Myelin Diseases of CNS - 1

Demyelinating diseases of CNS

Dr. Nisreen Abu Shahin, MD

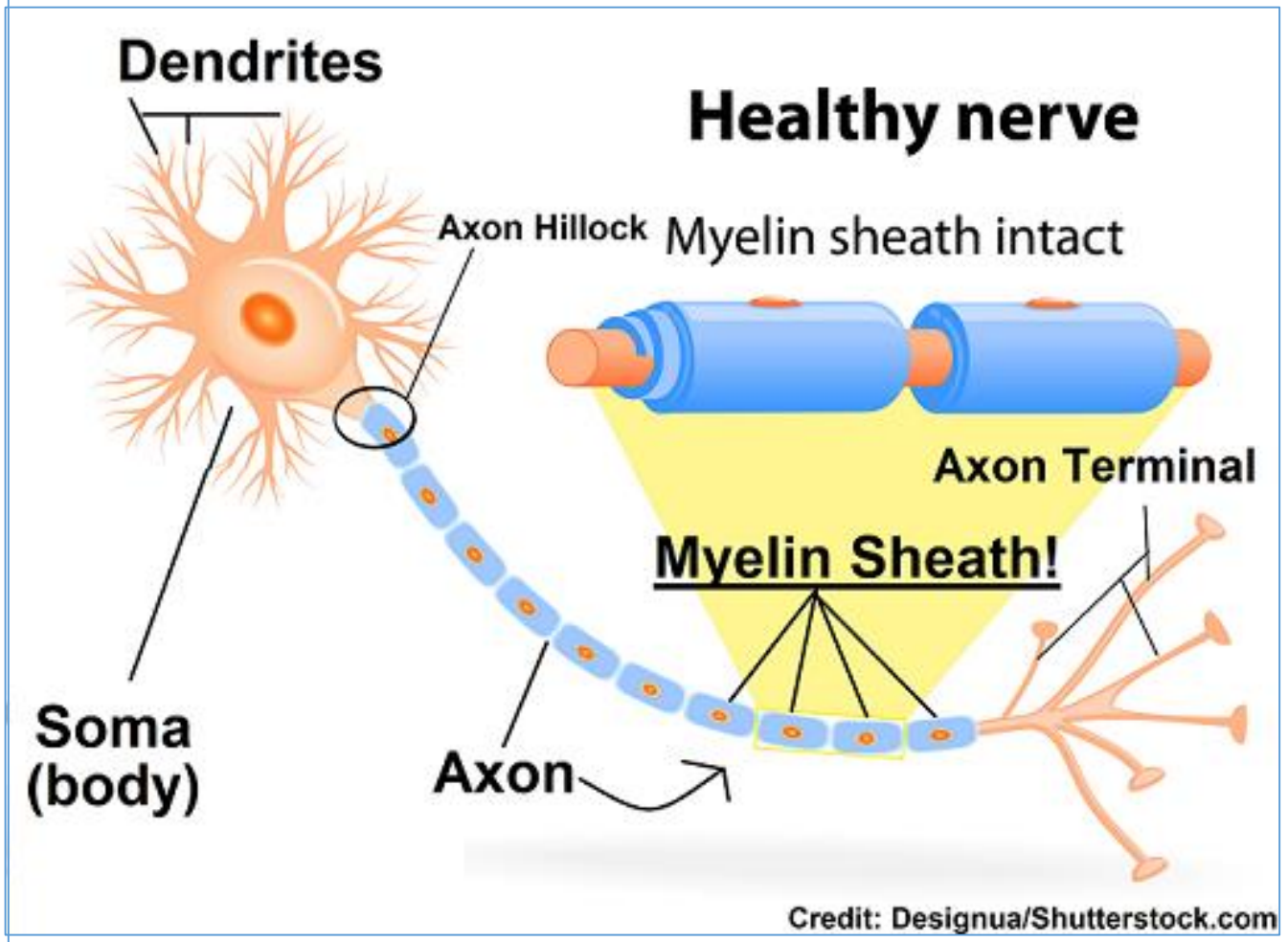
Associate Professor of Pathology

Pathology Department

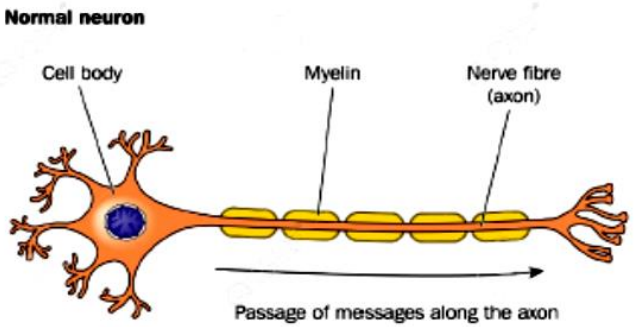
University of Jordan

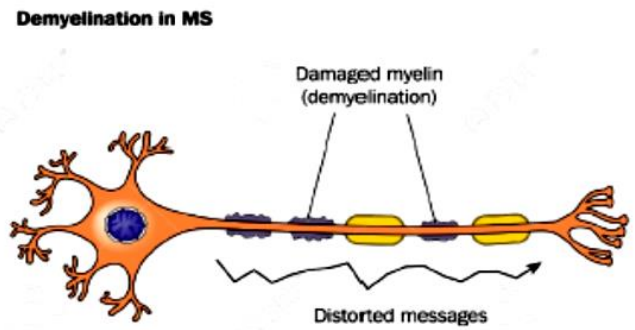
Myelin Sheath

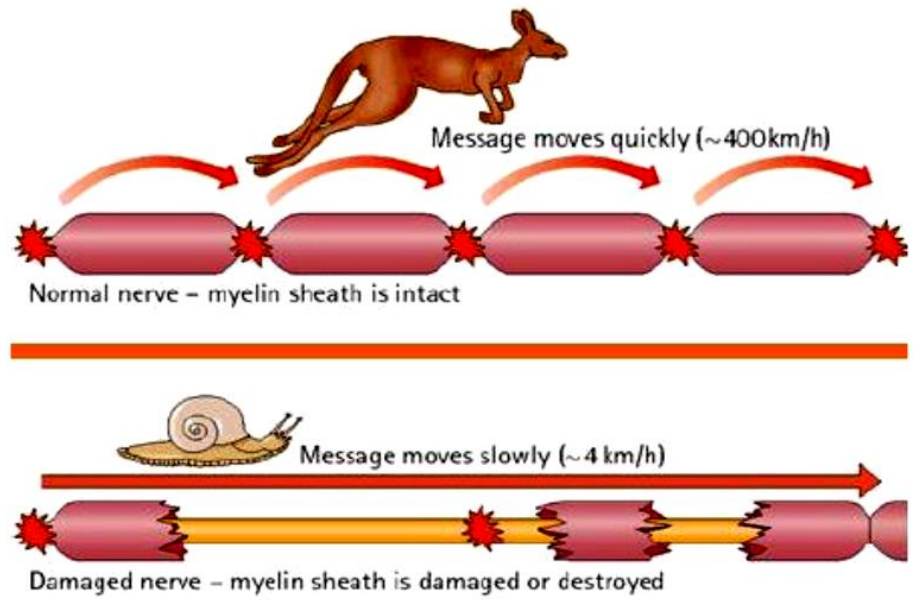
- CNS Nerve axons are tightly ensheathed by myelin
- consists of multiple layers of highly specialized, closely apposed plasma membranes
- assembled by oligodendrocytes
- an electrical insulator that allows rapid propagation of neural impulses
- myelinated axons are present in all areas of brain, however, they are a dominant component of white matter; therefore, most diseases of myelin are white matter disorders



Function of myelin: to insulate axons and allows quick transmission of neural signals







CNS diseases involving myelin are separated into two broad groups:

1- Demyelinating diseases of the CNS

2- Dysmyelinating diseases or Leukodystrophy

1- Demyelinating Diseases of the CNS

- are acquired conditions
- characterized by damage to previously normal myelin
- m/c: due to immune-mediated injury (e.g. Multiple Sclerosis → MS)
- Other causes:
- viral infection of oligodendrocytes (e.g. progressive multifocal leukoencephalopathy (PML)
- injury caused by drugs
- other toxic agents.
- MS is the subject of today's lecture

2-Dysmyelinating diseases/ Leukodystrophy

- Myelin is not formed properly (**abnormal** turnover kinetics).
- Mostly caused by **mutations** that disrupt the function of proteins required for the formation of normal myelin sheaths.
- Discussed in the upcoming lecture…

Demyelinating Diseases of the CNS

- Main types are:

1. Multiple sclerosis (MS):

- autoimmune destruction of myelin
- most common type in **Demyelinating Diseases**

2. Neuromeylitis optica :

3.Post infectious demyelination

4.Central pontine myelinolysis

Multiple Sclerosis (MS)

- An autoimmune demyelinating disorder

- *"Episodes of disease activity, separated in time, that produce white matter lesions that are separated in space"*

Multiple Sclerosis (MS)

- Prevalence: 1/ 1000 individuals in USA and Europe
- Incidence appears to be increasing
- May present at any age (usually 20-40)
- onset in childhood or after 50 years of age is rare
- Women are affected twice as often as men

Multiple Sclerosis (MS)--Pathogenesis

- an autoimmune response directed against components of the myelin sheath.

- As in other autoimmune diseases, the development of MS is related to:
  - **genetic** susceptibility
  - undefined **environmental** triggers.

Multiple Sclerosis (MS)--Pathogenesis

- Incidence 15-fold higher when disease is present in a **first-degree relative** and ≈ 150-fold higher with an affected **monozygotic twin**.
- Only a portion of the genetic basis of the disease has been explained, and many of the identified loci are associated with **other autoimmune diseases.**

Pathogenesis- Genetics

- **<u>Genetic loci that are associated with MS:</u>**
- Major histocompatibility complex (**HLA**)
- **HLA-DRB1*1501** . each copy of the allele an individual inherits brings with it 3-fold increase in the risk for MS.

- **IL-2 and IL-7 receptor genes**
- **Other genes encoding proteins involved in immune responses**.

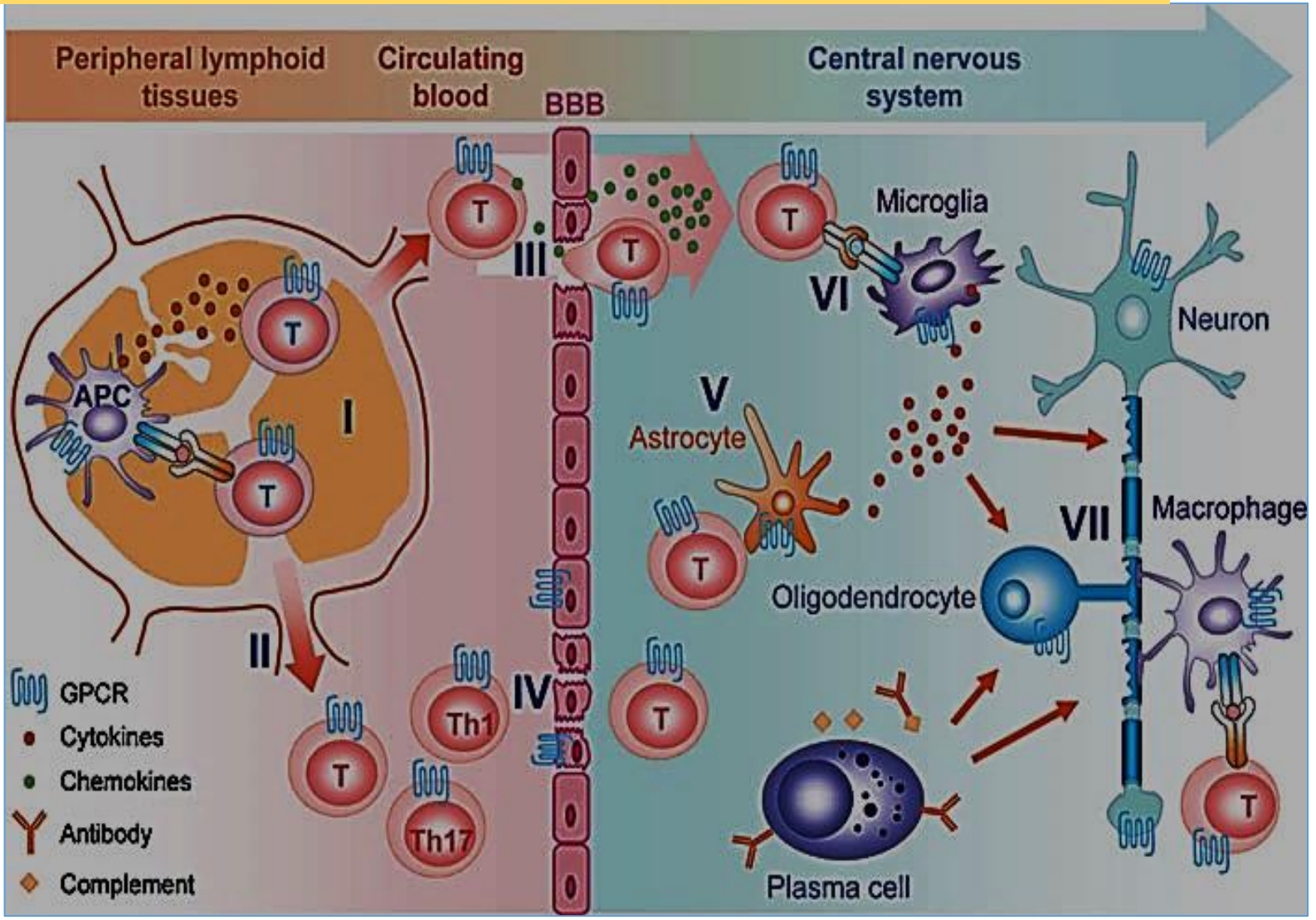
Multiple Sclerosis (MS)--Pathogenesis

- focus of much ongoing investigation
- available evidence indicates that disease is initiated by:

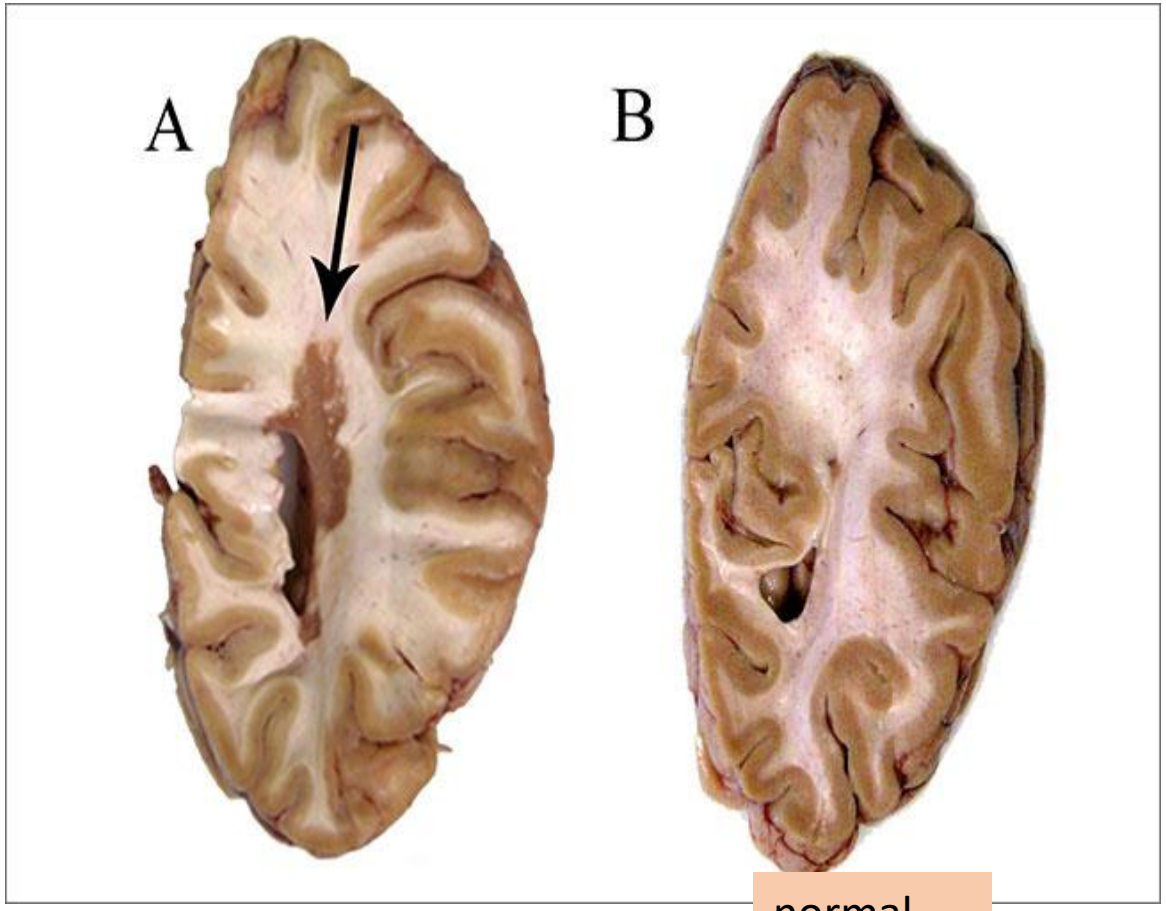
❑ *T lymphocytes* that react against myelin antigens and secrete cytokines

- **TH1 T cells:** secrete IFN-γ, which activates macrophages
- **TH17** T cells: promote the recruitment of leukocytes

❑*B lymphocytes* and *antibodies*: poorly defined role in MS, as indicated by the surprising success of B cell depleting therapies.



MS- MORPHOLOGY

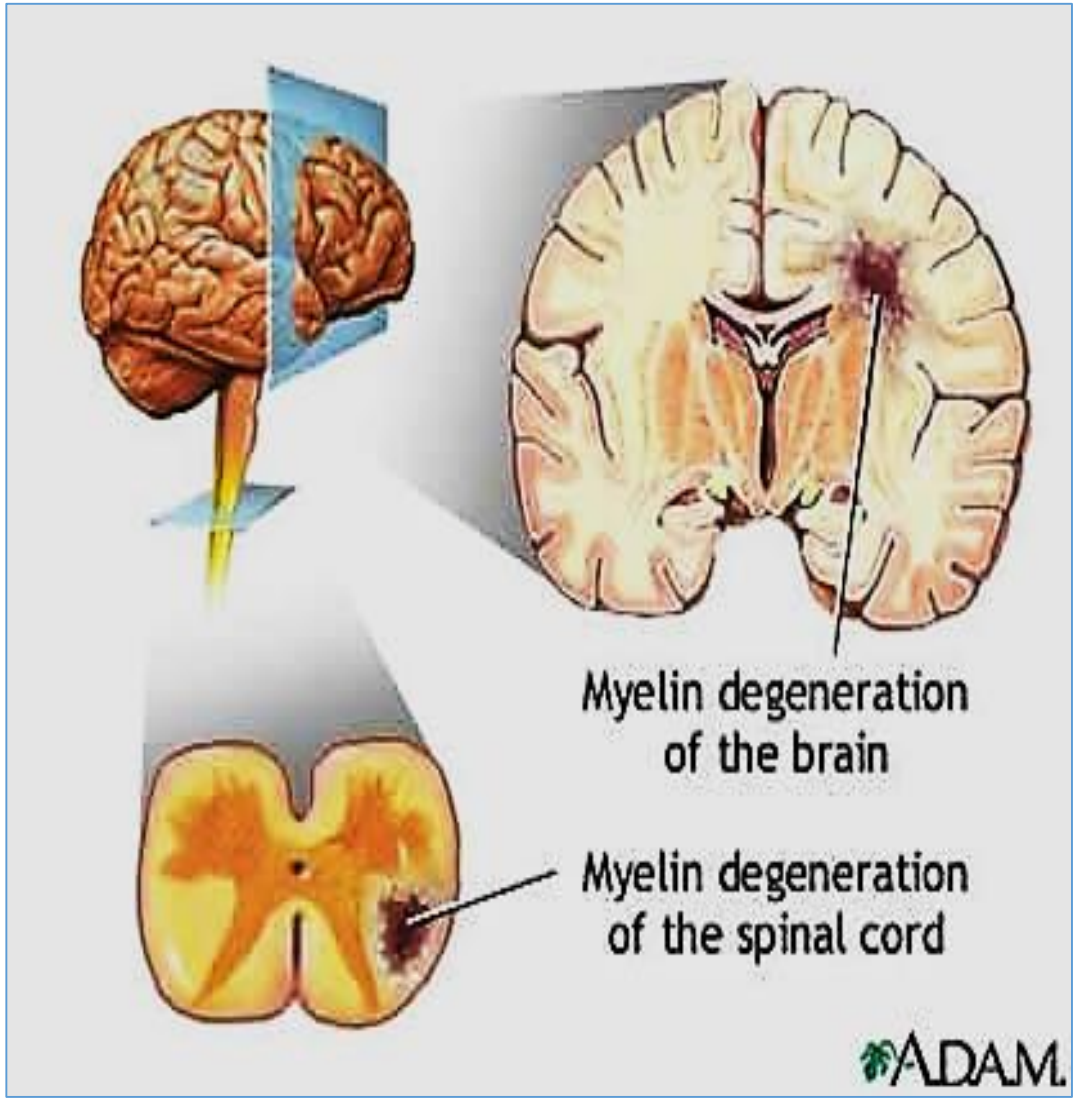


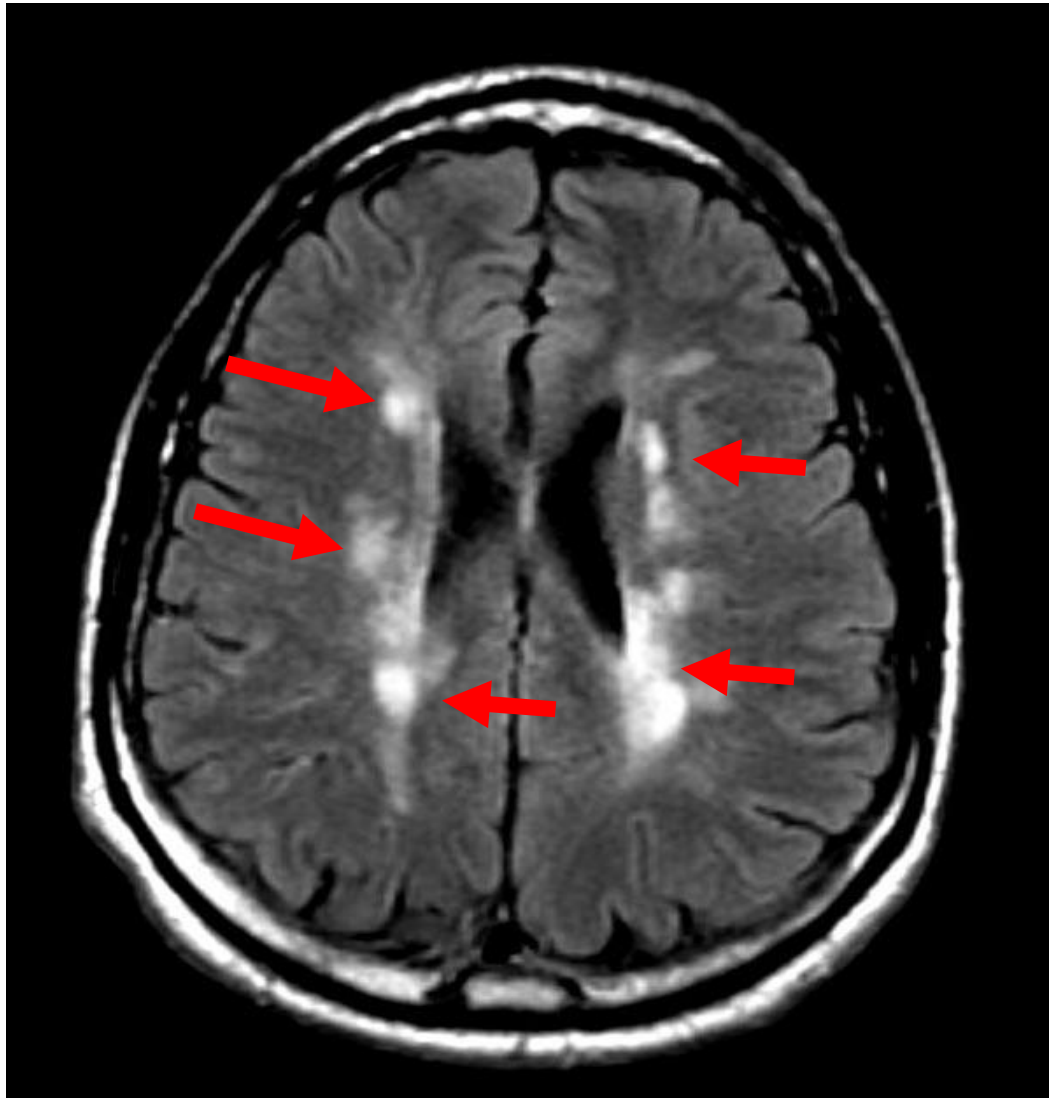
normal

- MS is a multifocal white matter disease
- grossly, the characteristic lesions of MS are called **Plaques** (discrete, slightly depressed, glassy-appearing, and gray-tan in color)

Gross morphology

- lesions common near ventricles and also optic nerves, chiasm, brain stem, ascending and descending fiber tracts, cerebellum, and spinal cord.





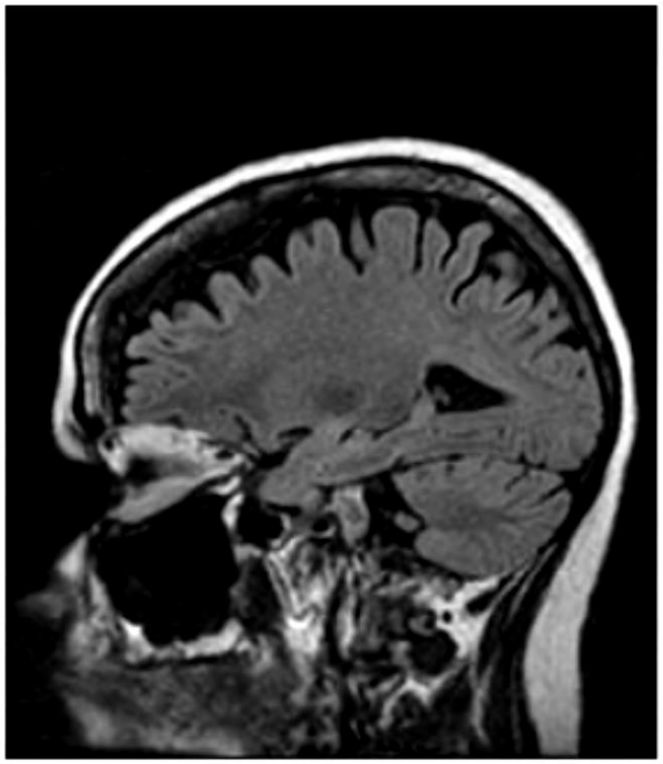
Radiological Morphology

- Magnetic resonance imaging (MRI) is a type of imaging test and important tool in **diagnosing** MS.

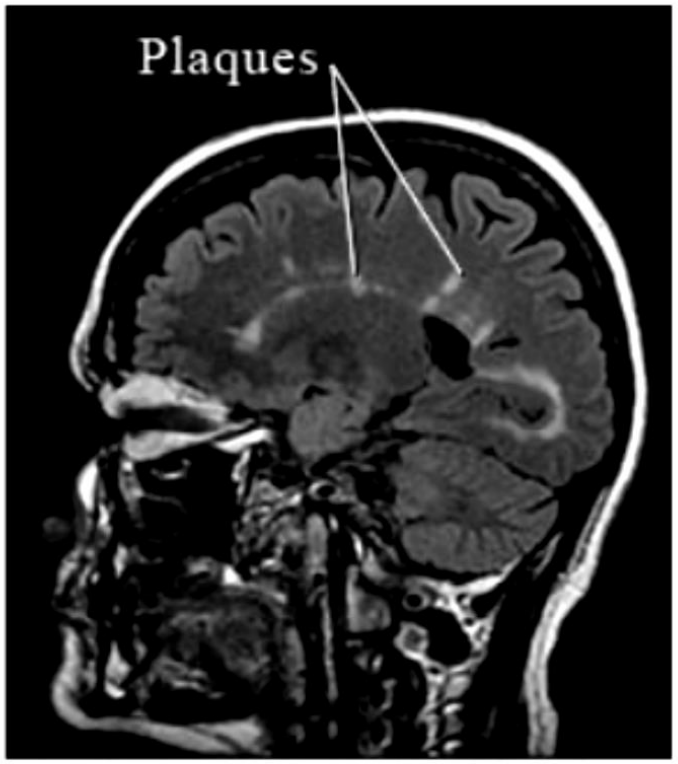
- MRI can reveal areas of damage (MS **plaques**) on brain or spinal cord.

- Also used to **monitor disease activity and progression**

Normal brain vs MS brain (active plaques)

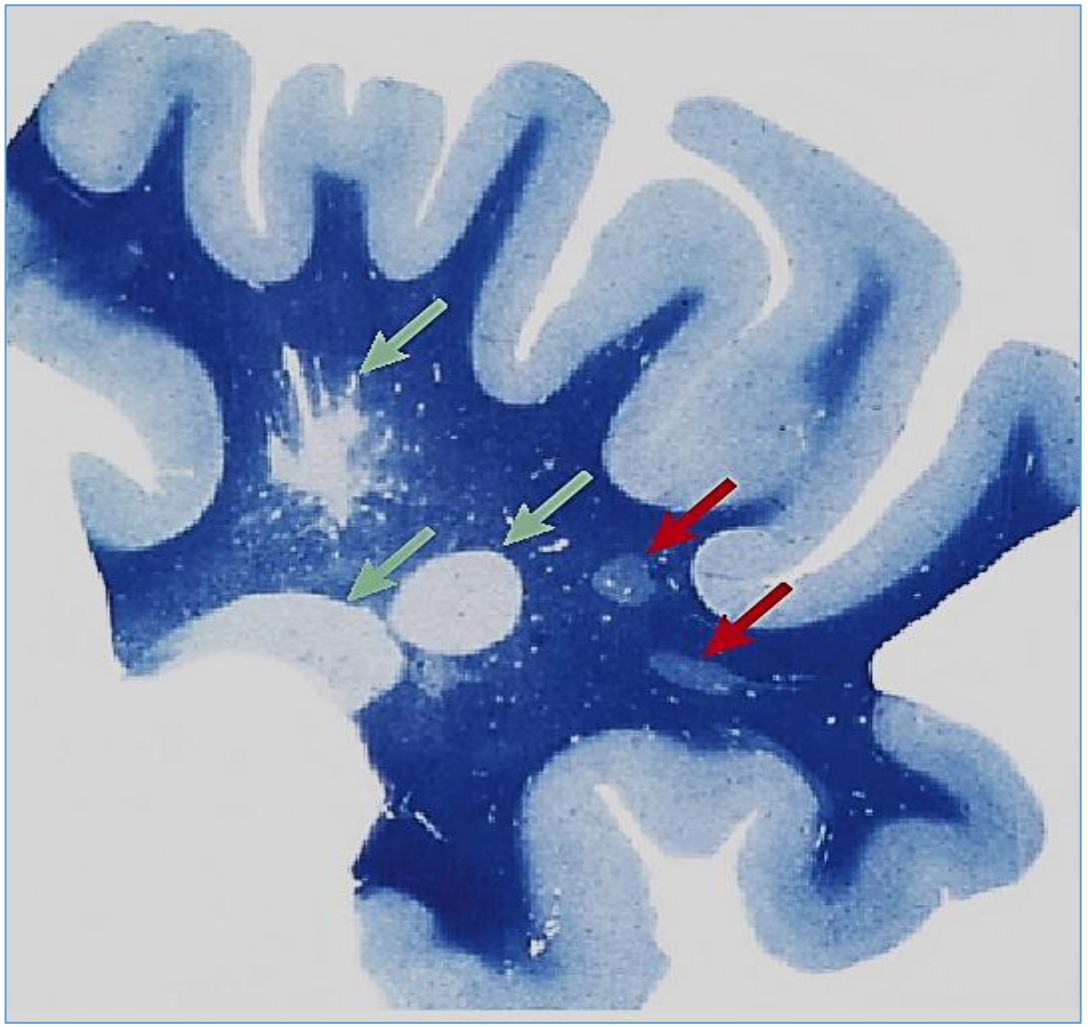


Healthy brain



Brain with damage (lesions or plaques) caused by MS

Histological Morphology

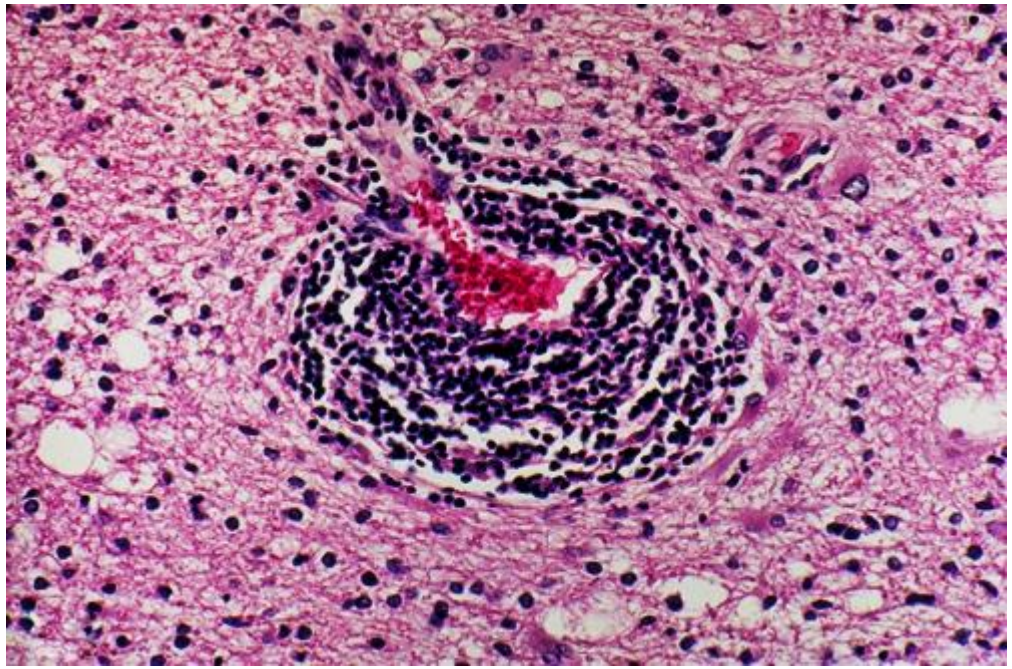


This microscopic image shows brain tissue stained with **luxol-fast-blue**, so that myelin appears blue.
The pale staining areas (arrows) are MS plaques.
Usually, areas of demyelination (light colored) are seen surrounding vessels.

Types of MS plaques

- **<u>Active plaques:</u>**

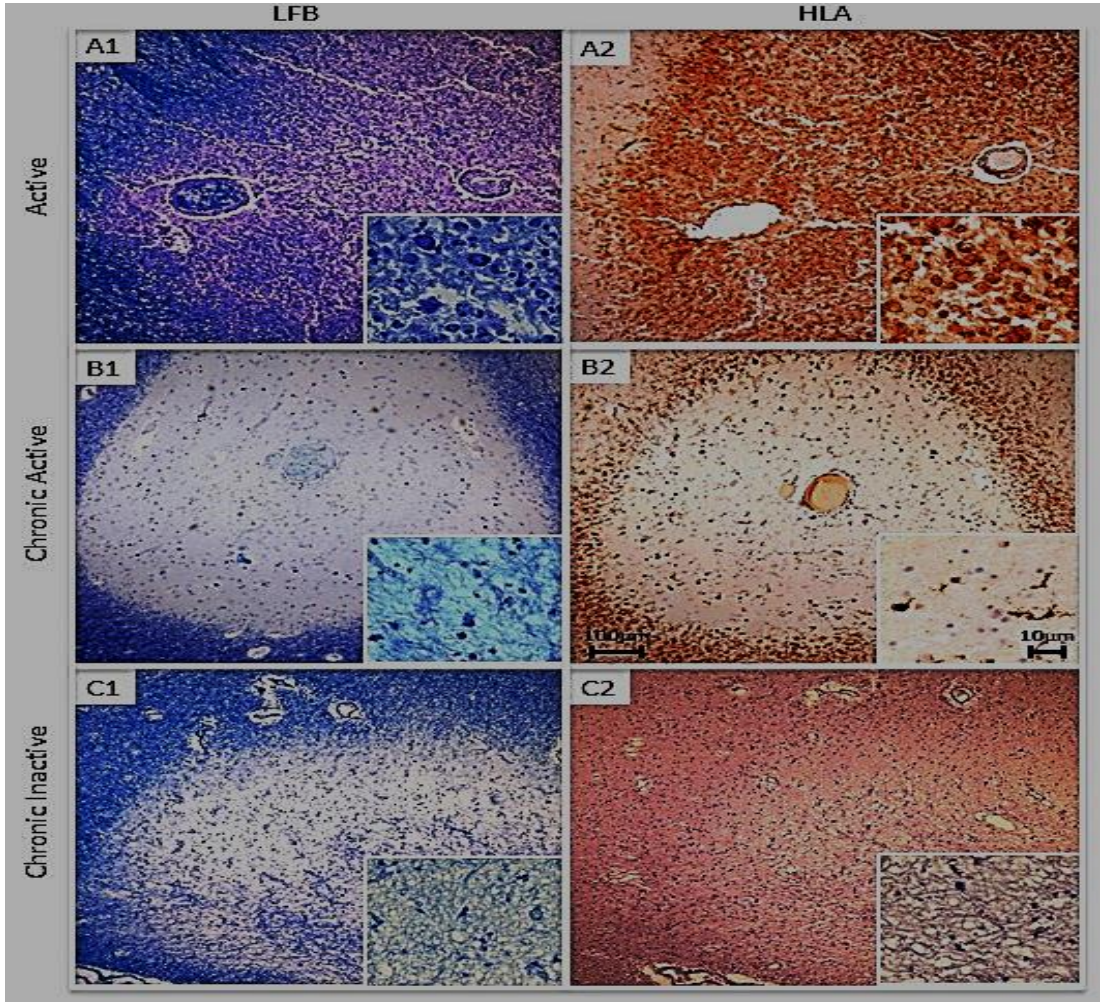
- contain abundant macrophages stuffed with myelin debris, evidence of ongoing myelin breakdown.
- Lymphocytes also are present, mostly as perivascular cuffs.
- Small active lesions often are centered on small veins.
- Axons are relatively preserved.



Types of MS plaques

- **<u>Quiescent (inactive plaques):</u>**

- the inflammation mostly disappears
- leaving behind little to no myelin
- Evidence of astrocytic proliferation, and gliosis

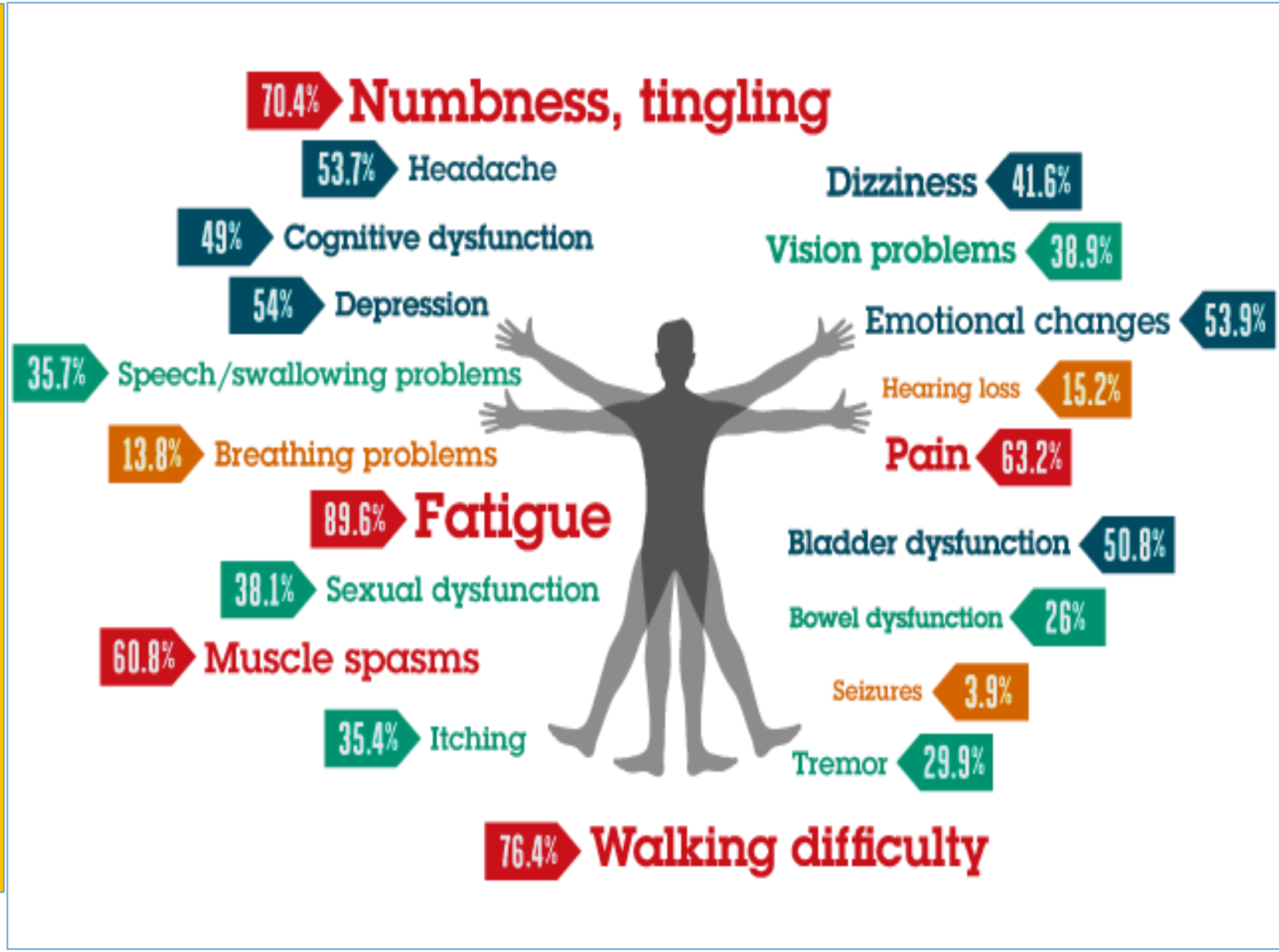


MS - Clinical Features

- The course of MS is variable
- commonly there are multiple relapses followed by episodes of remission
- typically, recovery during remissions is not complete
- over time there is usually a gradual, often stepwise, accumulation of neurologic deficits.

Clinical Features

- depend on location of lesions.
- Symptoms are reversible but tends to recur.
- When it recurs, symptoms might differ from initial ones
- ***Note: Don't memorize any percentages!***



Clinical Features

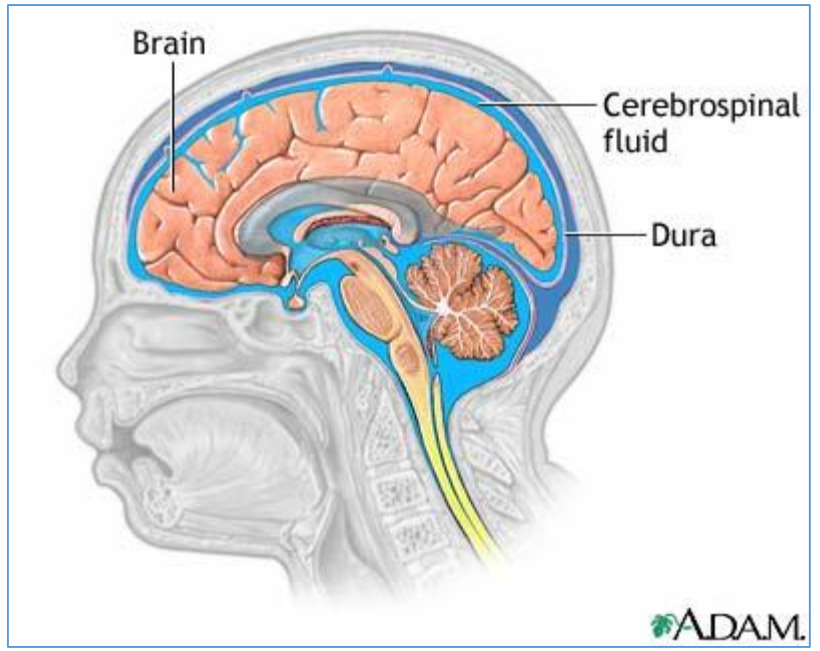
- Changes in cognitive function can be present, but are often much milder than the other deficits.
- In any individual patient, it is difficult to predict when the next relapse will occur

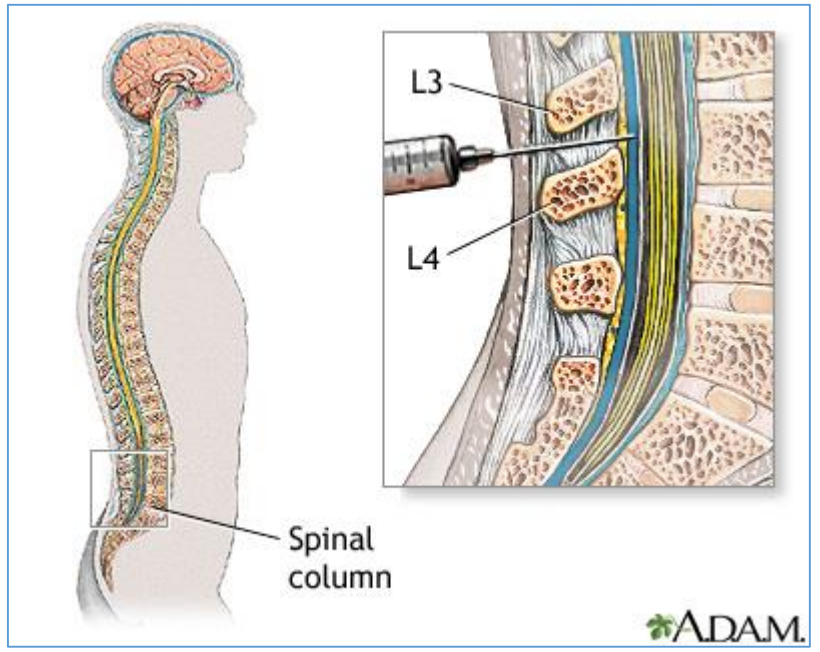
MS --Lab tests

- **The cerebrospinal fluid (CSF) in patients with MS shows:**
- **elevated *protein* level** with an **↑ *immunoglobulin***
- moderate ***pleocytosis***: presence of abnormally large number of lymphocytes in CSF (in 1/3 of cases)
- When the immunoglobulin is examined further by **protein electrophoresis**, ***oligoclonal bands*** usually are identified.

What is **cerebrospinal fluid ?**

- **A clear fluid that surrounds brain and spinal cord**.
- **Ultrafiltrate of plasma with low protein content and few cells**.
- Mainly produced by choroid plexus; also by ependymal cells of brain ventricular system
- It cushions brain and spinal cord from injury and also serves as a nutrient delivery and waste removal system
- CSF can be tested for the diagnosis of a variety of neurological diseases, usually obtained by a procedure called **lumbar puncture**





What is Protein electrophoresis ???

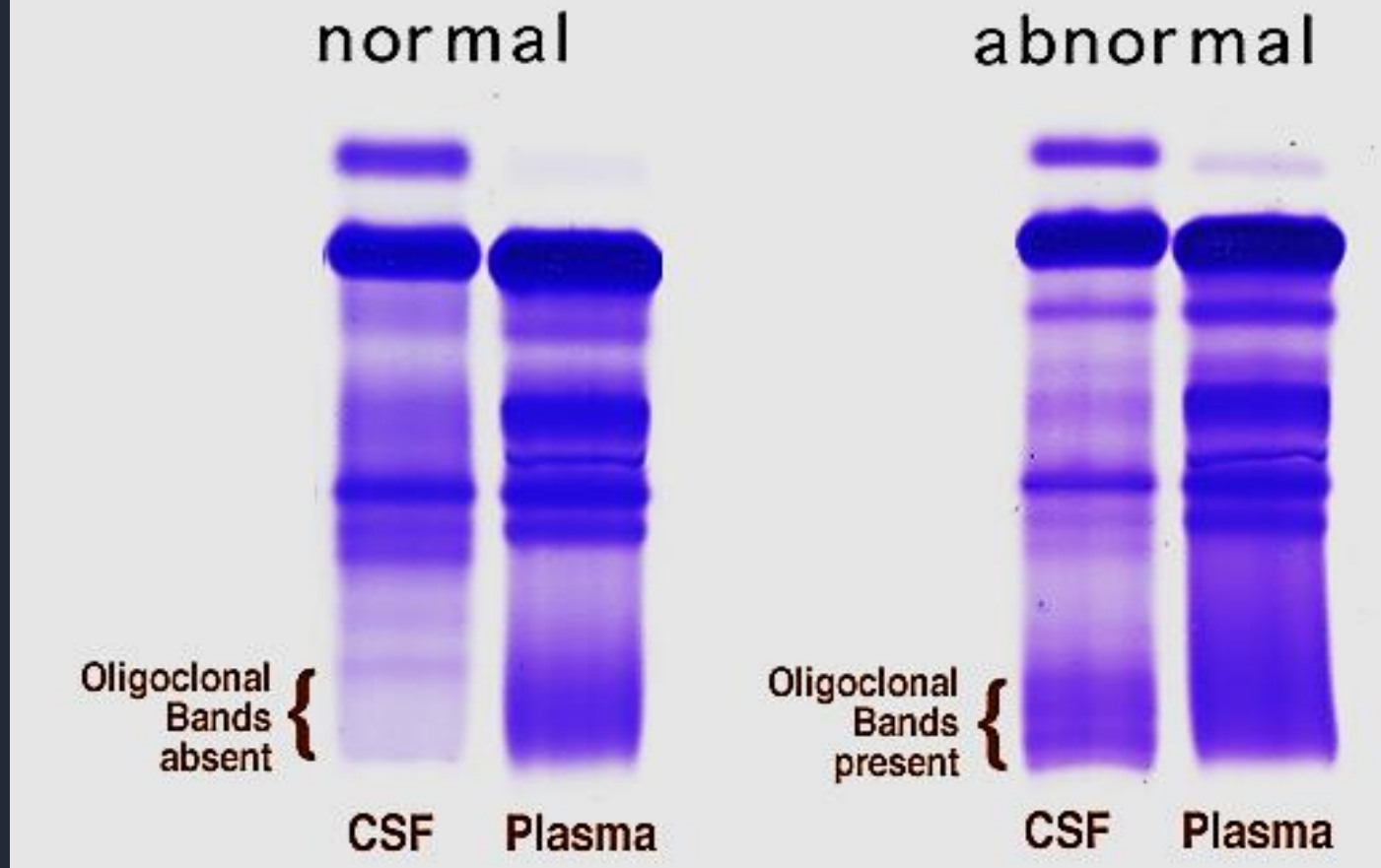
- A test that detects presence of proteins in fluids
- separates proteins according to their size and charge
- Used to compare proteins in serum and CSF
- It shows proteins as bands
- CSF is a filtrate of plasma, so **normally** CSF has the same serum proteins or even less (large proteins will not be filtrated)
- So: the presence of these extra bands in CSF means that these are proteins are secreted **intrathecally** (within the CSF) → **abnormal** → **inflammation** of CNS

What are Oligoclonal Bands?

- are **IgG** (or **IgM**) bands in CSF.
- These are detected by a lab test called **protein electrophoresis**.
- In MS, plasma cells produce IgG (and less frequently IgM), and these will be detected as oligoclonal bands which are **not** present in the patient's serum

- These antibodies are directed against a variety of antigenic targets
- they can be used as **markers of disease activity**
- these antibodies' contribution to MS process is unclear

Oligoclonal Bands in CSF



Treatment of MS

- most current treatments are intended to control the immune response
- they aim at:

- Treating relapses of MS (manage symptoms; physiotherapy; …etc.)

- Decreasing rate and severity of relapses (immune-related treatment: disease-modifying therapies)

- Unfortunately, yet NOT recovering the lost function

MS-- Outcome

- Limited capacity of CNS to regenerate normal myelin (although myelin can be restored in CNS, this is less efficient than in PNS)

- Secondary damage to axons that might occur after repeated relapses and occurs **late** in the course of the disease