وَقُل رَّبِّ زِدْنِي عِلْمًا

النادي الطبي

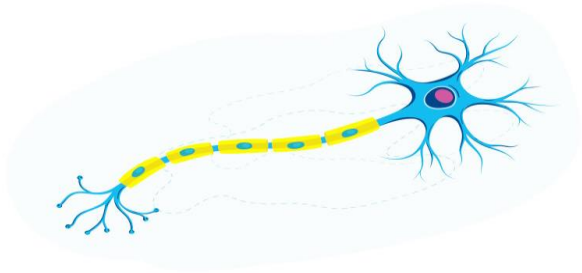
PERIPHERAL NERVOUS SYSTEM

SUBJECT : Pathology

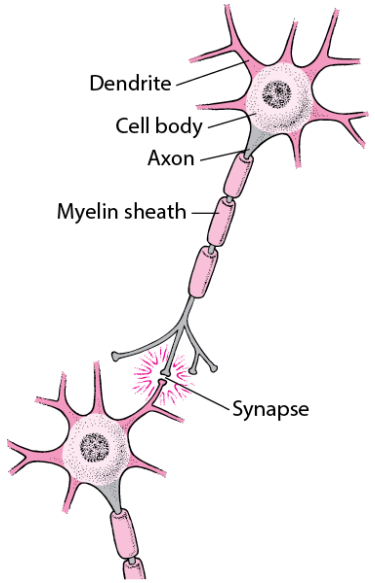
LEC NO. : 3

DONE BY : Dania Abdullah

#كلينيكال_إلا_شحطة



Neurosciences II Module



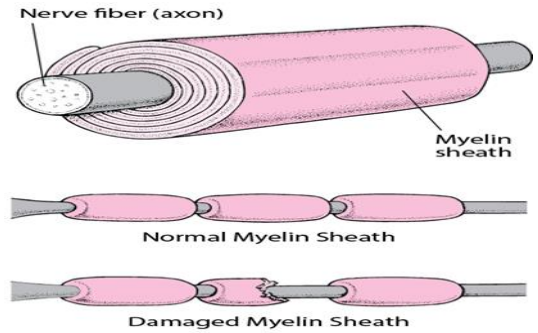
Dr. Ola Abu Al Karsaneh

Diseases of Myelin

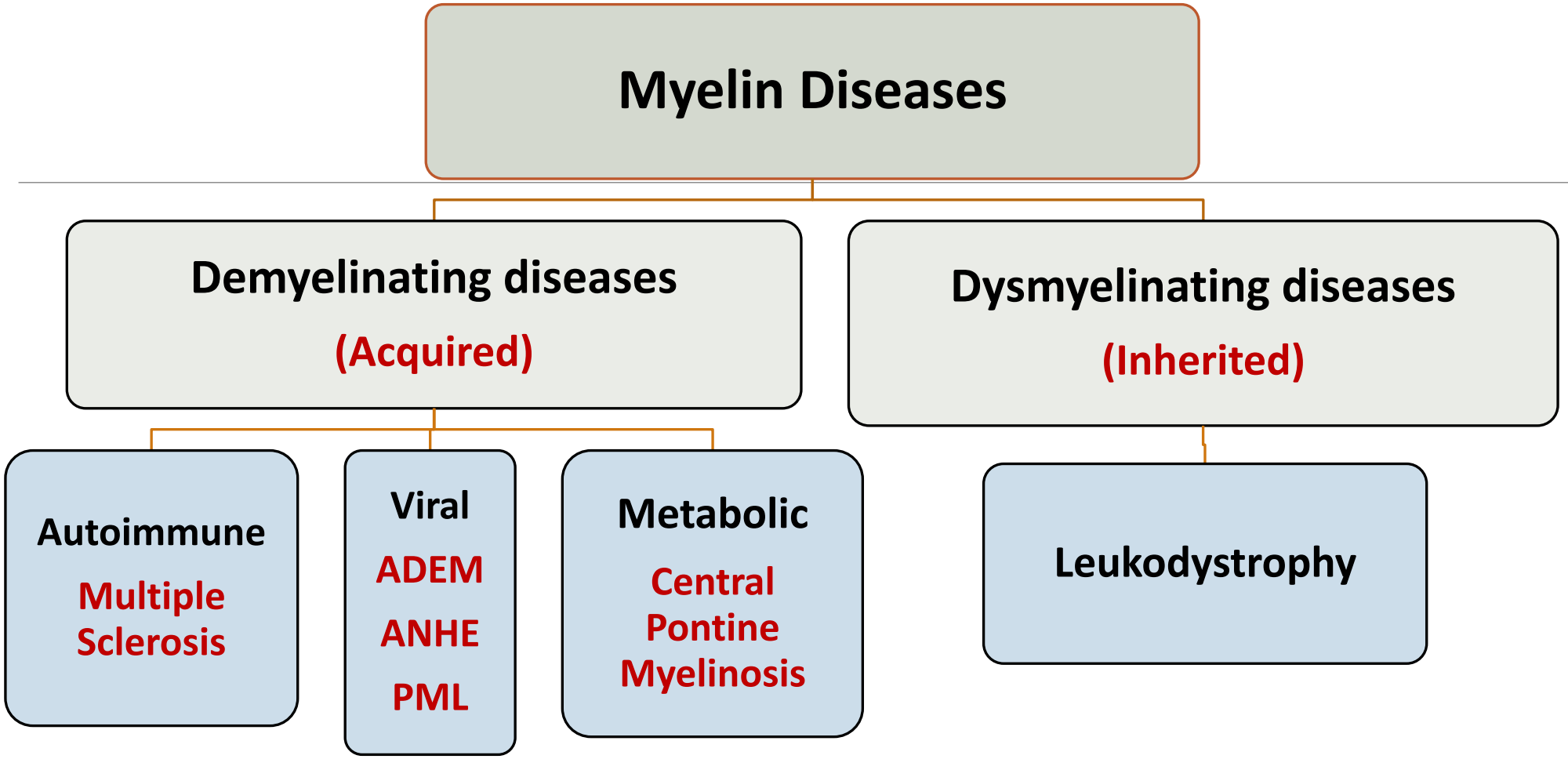
- Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa.
- Loss of myelin interferes with electric impulse transmission along axons
- **CNS myelin diseases are separated into two groups:**

• **Demyelinating diseases:** acquired conditions characterized by damage to previously normal* myelin, most severe in white matter, with relative preservation of axons in early stages.

• **Dysmyelinating diseases or leukodystrophy:** myelin is not formed properly or has abnormal turnover.



* Previously normal myelin
يعني الmyelin بكون تكون بشكل طبيعي بعدين صارله destruction


Myelin Diseases
Demyelinating diseases
(Acquired)
Dysmyelinating diseases
(Inherited)
Autoimmune
Multiple Sclerosis
Viral
ADEM
ANHE
PML
Metabolic
Central Pontine Myelinosis
Leukodystrophy

Multiple Sclerosis (MS)

- An **autoimmune demyelinating disorder** characterized by episodes of neurologic deficits, separated in time, that produce white matter lesions separated in space.

بيجي على شكل هجمات\ attacks
بعدين بصير في remission و الأعراض بتختفي (تقريبا) و المريض بكون relatively normal بعدين بترجع الأعراض يعني another attack وهكذا

- The **most common** demyelinating disorder.

- Relatively common (1:1000).

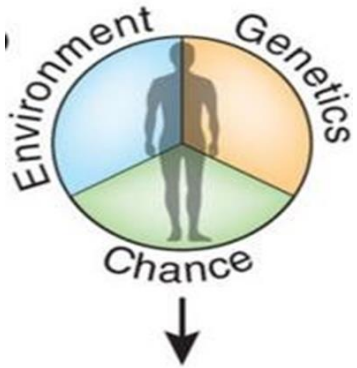
- Present at any age (typically **20-40 yrs**) (but onset in childhood or > 50 years is rare), **F**:M: 2:1.

Commonly (young female), very rare in children

❖ Pathogenesis

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

- Related to **genetic susceptibility** and largely undefined **environmental triggers**.



❑Genetic predisposition:

- The incidence is 15-fold higher when the disease is present in a first-degree relative and 150-fold higher with an affected monozygotic twin.

- A strong effect of the **MHC; HLA-DRB1** Human leukocyte antigen-BRB1

- Other genetic loci that are associated with MS: **IL-2** and **IL-7** receptor genes

هدول الجينات مسؤولين عن تنظيم عمل الT lymphocytes

❑ Immunological mechanisms

-The disease is initiated by TH1 and TH17 cells that react against myelin antigens and secrete cytokines.

- TH1 cells secrete IFN-γ, which activates macrophages, and TH17 cells promote the recruitment of leukocytes.

-The demyelination is caused by activated leukocytes and their injurious products.

- B lymphocytes and antibodies also play a role in the disease.

-These cytokines cause direct damage to oligodendrocytes

❑Environmental factors Undefined so far

- Infection, viral

Immunological rxns against myelin antigens;
-TH1 and TH17 by cytokins secretion
-B cells by Antibodies formation

❖ Clinical features

- 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.

- In any individual patient, it is difficult to predict when the next relapse will occur.

- **Unilateral visual impairment** is a frequent initial symptom of MS due to optic nerve involvement **(**optic neuritis, retrobulbar neuritis**).**
- Involvement of the **brain stem** produces cranial **nerve signs & ataxia** & can disrupt conjugate eye movements.
- **Spinal cord** lesions give rise to **motor & sensory impairment of trunk & limbs,** spasticity, & difficulties with the voluntary control of bladder function

- Changes in cognitive function can be present but are often much milder than the other deficits.

الأعراض حسب وين صارت ال lesion لكن غالبا بتكون صارت بال optic nerve و
بتكون بالبداية الأعراض visual impairment

Multiple sclerosis (MS)

Changes to your vision.

Muscle weakness, stiffness and spasms.

Numbness or pain.

Loss of balance.

Difficulty with cognitive function.

Mood changes.

❖ Disease course, clinical types

- Relapsing remitting MS (RRMS) — Most common
  - Episodic neurologic deficits that may partially or fully resolve but are followed by additional relapses
- Primary progressive MS (PPMS) — بتبدأ الاعراض و بتضل تتطور بدون ما يصير remission
  - Nonepisodic progression of disease from the initial onset of symptoms
- Secondary progressive MS (SPMS)
  - Typically follows RRMS, where the disease transitions from episodic to continued progression

بالبداية بتكون relapsing then remitting لحد ما بعد attack ما يصير remitting و بتحول وقتها لprogressive لهيك سميناها secondary

❖Investigations

The CSF shows:

Specific antibodies agains
Specific myelin AGs

-In one-third of cases, there is **moderate pleocytosis** (increase in WBC count).

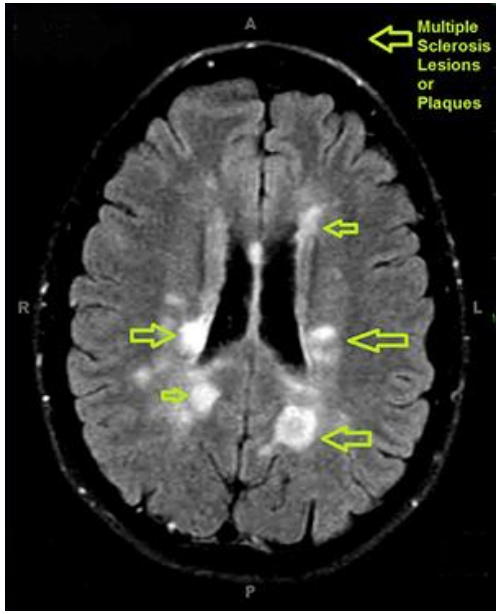
-A mildly elevated protein level with an increased proportion of immunoglobulin

- ↑ **Oligoclonal IgG bands** — Elevated proteins due to myelin destruction

- There is no oligoclonal band in the serum

MRI: The most accurate test, can show the distribution of lesions across the CNS during active disease.

Separated in space by normal white matter



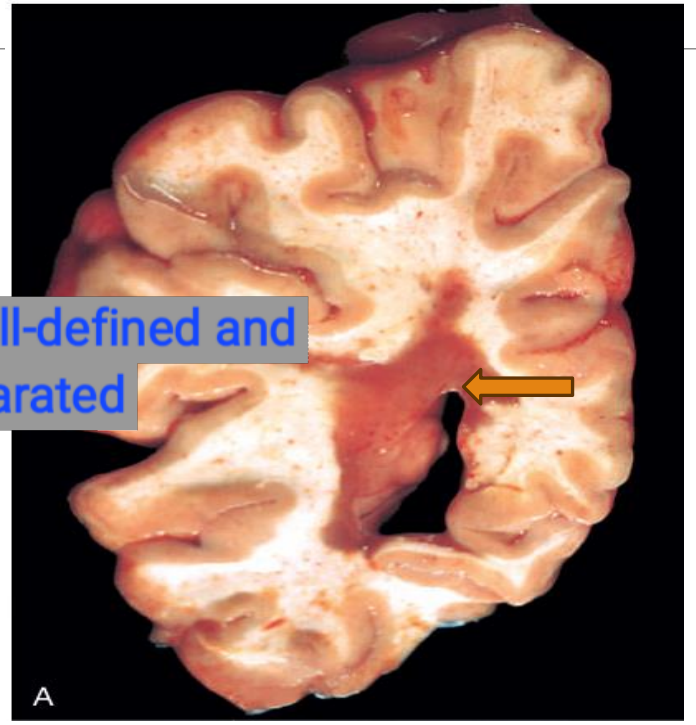
❖ Morphology

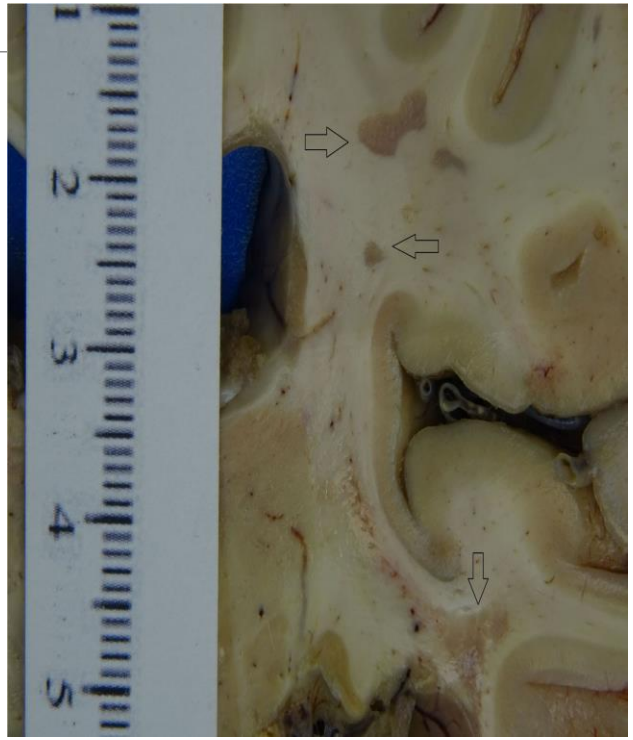
- A multifocal white matter disease.

Grossly: autopsy بال بنشوفهم

- Plaques are discrete, slightly depressed, glassy-appearing, and gray-tan in color

- Plaques are **common near the ventricles** and also frequently occur in the optic nerves and chiasm,brain stem, ascending and descending fiber tracts, cerebellum, and spinal cord.





(A) Section of the fresh brain showing a plaque around the occipital horn of the lateral ventricle.

Microscopically:

The lesions have sharply defined borders

Well- defined
يعني مفصولين و بسهولة بميزهم عن المناطق الطبيعية

❖Active plaques (soft pink):

- 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 but may be reduced in number.

بما انها اكيد ongoing process of myelin destruction
رح نلاقي macrophages and myelin debris

❖Inactive plaques (hard grey): quiescent

Process of destruction has ended

- The inflammation mostly disappears, leaving behind little to no myelin, astrocytic proliferation, and gliosis.

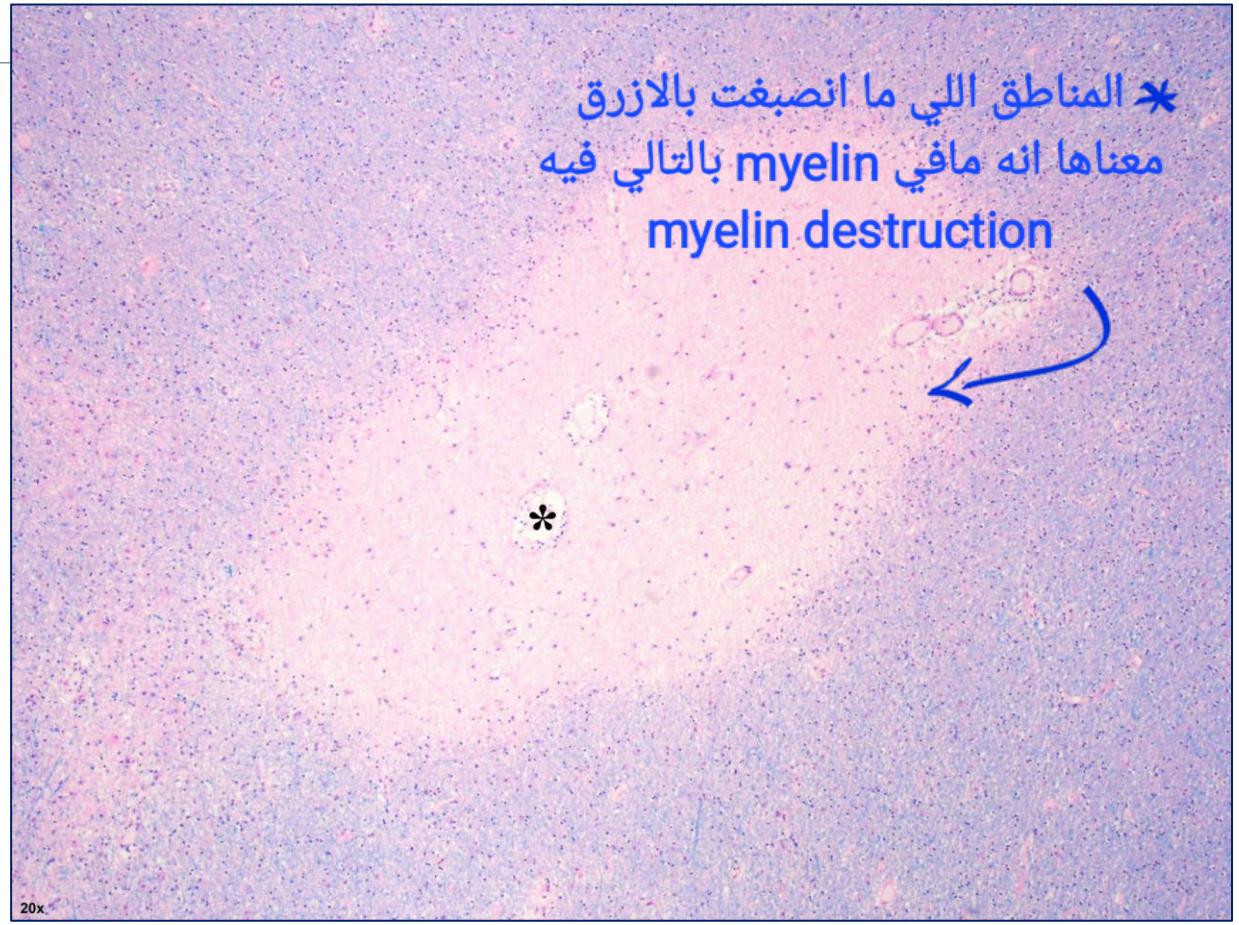
❖Shadow plaques:

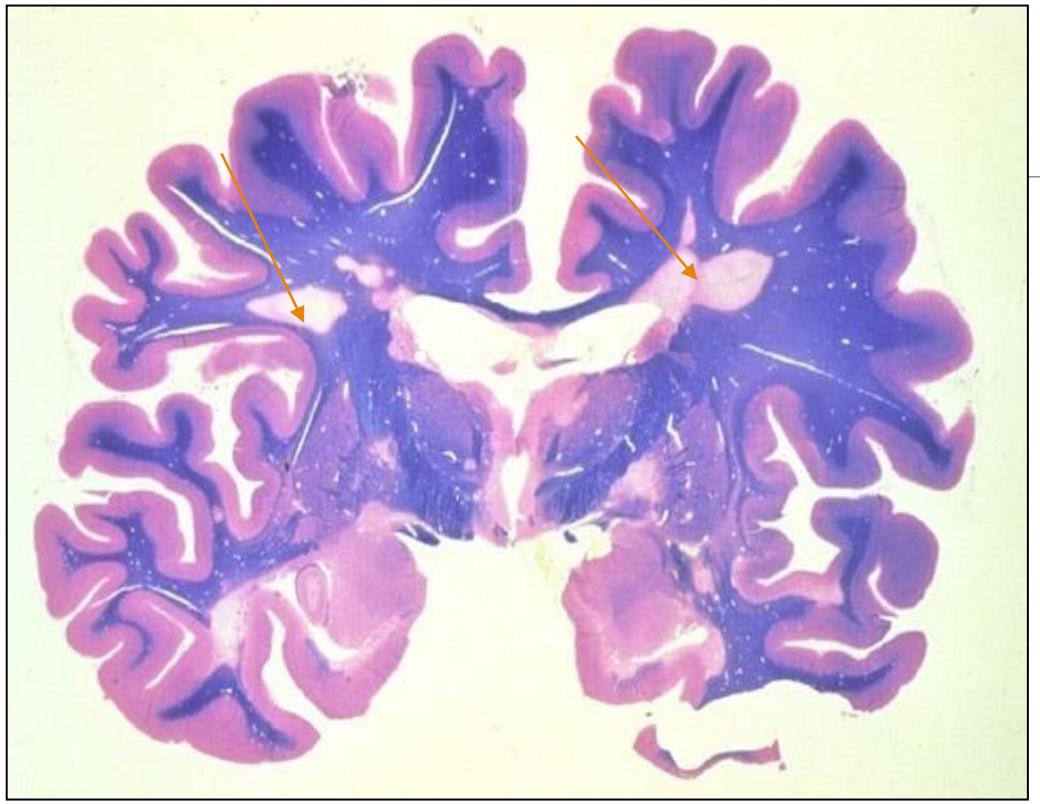
- **Border** between normal and affected white matter representing partial remyelination or incomplete myelin loss .

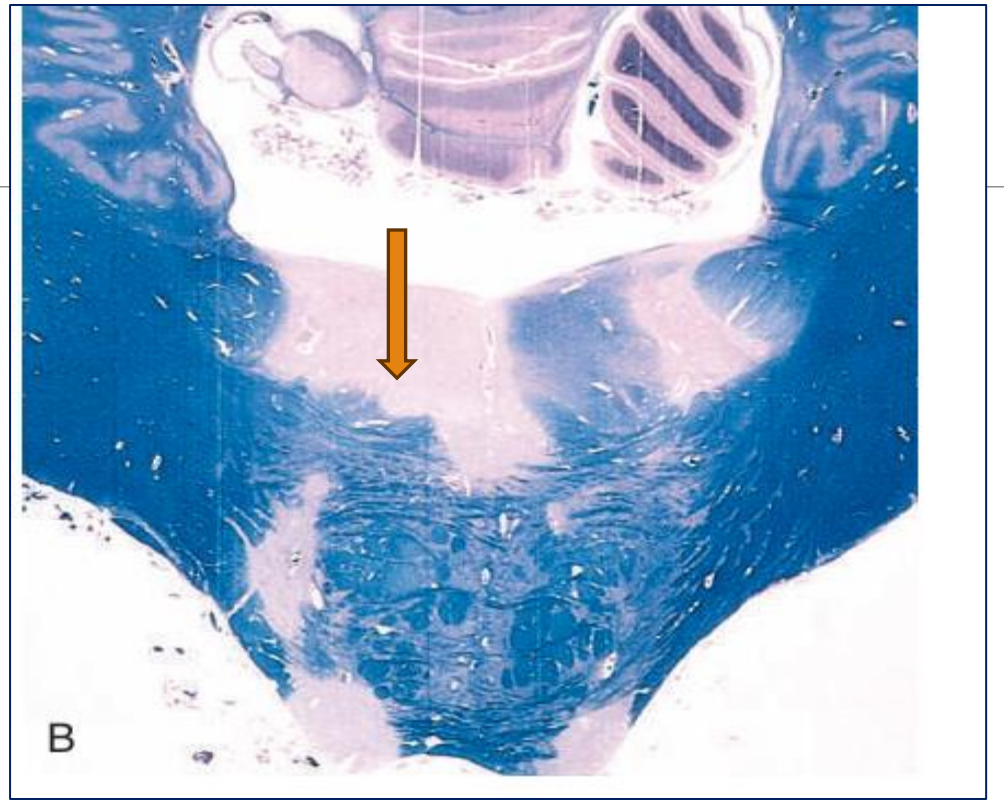
يعني بعد ما صار myelin destruction (demyelination)
بصير عنا remyelination .
في بعض الدراسات بتقول انه ممكن يصير عملية remyelination عند بعض المرضى

صبغات مخصصة لل myelin و
بتصبغ باللون الأزرق

- **Luxol fast blue/ periodic acid–Schiff stain** for myelin: section with a well-demarcated area of demyelination centered around a vein (*)







Unstained regions of demyelination (MS plaques) around the fourth ventricle. Luxol fast blue/ periodic acid–Schiff stain for myelin.

❖ Prognosis

بشكل عام ما عنا
Well-defined prognostic factors
بحيث نقدر نحدد ال prognosis

- Better in women

- Better in patients with 2 or less attacks in the first year.

Acute disseminated encephalomyelitis (ADEM)

Acquired

- **Postinfectious or Post-vaccinial autoimmune** reactions to the myelin.

- Occurs after systemic infectious illnesses, such as viral diseases.

- Not related to the direct spread of infectious agents to the nervous system. Rather, it is believed that immune cells responding to pathogen-associated antigens cross-react against myelin antigens, resulting in myelin damage.

- Unlike MS, associated with **acute-onset monophasic illnesses.**

يعني بكون فيه تشابه بين ال microorganism's antigens
و ال Myelin antigens
which leads to cross reactivity

المرض ما بيجي على شكل separated attacks
بالعكس بيجي على شكل acute onset بعدها يا اما
بصير progression و ممكن يأدي للوفاة بنسبة 20%
او بصير complete recovery

- Symptoms typically develop 1 or 2 weeks after an antecedent infection and are nonlocalizing (headache, lethargy, and coma), in contrast with the focal findings of MS.

- Symptoms progress rapidly, and the illness is fatal in as many as 20% of cases; in the remaining patients, there is complete recovery.

- Acute necrotizing hemorrhagic encephalomyelitis (ANHE) is a **more devastating related disorder**, which typically affects young adults and children.

Same pathogenesis of ADEM but more severe (includes hemorrhage and necrosis) and affects younger adults and children

Progressive multifocal leukoencephalopathy (PML)

- A demyelinating disease that occurs after reactivation of the **JC virus in immunosuppressed patients.**

Optica = Optic.N

Neuromyelitis optica (NMO)

- An antibody-mediated demyelinating disease (**Antibodies to water channel aquaporin-4 (diagnostic & pathogenic)** Water channel aquaporine-4 in asrocytes

- Centered on the optic nerves and spinal cord

- Spinal cord lesions lead to varying degrees of weakness or paralysis in the legs or arms, loss of sensation, and/or bladder and bowel dysfunction.

While optic nerve lesions lead to visual abnormalities

Pontine = Pons

Central pontine myelinolysis

- Caused by nonimmune damage to oligodendrocytes, typically after sudden correction of hyponatremia and Acid-base imbalance
- Alcohol-induced

Due to metabolic causes

- Involve the center of the pons.

- May result in a rapidly evolving quadriplegia.

❖ **Pathology:**

- Cellular edema, caused by fluctuating osmotic pressures → compression of fiber tracts → demyelination in center of PONS & other areas in brain

اهم شيء للتفريق بينهم ال pathogenesis

Dysmyelinating diseases or leukodystrophy

Non- acquired

-Inherited disease caused by abnormal myelin synthesis or turnover.

-They are caused by mutations of genes whose products are involved in the generation, turnover, or maintenance of myelin.

هون على عكس الأمراض السابقة ال myelin ما
بكون تكون بشكل طبيعي بعدين صرله
destruction, المشكلة اساسا بالتكوين

-Some of these mutations affect lysosomal enzymes, while others involve peroxisomal enzymes; a few are associated with mutations in myelin proteins.

-Most are of autosomal recessive inheritance, although X-linked diseases also occur.

بنسبة اقل X-linked diseases

❖ Examples:

- Metachromatic leukodystrophy
- Adrenoleukodystrophy
- Krabbe disease

بتختلف ال clinical
باختلاف manifesations
الجين و الانزيمات المتأثرة

- Clinically, each disorder of the various leukodystrophies has a characteristic clinical presentation, and most can be **diagnosed by genetic or biochemical methods.**

- Affected children are normal at birth but begin to miss developmental milestones during infancy & childhood.

Diffuse involvement of WM.
multiple lesions separated in time and place بتكون MSعكس ال

-There is typically diffuse involvement of white matter, leading to deterioration in motor skills, spasticity, hypotonia, or ataxia.

- **Several clinical features distinguish leukodystrophies from demyelinating diseases:**

- The leukodystrophies typically present with an insidious and progressive loss of function

- Often begin at younger ages.

- Associated with diffuse and symmetric changes in imaging studies مهم

❖ Morphology

- Much of the pathologic change is found in the white matter, which is diffusely abnormal in color (gray and translucent) and volume (decreased).

- Early, some diseases may show patchy involvement, while others have a predilection for occipital lobe involvement.

بس مع الوقت بصير diffuse

- In the end, nearly all of the white matter usually is affected.

- With the loss of white matter, the brain becomes atrophic, the ventricles enlarge, and secondary changes can be found in the gray matter.

Microscopic:

Mainly

- Myelin loss is associated with infiltration of macrophages, which often become stuffed with lipids.

- Some of these diseases also show specific inclusions created by the accumulation of particular lipids.

demyelinated diseases vs dysmyelinated diseases

- Aquired
- multiple lesions in the WM
- Episodic

- Inherited
- diffuse in the WM.
- Progressive.