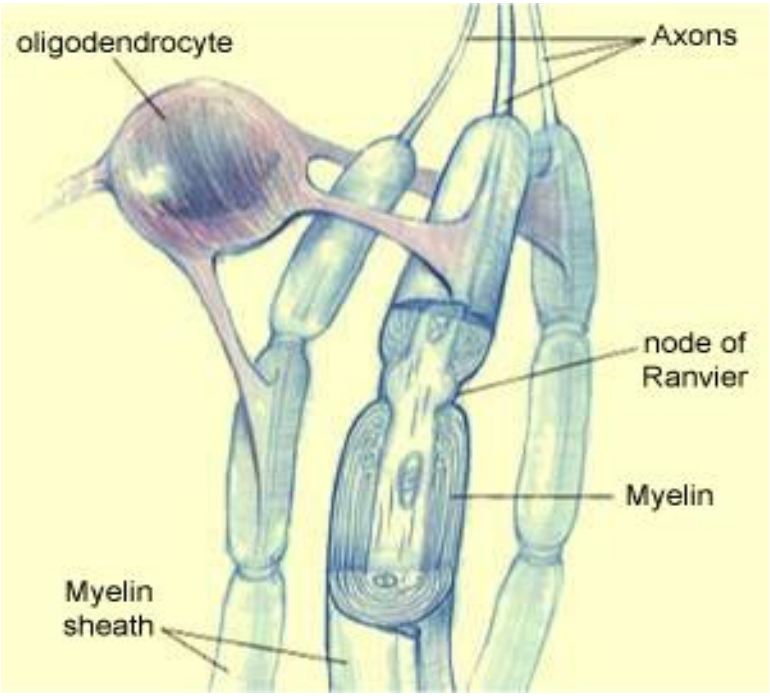

cm

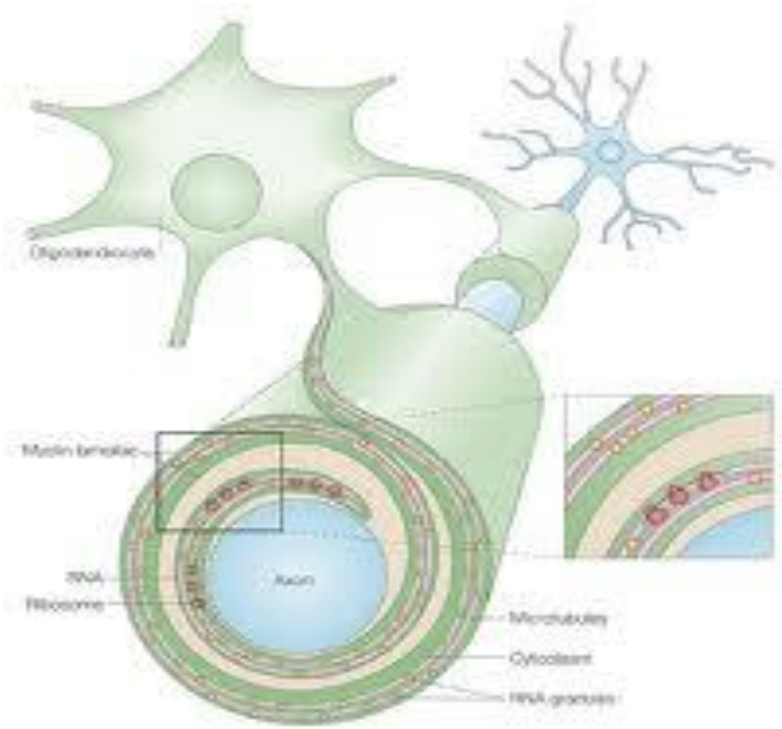
Myelin

- 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:

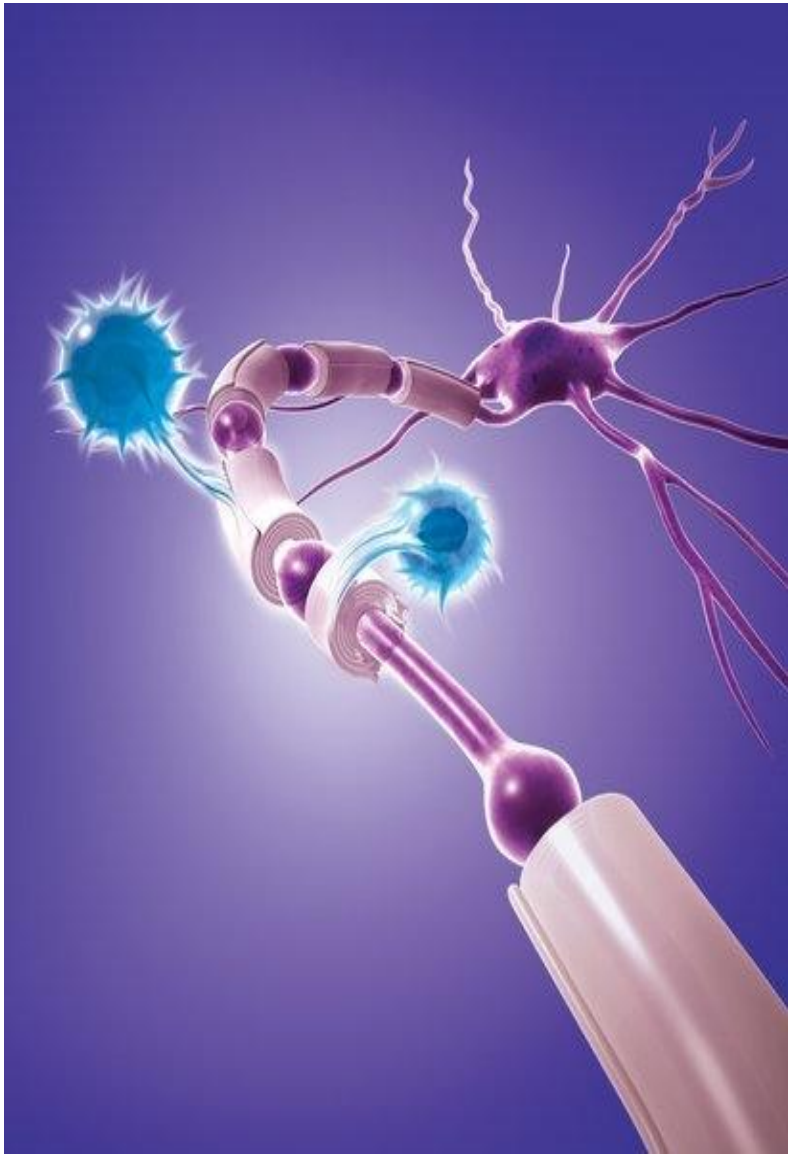
- Water 40%
- Lipid (70 to 85% of dry mass)
- Protein (15 to 30% of dry mass)

- 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 Function

Myelin;

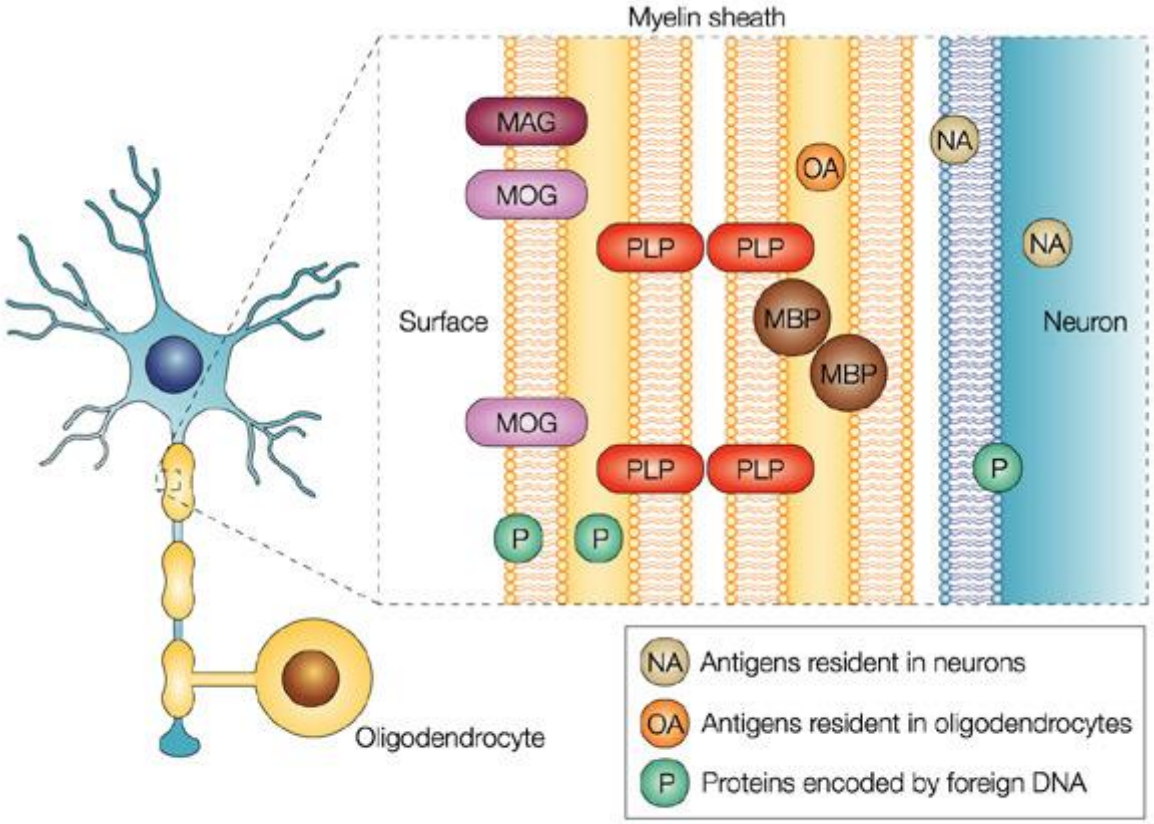
- Increases the conduction of impulses
- Protects axons from injury
- Contains growth factors for axonal survive



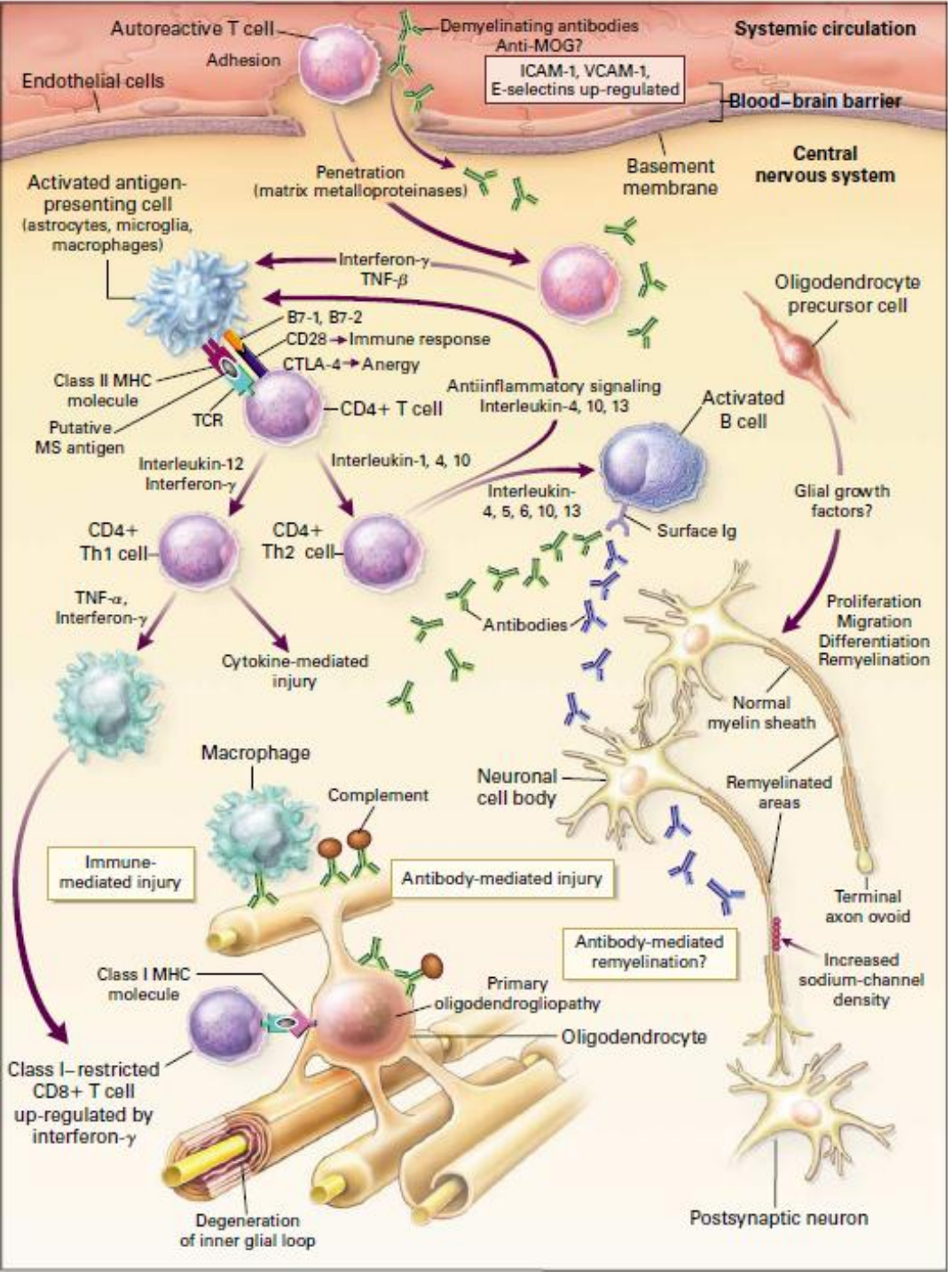
Central nervous system
(brain and spinal cord)

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

Immun Myelin Damage Mechanism in Multiple Sclerosis



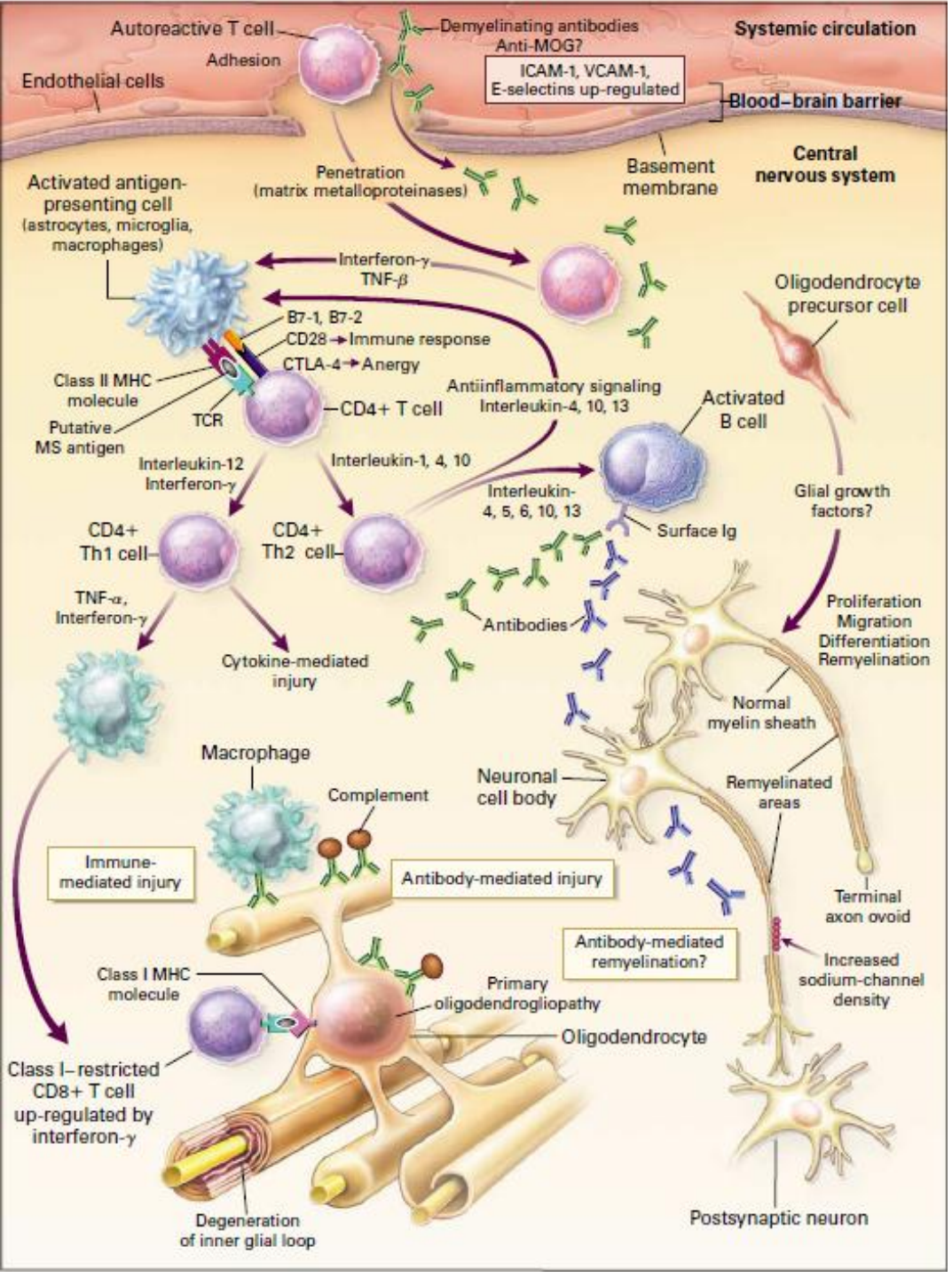
➢Proteins of the myelin sheath, oligodendrocytes and neurons are possible targets of the immune response in multiple sclerosis.



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.

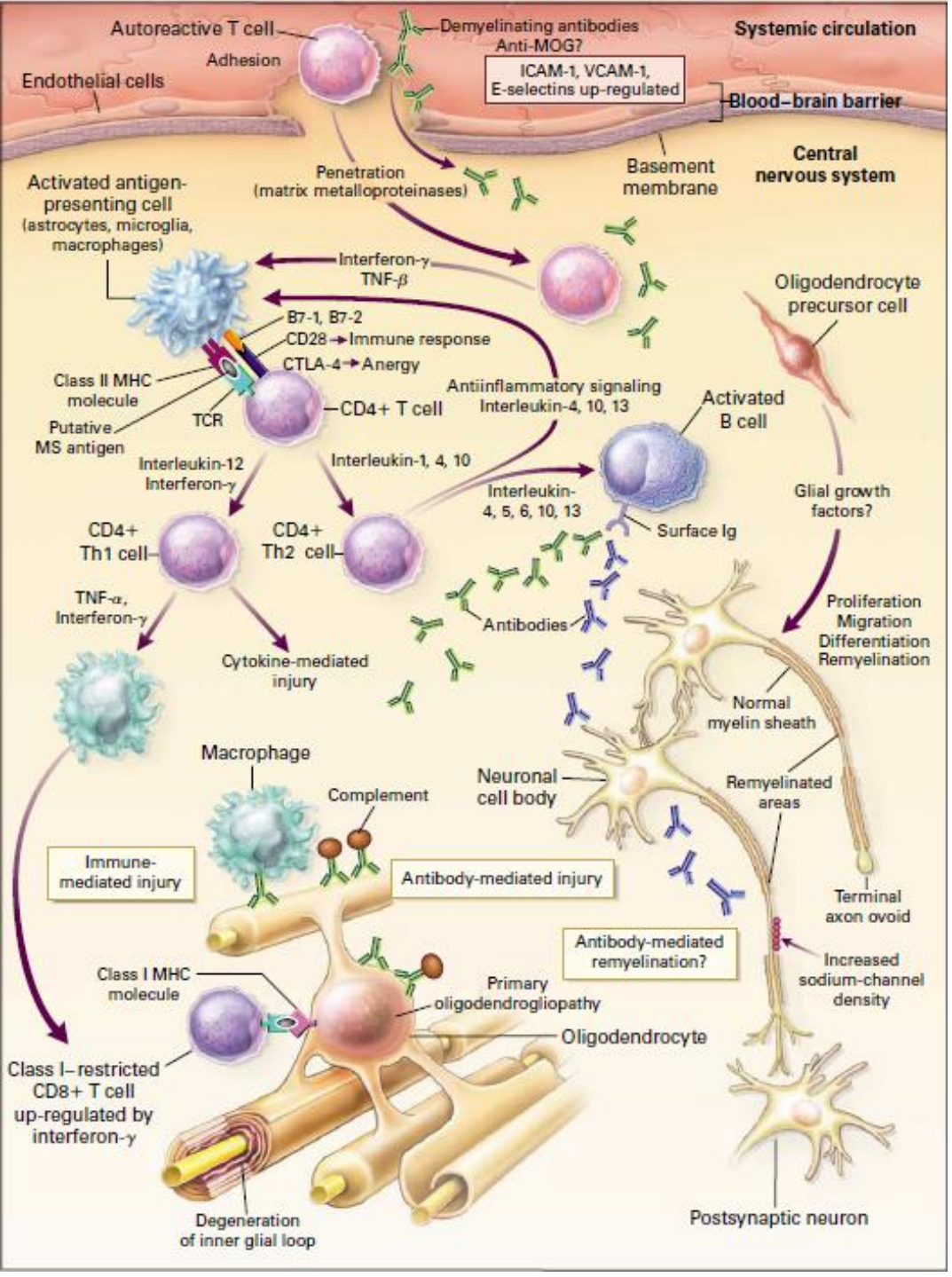


Proinflammatory cytokines such as Interferon *γ* and tumor necrosis factor *β* (TNF *β)* released by activated T cells

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*

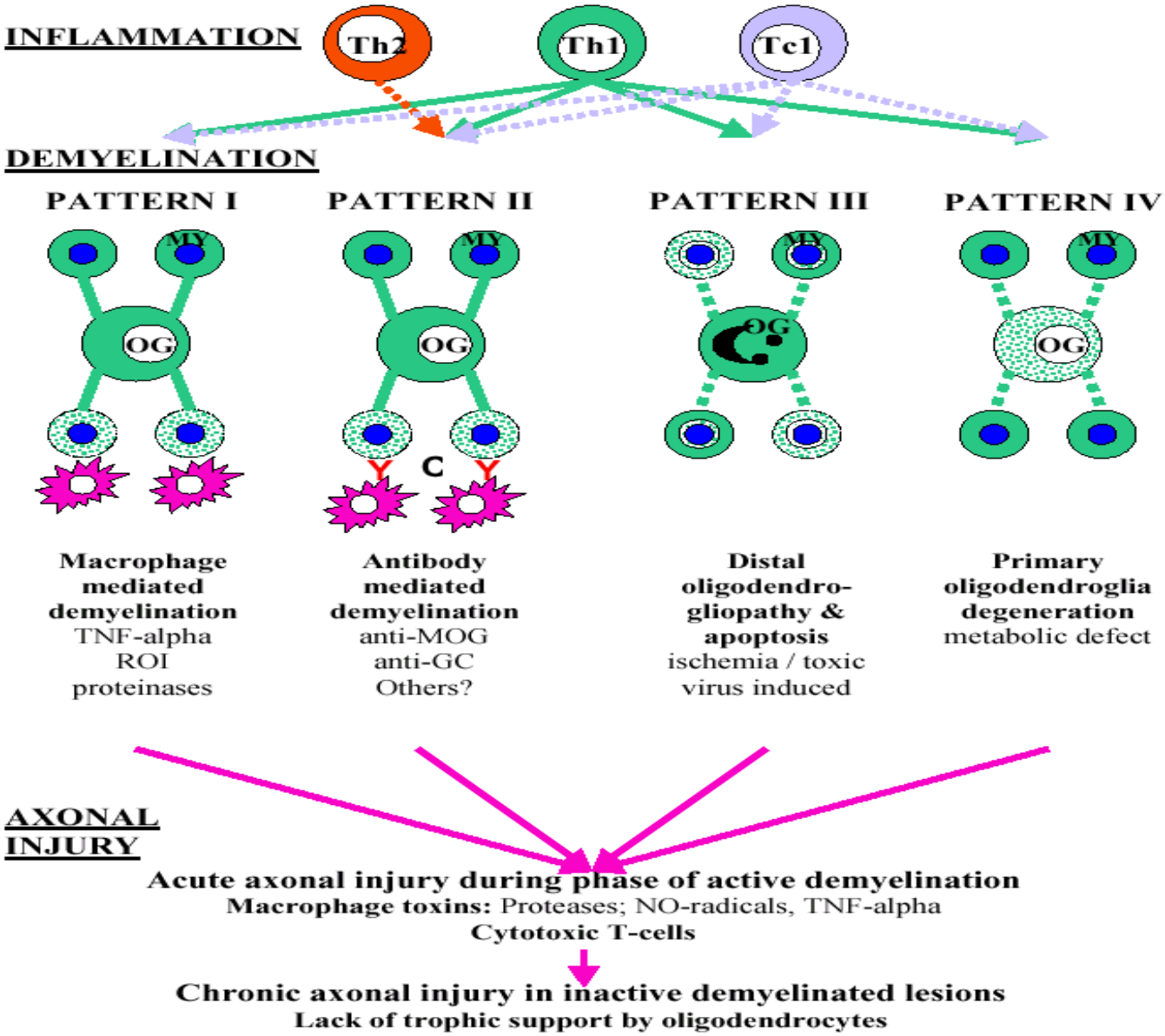


Cytokines from T cells activate B cell response and antibody syntesis

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

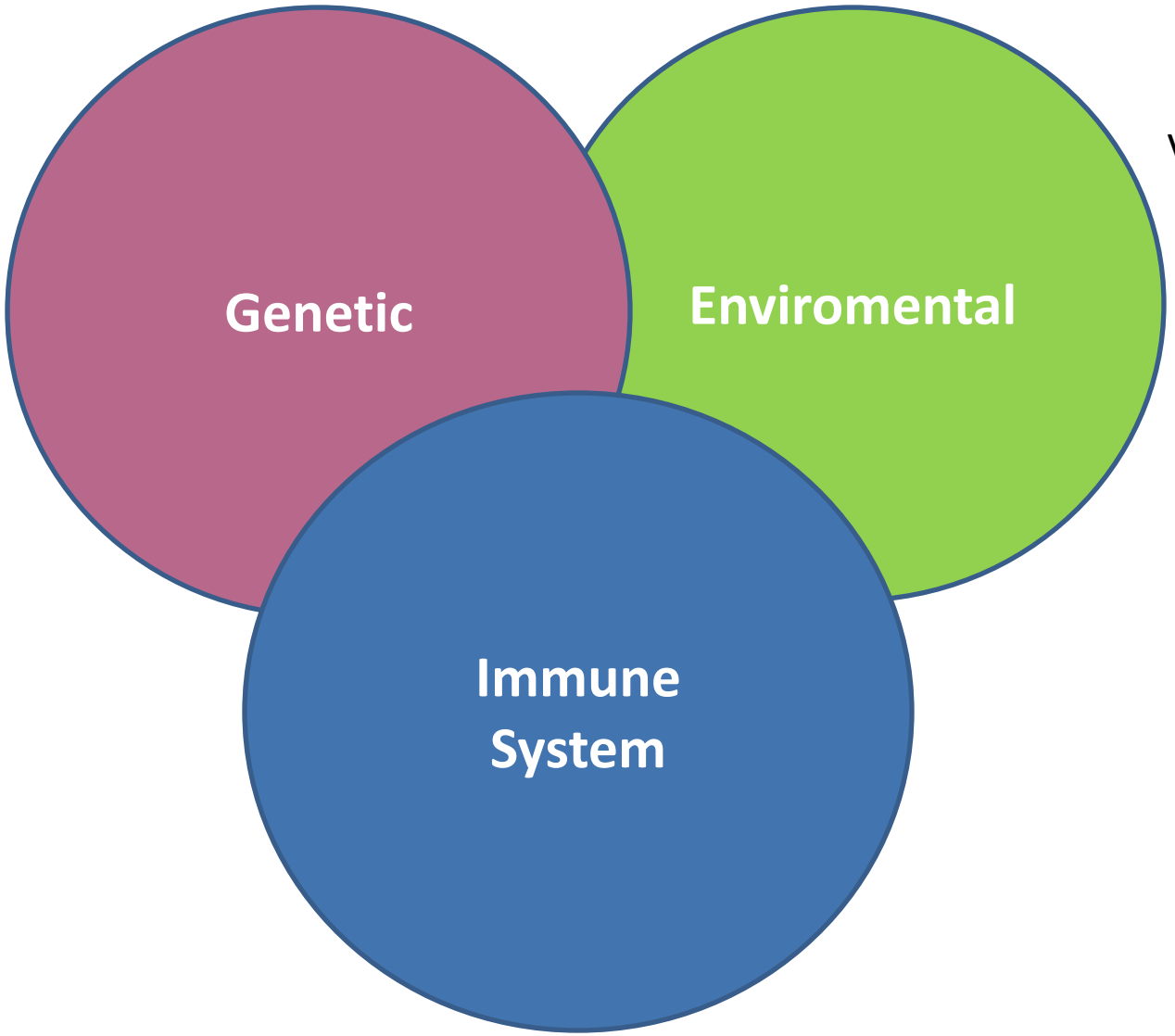
Direct injury of oligodendrocytes
by CD4+ and CD8+ T cells

PATHOLOGY OF MULTIPLE SCLEROSIS



Pathogenesis

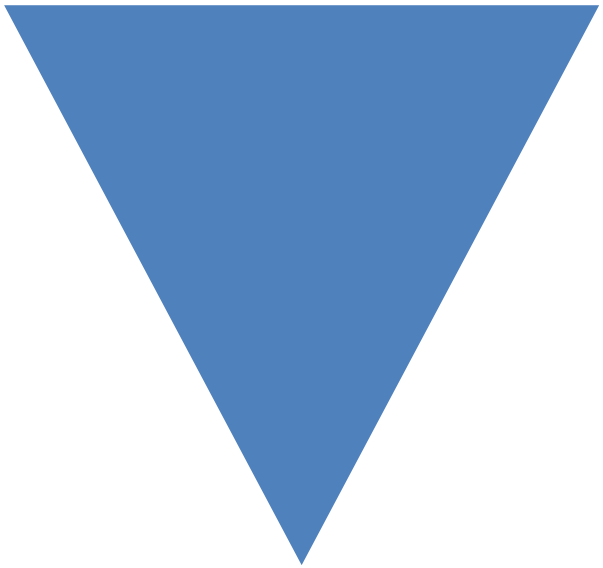
HLA DR2 allel



Virus

Multiple Sclerosis: Pathology

Inflammation and Eudema

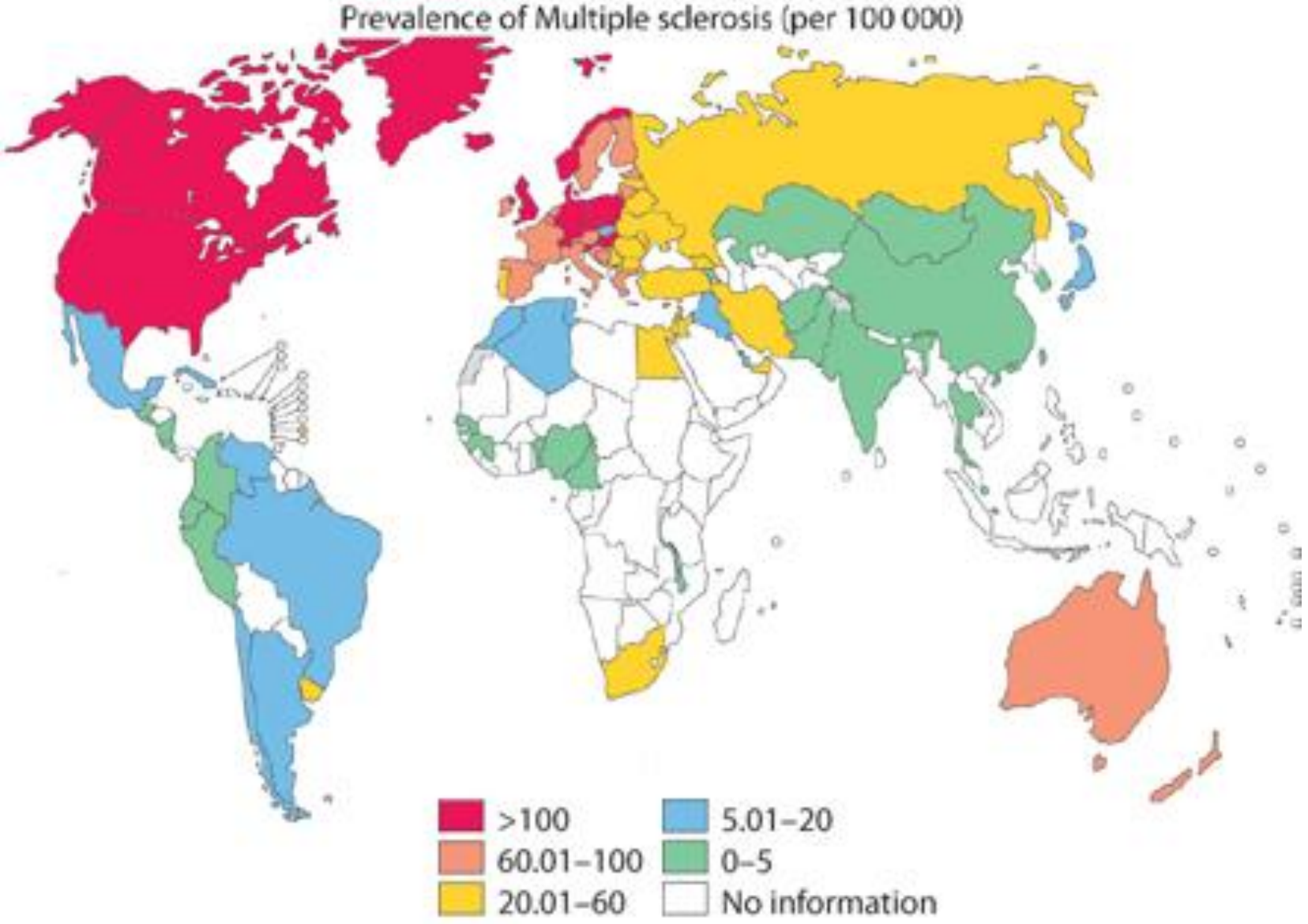


Demyelination

Axonal Loss / Neurodegeneration

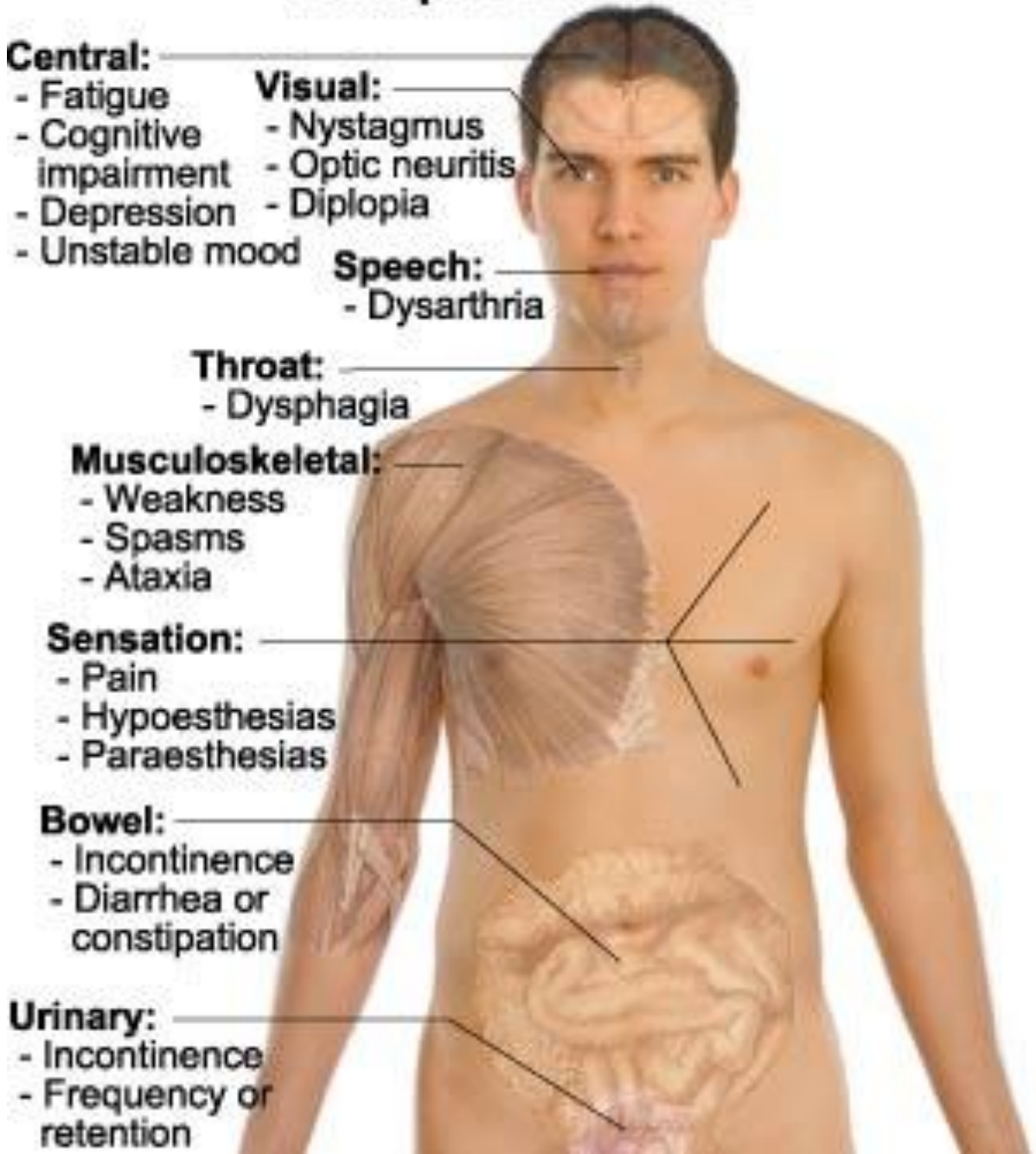
Epidemiology

- Common between 15-45 ages
- Symptom initiation age;
  - 70% between 20-40 yo
  - 10% <20y, 20% >40y
- F:M = 2:1
- Common in Northern countries

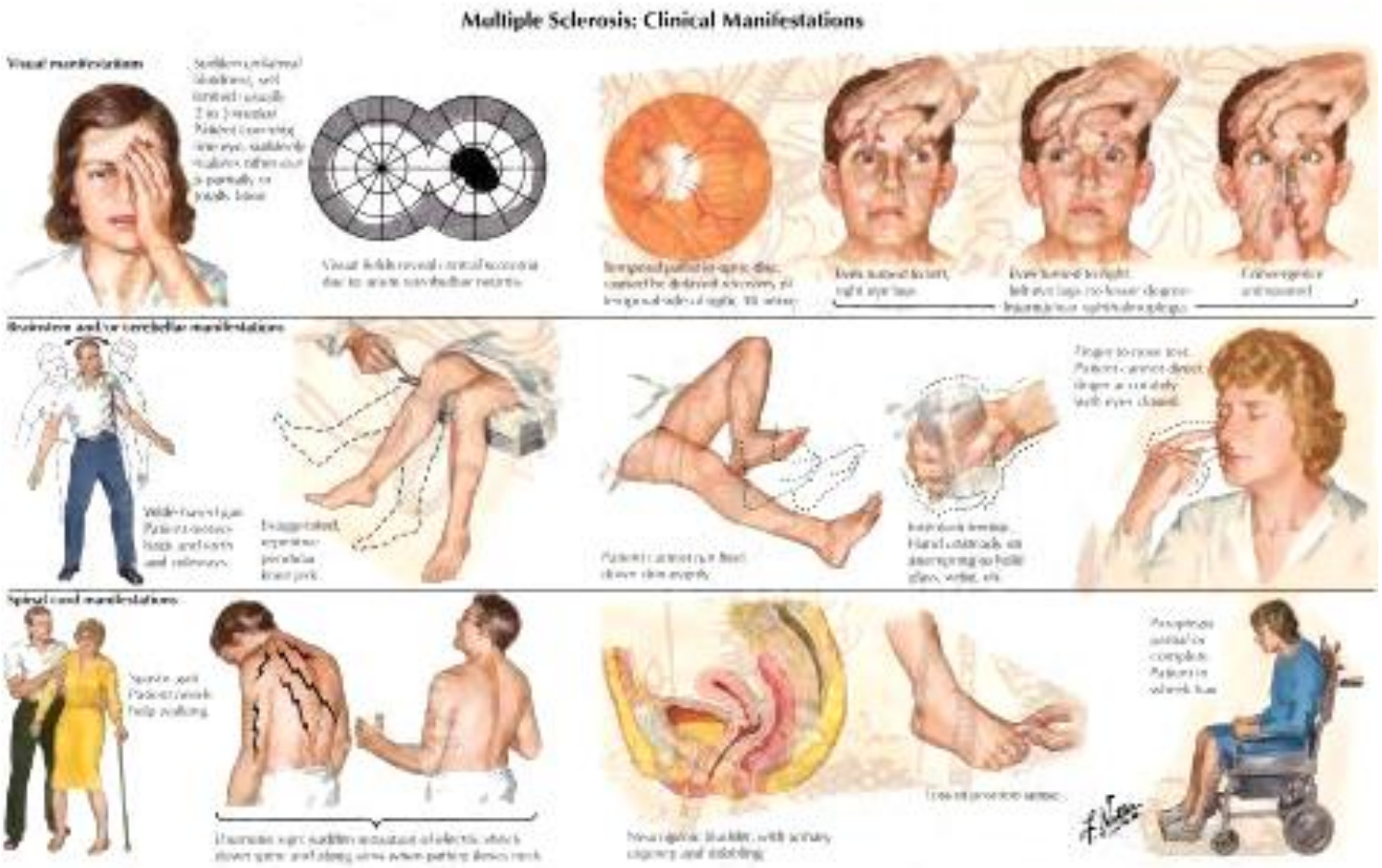

Prevalence of Multiple sclerosis (per 100 000)
>100
60.01–100
20.01–60
5.01–20
0–5
No information

Main symptoms of

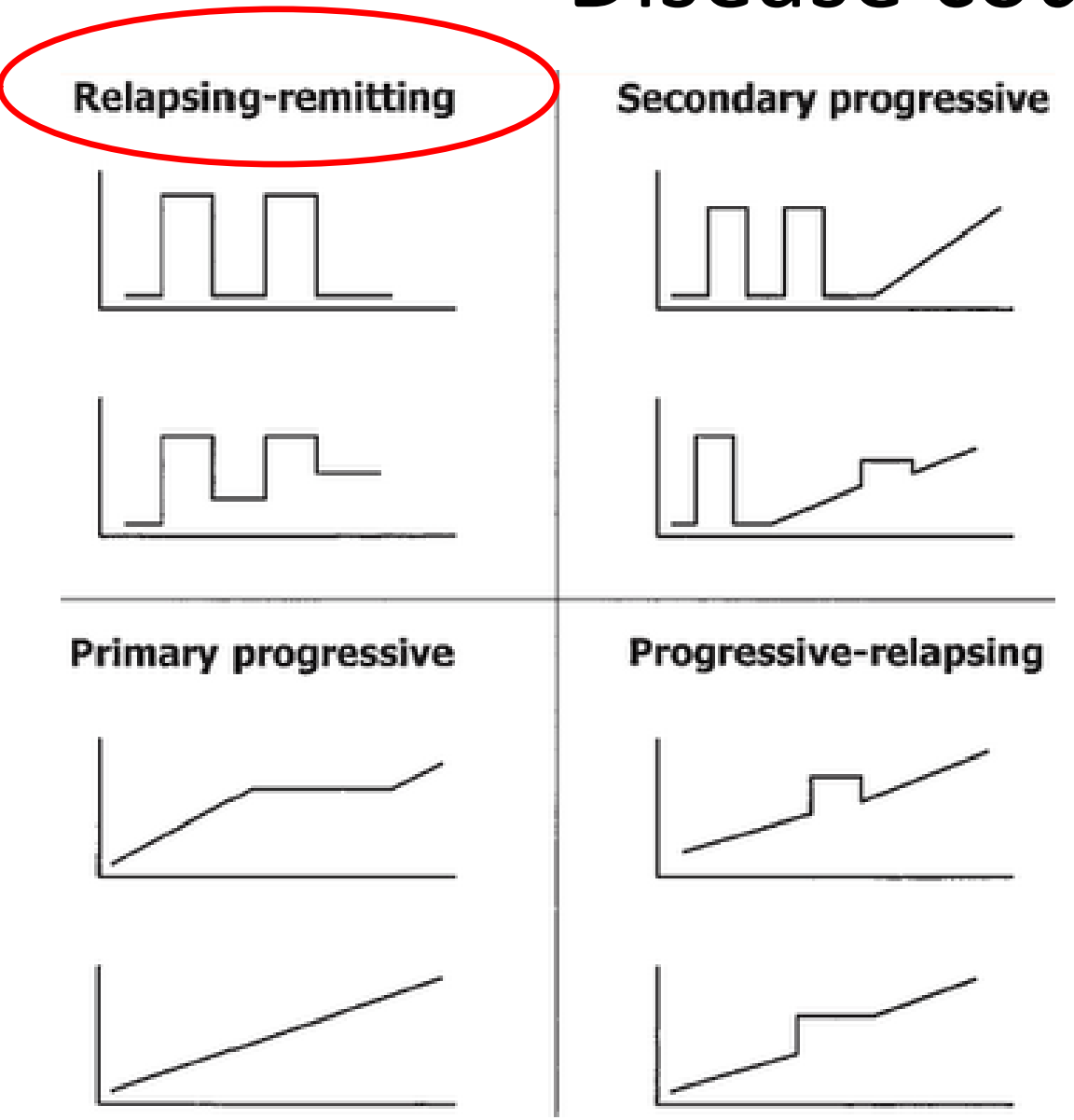
Multiple sclerosis



Symptoms and Clinical Findings

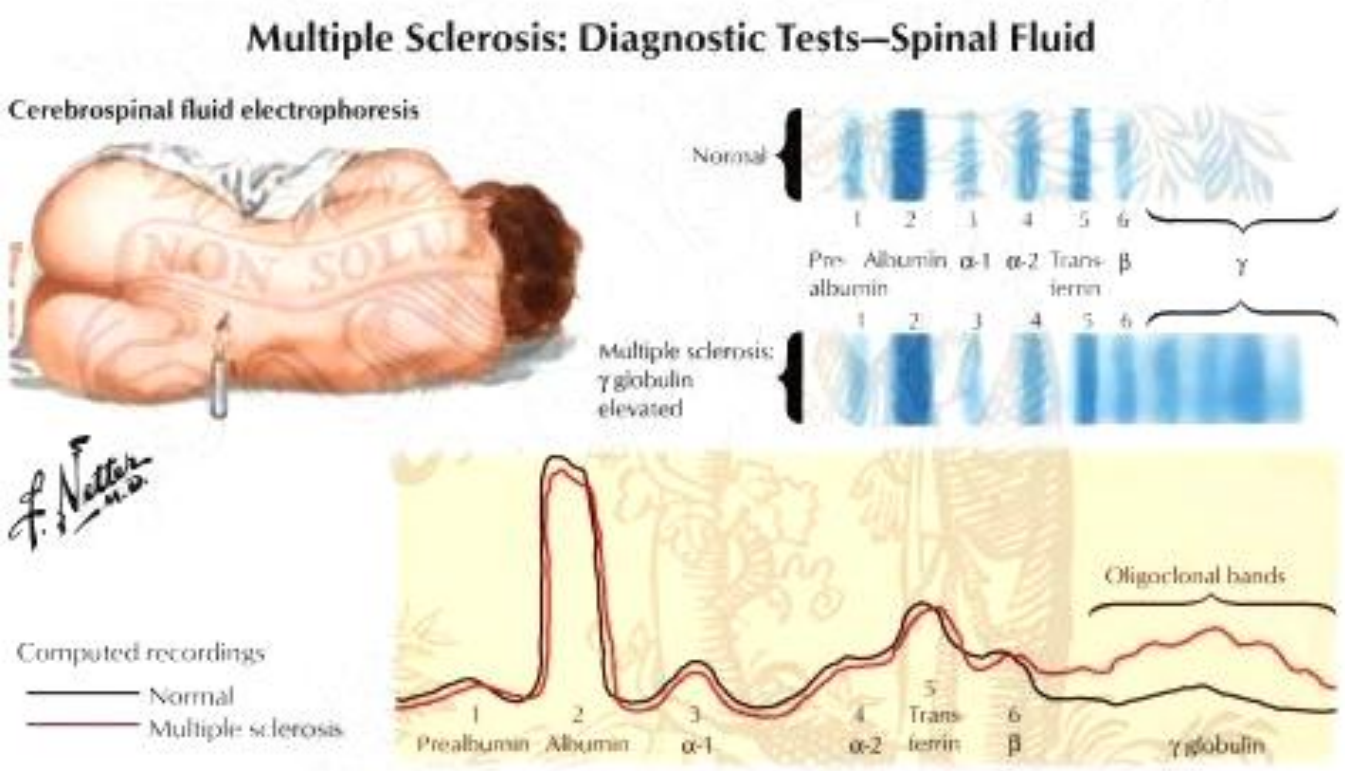


Disease course

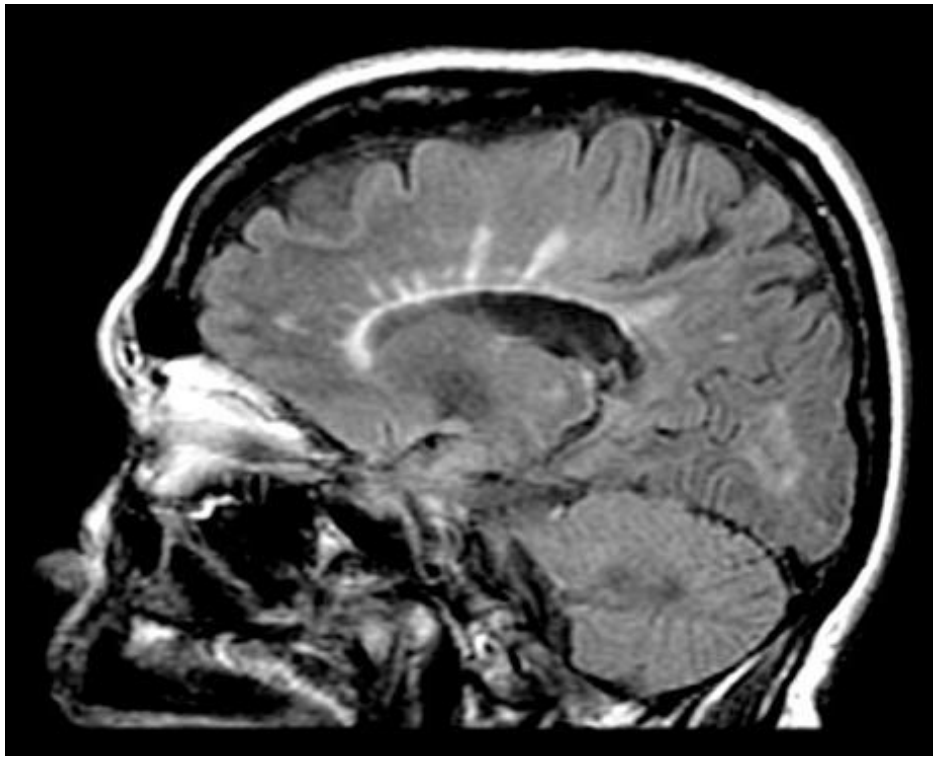


- 85% of patients have relapsing-remitting multiple sclerosis (RRMS) type course initially

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

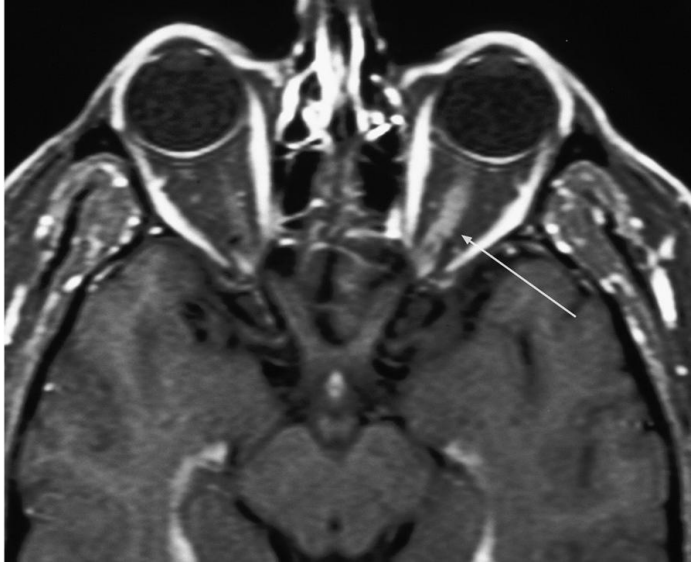
Magnetic Resonans Imaging



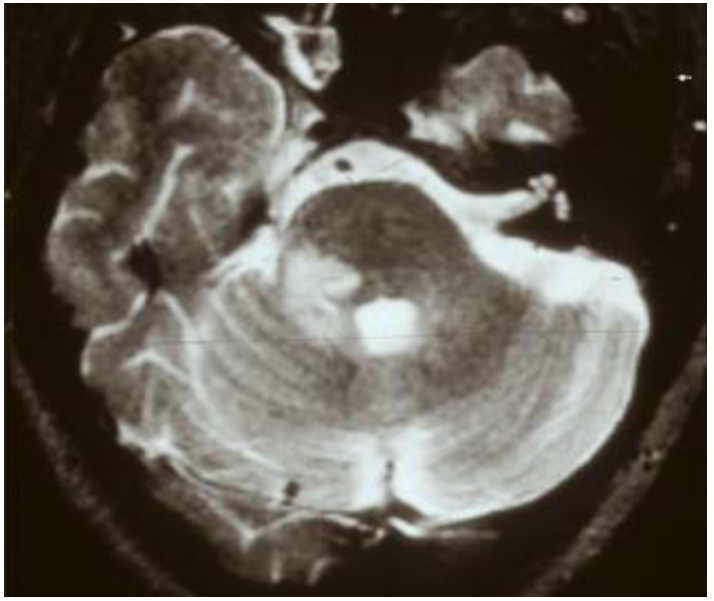
- Perivenulear inflammation

Dawson's Fingers

Spinal plaque

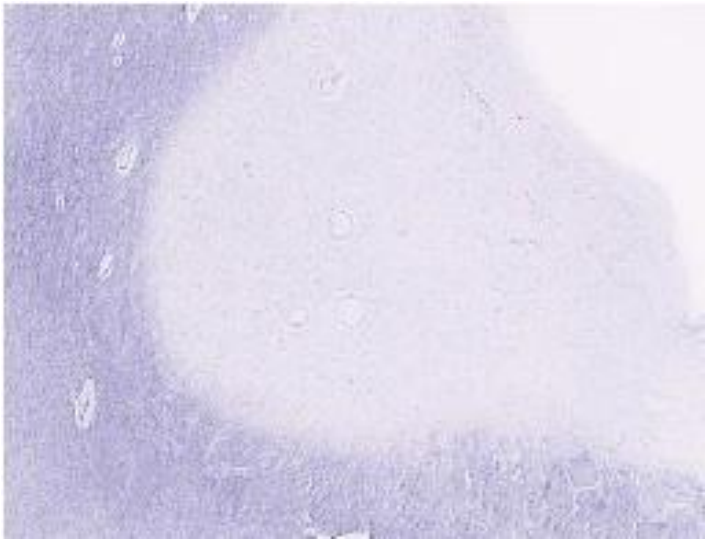


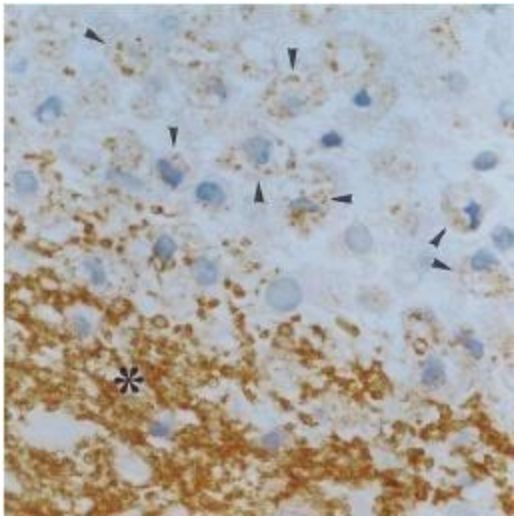
Optic neuritis

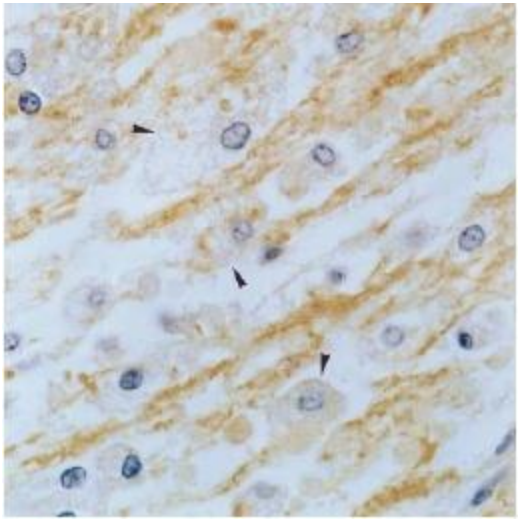


Cerebellar plaque

Plaque





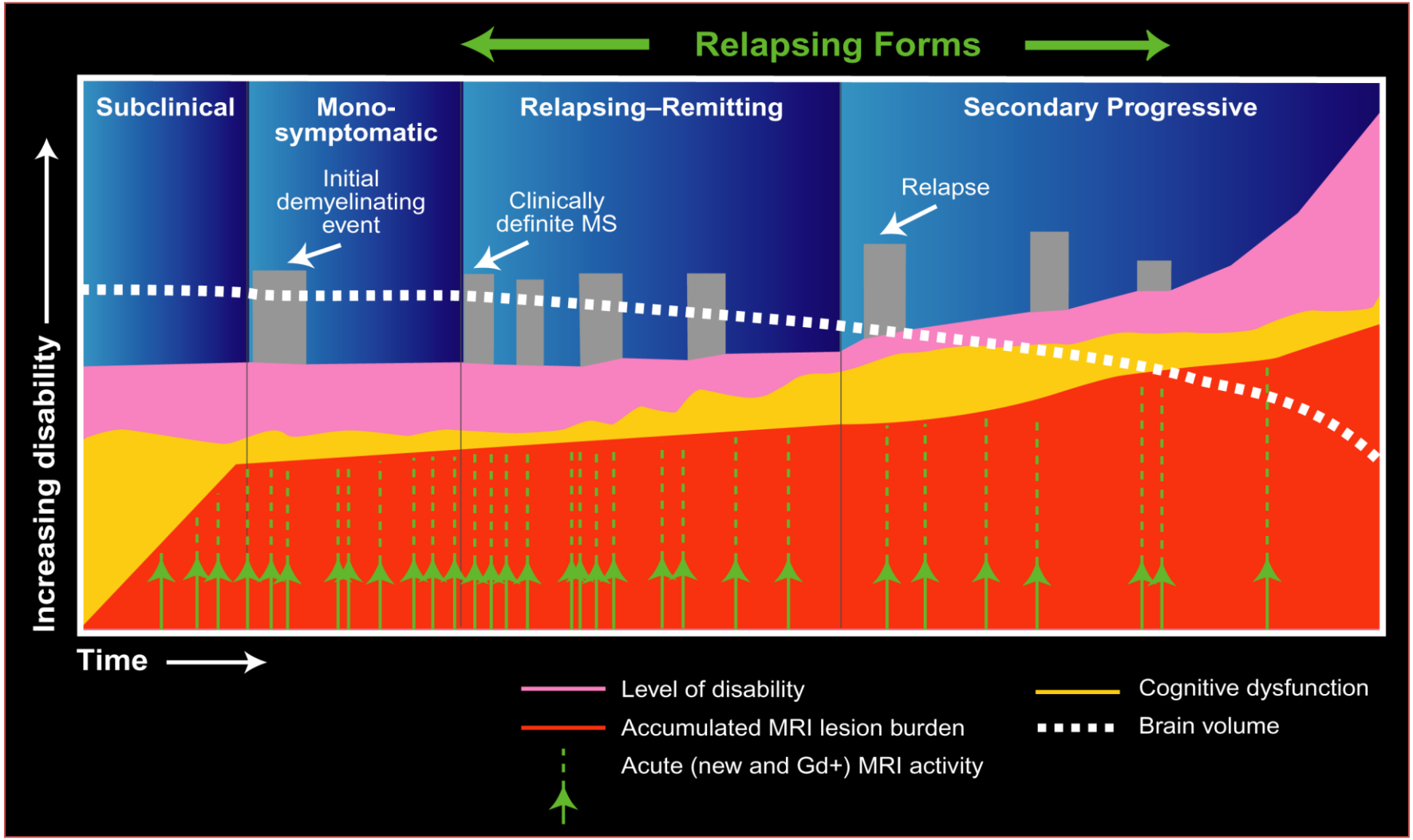


Treatment

- Acute attact treatment
  - Steroids
- Disease-modifying treatments
  - Immunomodulatory treatments
  - Immunosuppressive treatments

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

Natural Progression of MS



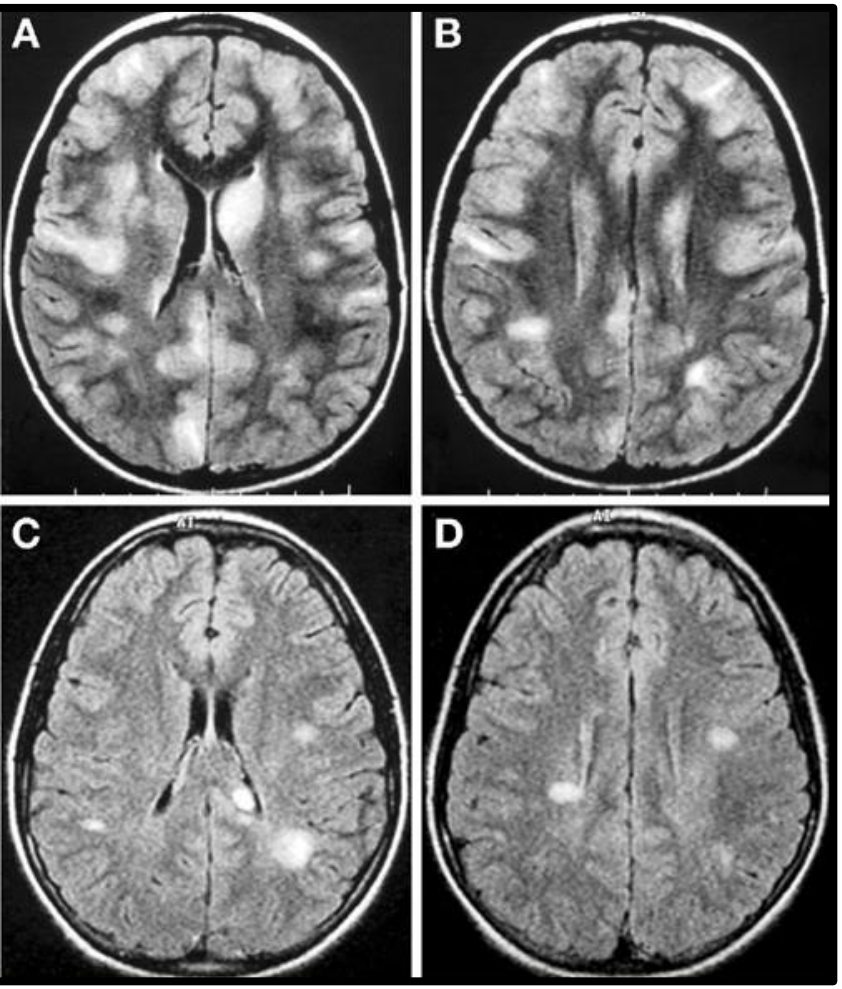
Other Demyelinating Disorders

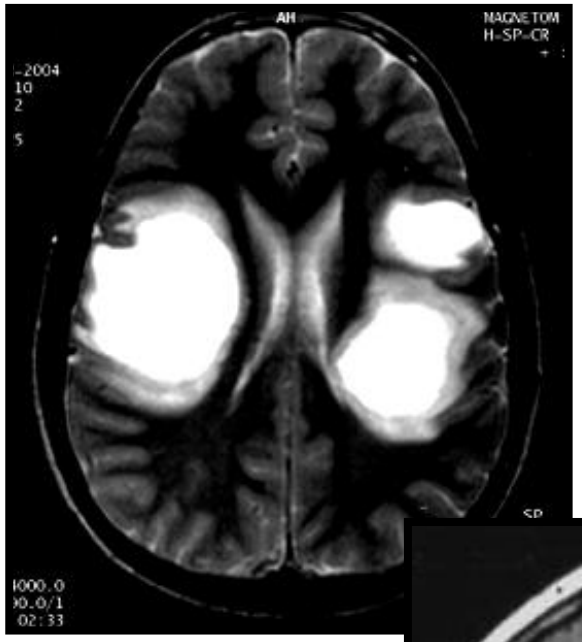
- Acute Disseminated Encephalomyelitis (ADEM)
- Neuromyelitis Optica (Devic's Disease)
- Marchiafava-Bignami Disease
- Central Pontine Myelinolysis
- Demyelinisation in Connective Tissue Diseases (SLE, Sjogren Disease, Neurobehcet Disease)
- Ischemic demyelination
- Progressive multifocal leukoencephalopathy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

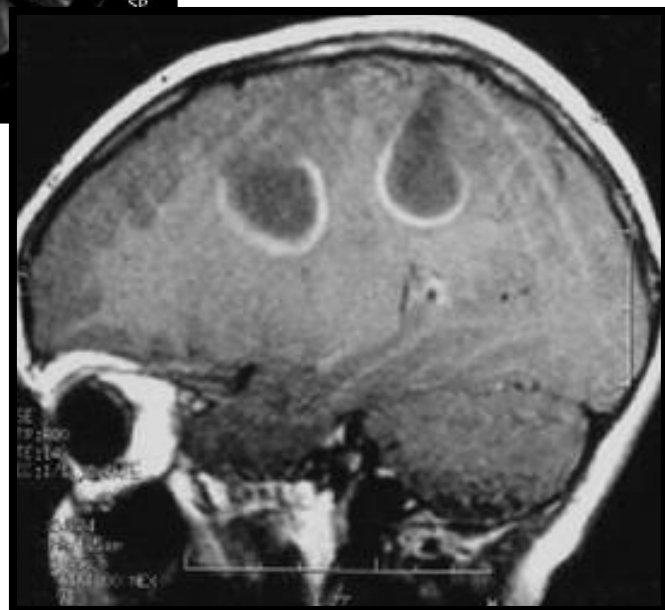
Acute Disseminated Encephalomyelitis (ADEM)

- 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)







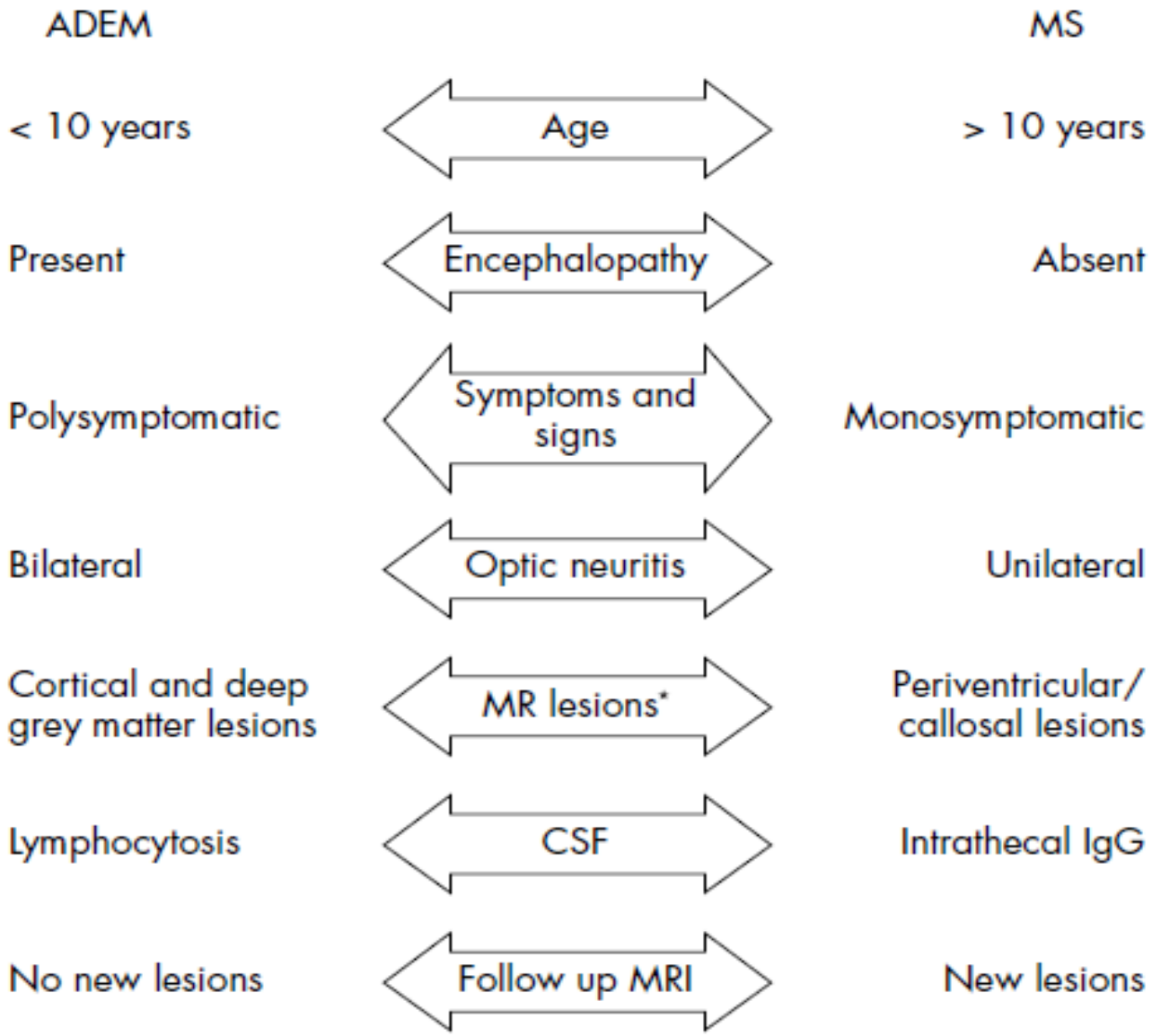
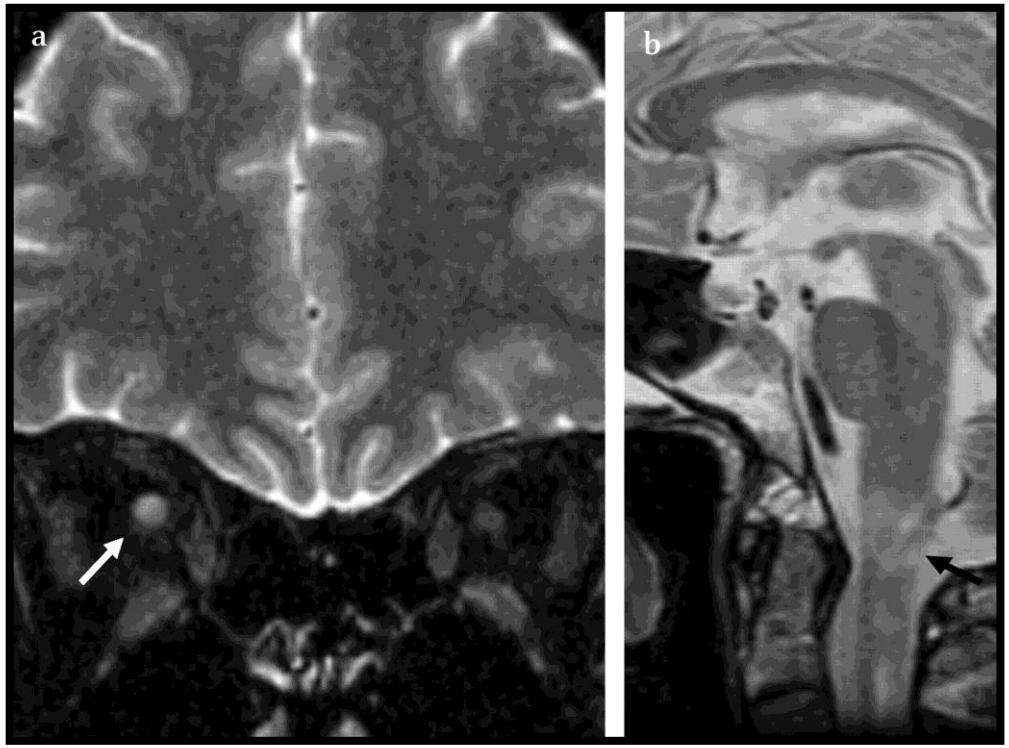


Figure 3 Clinical and investigation differences between ADEM and MS (trends only). *MR lesions other than white matter.

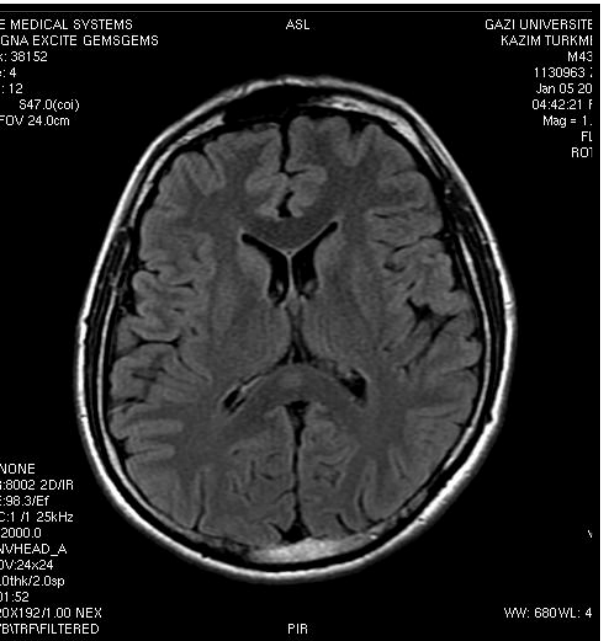
Neuromyelitis Optica (Devic's Disease)

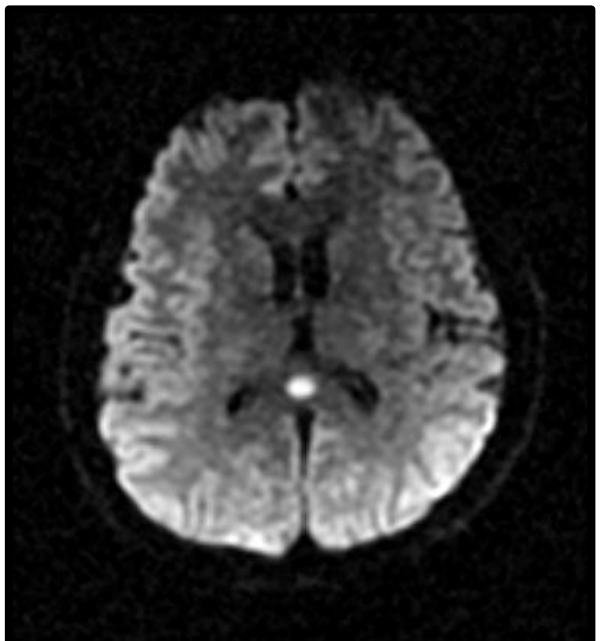
- Optic nerves and spinal cord inflammation
- AQP4 antibodies in %60

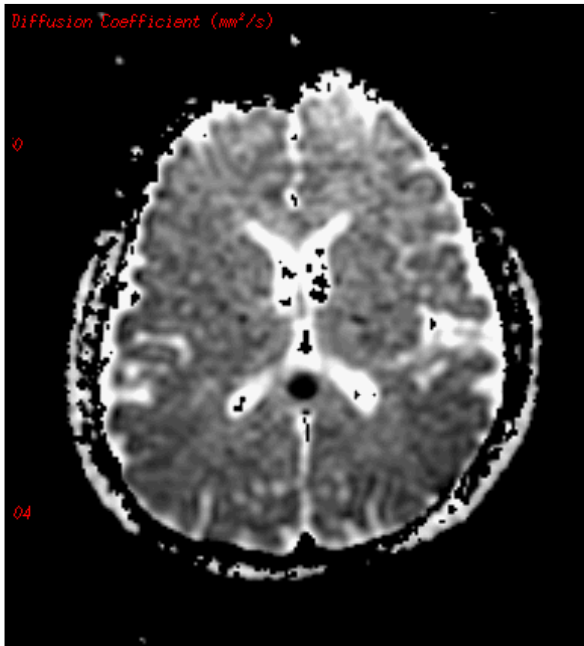


Marchiafava-Bignami Disease

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

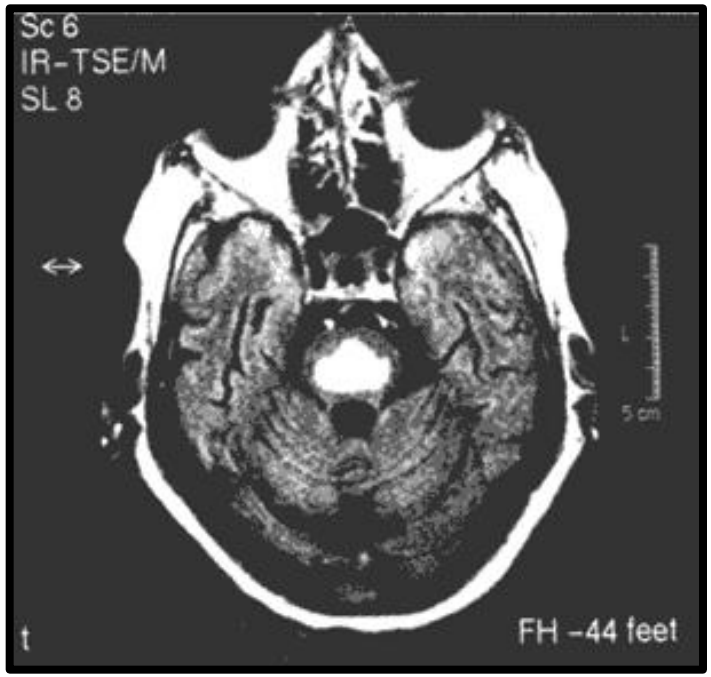


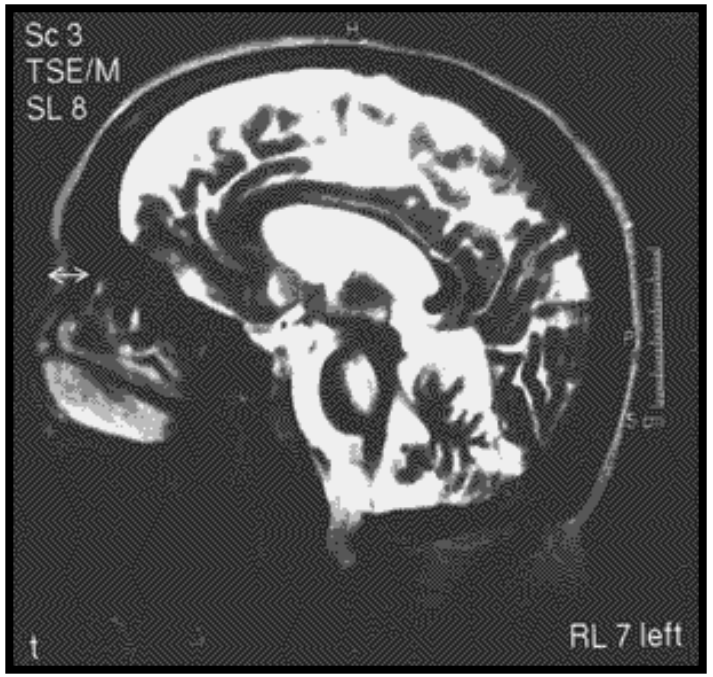




Central Pontine Myelinolysis

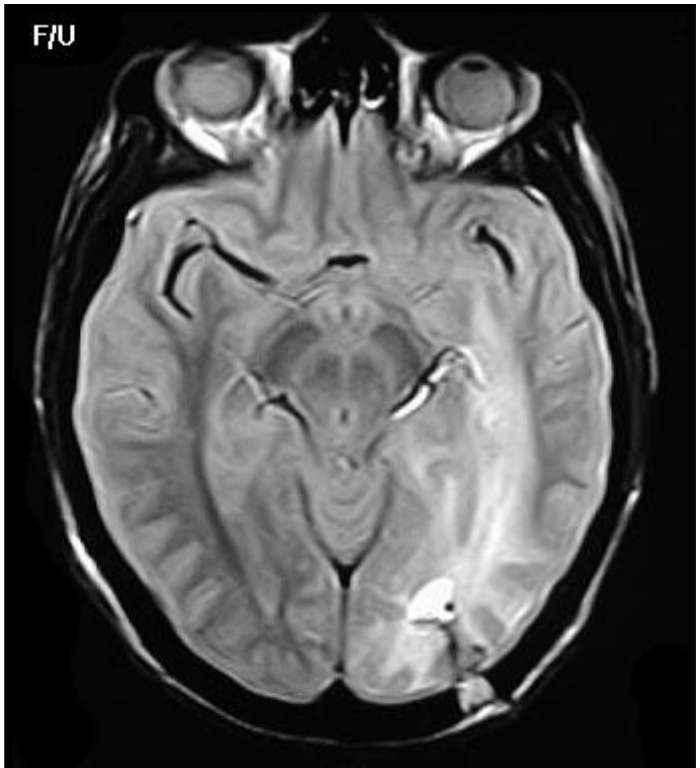
- Common mecanism is fast correction of hyponatremia /hypernatremia

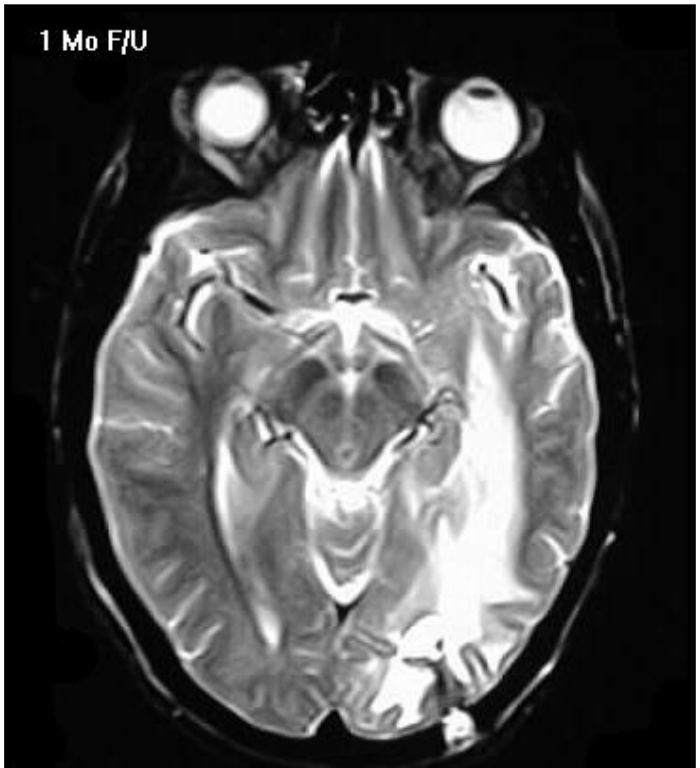




Progressive multifocal leukoencephalopathy (PML)

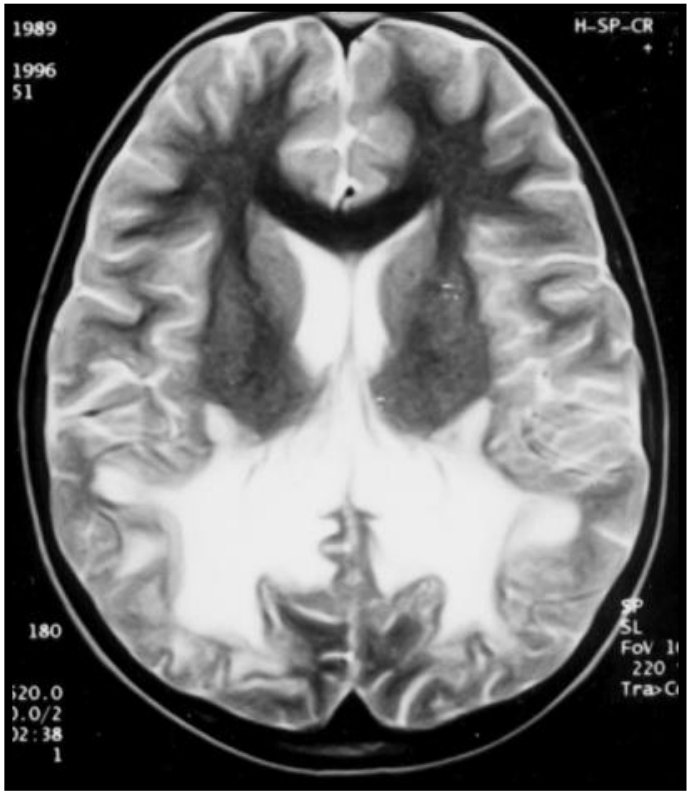
- Obseved in immunosuppressive patients
- Human papilloma virus JC virus infects oligodendrocytes and causes demyelination

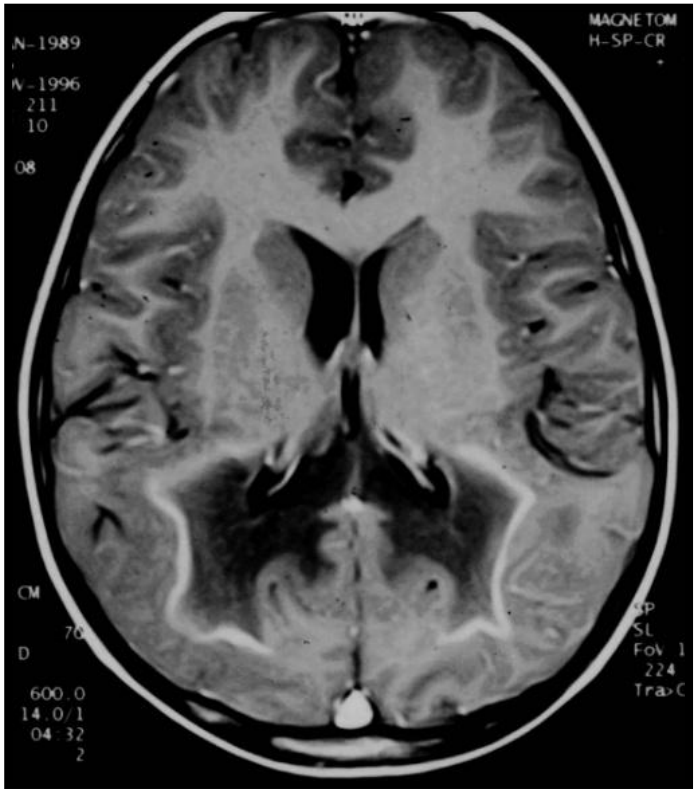


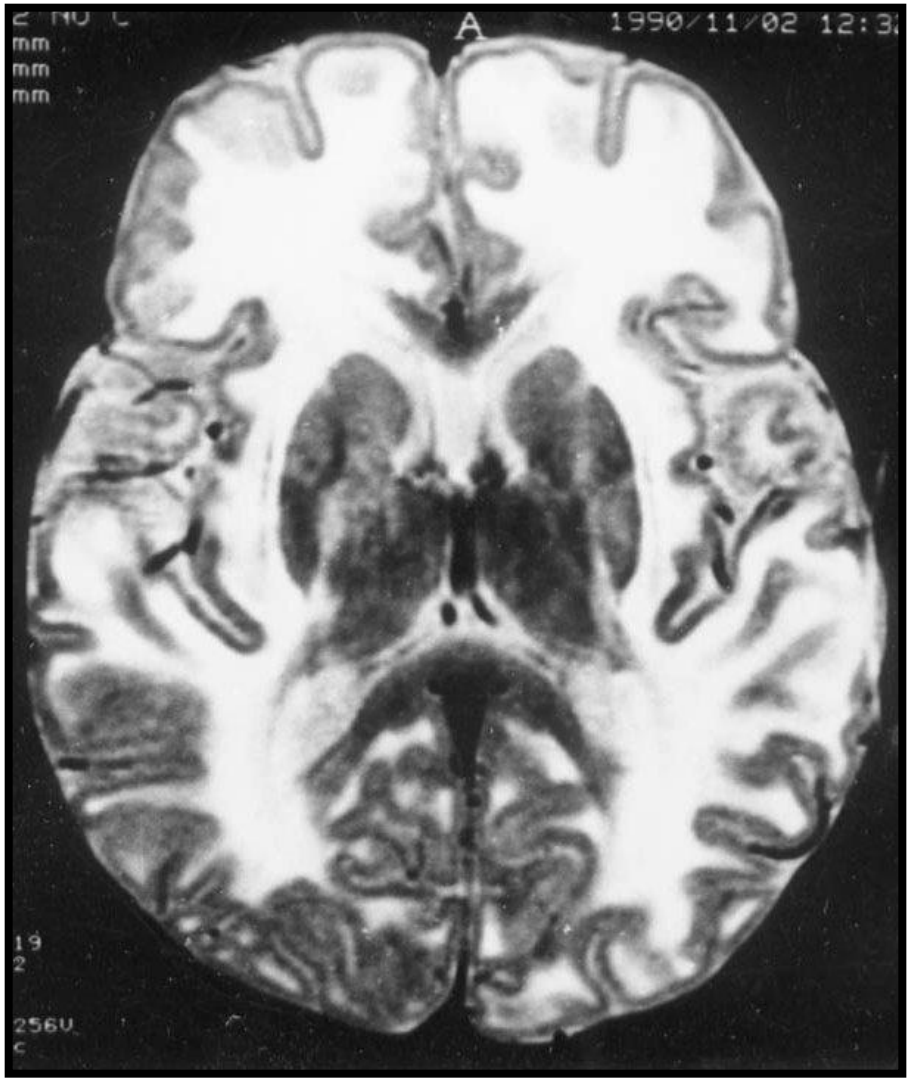


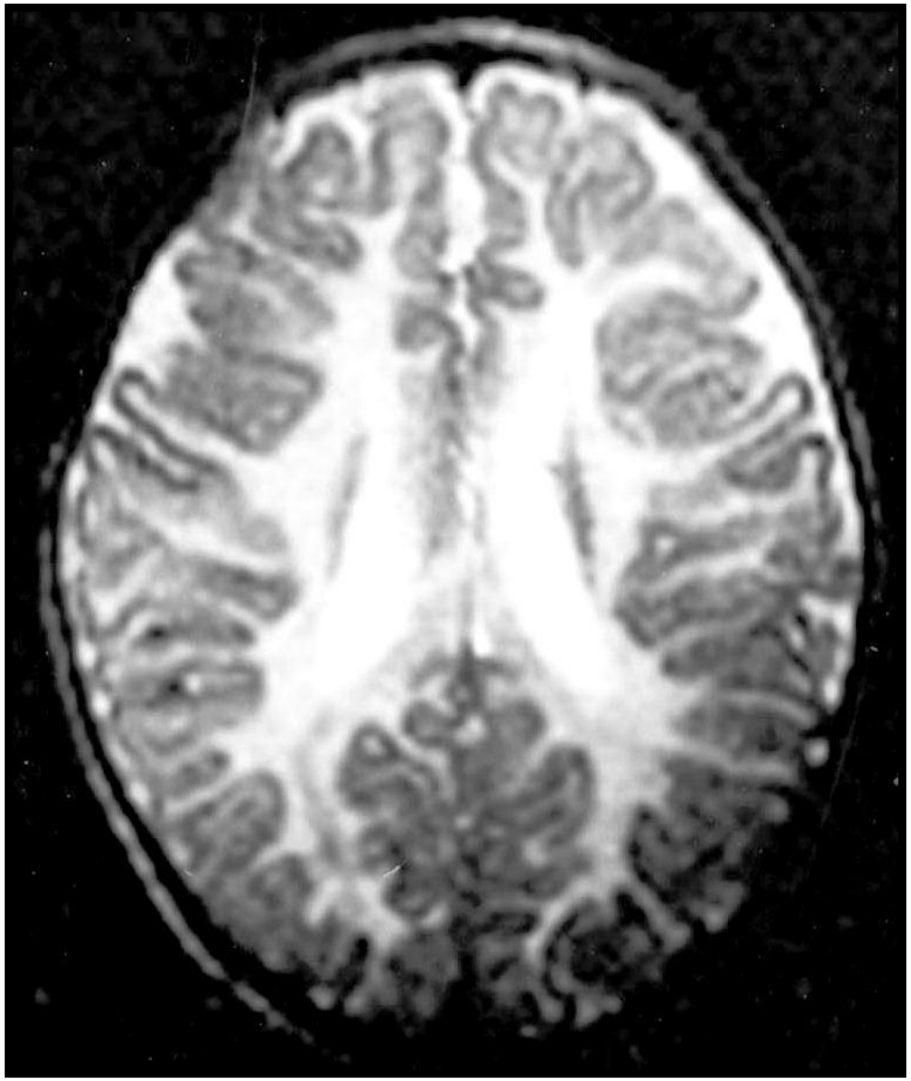
Leukodystrophies

Adrenoleukodystrophy









Canavan Disease

Pelizaeus-Merzbacher