Pathology

Sheet

Lec No: 5

Subject: **Diseases of Myelin**

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Diseases of Myelin

written according to section 2 recording.

• **Myelin**: protein-lipid complex that is wrapped around the axons.
• **Function**: allows rapid propagation of signals (isolation and fast conduction).
• **Composition**: layers of plasma membranes assembled by oligodendrocytes (CNS), schwann cells (PNS), so myelin diseases in CNS are different from those in PNS; myelin diseases of CNS do not affect myelin of peripheral nerves.
• Myelinated axons are the predominant component of white matter.
• Because Schwann cells are the source of myelin in peripheral nerves, so different specialized proteins and lipids are involved in myelin formation.

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Primary diseases of myelin

1. **demyelinating diseases** : acquired conditions where there is damage to previously normal myelinated axons.

Causes of damage:
- infections.
- autoimmune diseases.
- toxic substances.
- osmolality changes.
- anything that secondarily affects myelin.
- **Most common type:** multiple sclerosis.

2. **dysmyelinating diseases = leukodystrophy**, myelin not formed properly or has abnormal turnover kinetics , result from mutation disrupting function of proteins that form myelin.

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Multiple sclerosis

• Autoimmune.
• Demyelinating.

• Episodes of neurologic deficits separated in time, which are attributed to white matter lesions that are separated in space.

- If there is no myelin → slow transmission of signal → neurological symptoms.

Separated in time means:

The patient will have certain attack → back near normal →another attack → back near normal.

Separated in space means:
symptoms depend on area of demyelination.

It might affect:

- Optic nerve.
- sensory nerves.
- motor nerves.
- speech nerves.

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Epidemiology

• 1 per 1000 persons in USA and Europe.
• Female : male ratio is 2:1 (because it is an autoimmune disease).
• Manifests at any age (usually 20-40), but onset in childhood or after 50 is rare.

(Relapsing and remitting episodes of neurologic deficit variable clinical course)

Multiple sclerosis in Jordan: a clinical and epidemiological study by Khalid El-Salem et al (study from KHCC, JUST and AlBashir):

• 224 patients (165 females, 87%; 59 males, 13%). The mean age of onset was 29.3 years. The prevalence of MS in the city of Amman was 39/100,000. The prevalence of MS in Irbid, north Jordan, was 38/100,000.

• The most frequent presentation was weakness (30.8%), followed by

optic neuritis (20.1%), sensory impairment (19.6%), and ataxia (14.3%). A relapsing remitting pattern was identified in 90.2% of patients, the rest being primary and secondary progressive, and one patient had a progressive relapsing course. Family history of MS was found in 9.4% of the cases. About 60% of the patients were using interferon beta.

Based on this study:
1)) more females in Jordan are affected than in western countries; 224 patients (165 females, 87%; 59 males, 13%).
2)) incidence is much less 39\100,000 = 0 .39\1000.
3)) age of onset is the same.

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Natural history of MS is determined by:
1. the limited capacity of the CNS to regenerate normal myelin.
2. the secondary damage to axons.
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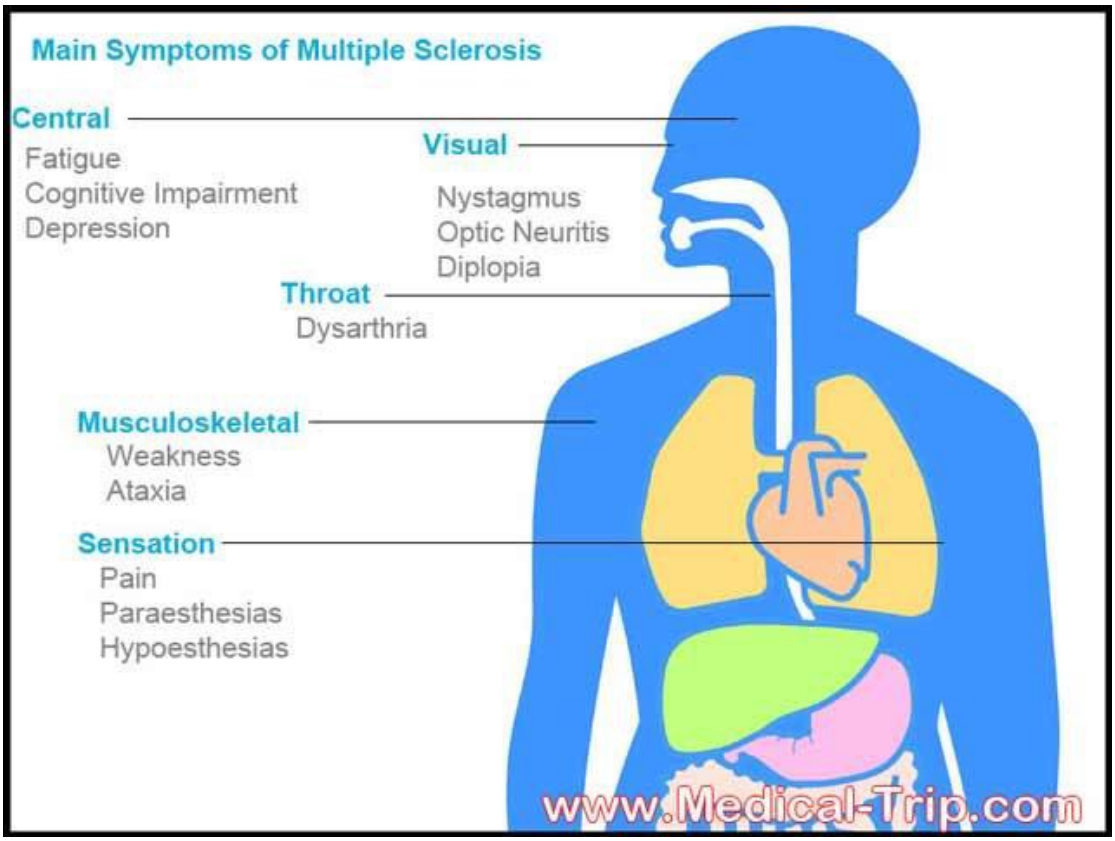
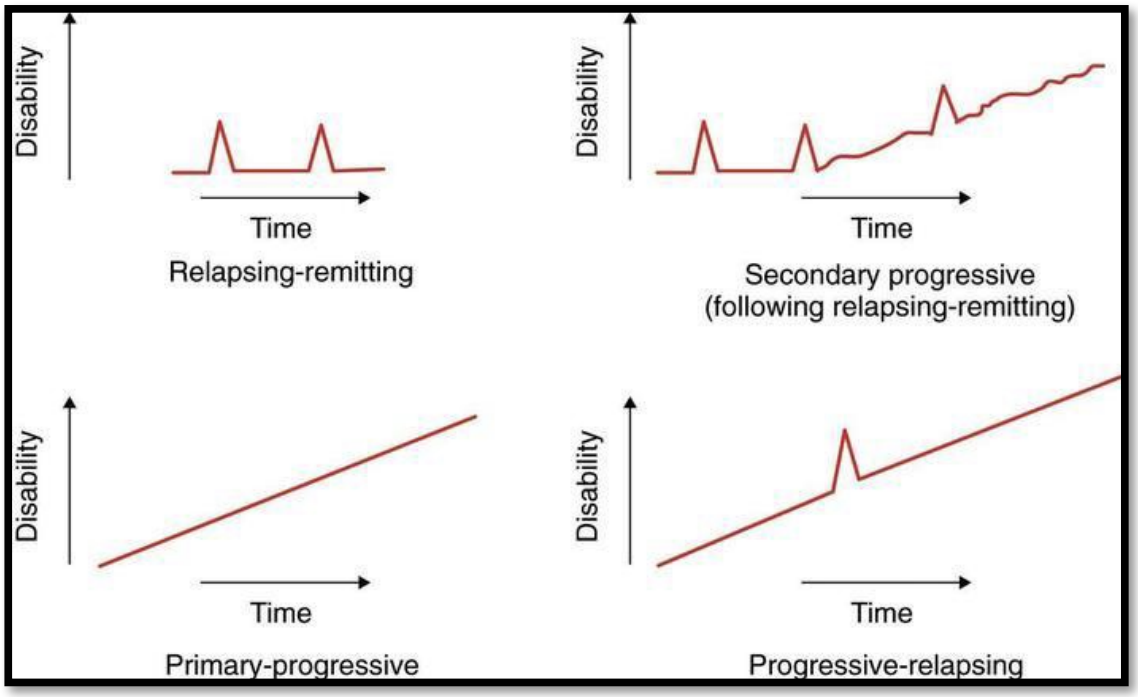
Signs and symptoms:
-sudden onset of symptoms
المريض يصف حالته ب :"كنت نايم وصحيت مش قادر أشوف... كنت نايم وصحيت مش قادر أحكي....!!!!



clinical course:



1) **Relapsing – remitting:(**occurs in 80% of patient).

- The patient will have certain attack → back near normal (actually with fatigue) →another attack → back near normal (with fatigue).

2) **primary progressive:**
no areas of remission.

3) **secondary progressive:**
begins as relapsing – remitting course, then it worsens.

4) **progressive – relapsing:**
at certain time it becomes very worse.

After diagnosing patient with MS, we cannot predict whether course the patient will undergo, how is the coming attack will be, and when.

Pathogenesis of MS :

From slides:
MS is an autoimmune disease , So there is loss of tolerance of self-proteins in the myelin sheath.
•**Genetic polymorphisms and environmental** factors play a role in this loss of tolerance.

-The first step in pathogenesis of an autoimmune disease is genetic predisposition (it's a must) , same applies here , there is a genetic polymorphism in IL-2 and IL-7 receptors .

-Why this polymorphism (in IL-2,7 receptors) is important in predisposing this disease ??

Because they have a role in activation of T cells , so if they have a polymorphism they can make T cells auto reactive .

From slides:
Disease is 15 fold higher in first degree relatives.
Concordance rate of monozygotic twins around 25%.

The genetic studies done to find associations between MS and genetic variations failed to explain the variations in the clinical course of the disease.

-**Another genetic factor is HLA DR2 :**
it could come with the first polymorphism or alone causing MS.
Not all people having these genetic predisposition will develop the disease they need environmental triggers .

Step 2 : Environmental factors that triggers the disease , which is thought to be **viral infections** and it is not proven although some say that EBV(Epstein-Barr virus) is one of the triggers .

Step 3 : T helper activation , then they'll secrete IFN Gama(step 4) that will stimulate Macrophages (step 5)

Step 6 : stimulating the macrophages will cause them to phagocytose the myelin.

Note: Beside T helper1 activation, T helper 17 will recruit the WBCs attacking the myelin ending up with loss of it .

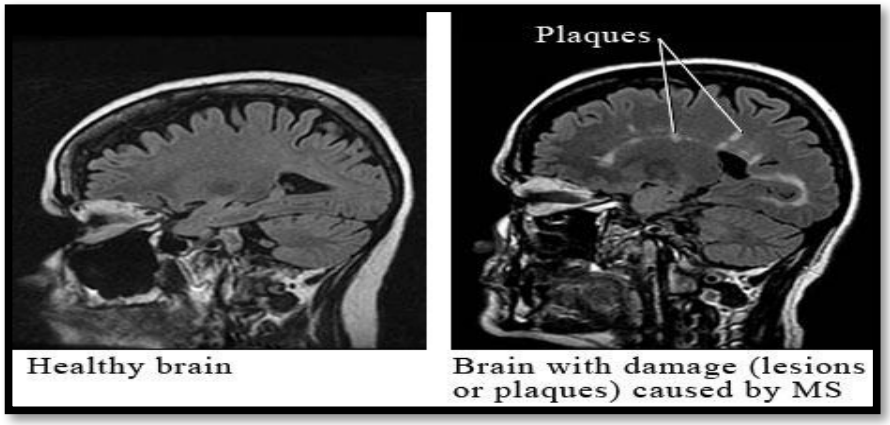
Note : CD 8 T lymphocytes + B lymphocytes might also play a role in myelin destruction.

- MS is a disease of MYELIN , so at the beginning the axons are not affected ,but attack after attack there will be some damage to the axons mainly by the WBCs .

- In addition to demyelination; axonal damage can occur **secondary** to toxic effects from lymphocytes, macrophages and the chemicals they secrete.

Morphology :

MS is a white matter demylinating disease that can be seen forming plaques corresponding to the area that lost the myelin.
Commonly seen near ventricles, optic nerves and chiasm, brain stem, cerebellum and spinal cord.



Microscopically we can see two type of plaques:

1- **Active plaques**: we can see macrophages eating the myelin ,so they appear foamy , and this is seen during the attack.
2- **Quiescent(inactive plaques**): at a later stage of the attacks , no inflammation; the WBCs are gone and there are no macrophages , there is some myelin left behind (little or no) instead of them there'll be gliosis and gemistocytic astrocytes as in chronic inflammation in CNS .

How we treat MS ??
Its an autoimmune disease so we need to use immunotherapy (steroids and IFNs) and other new drugs suppressing the immune system .

Other demyelinating diseases:

1. post infectious, most common form.

2.Neuromeylitis optica.

3.Central pontine myelinolysis.

4.Progressive multifocal leukoencephalopathy.

1-Post infectious demyelination:

From its name, post-infectious: after an infection there'll be demylination .
It can happen after giving a life vaccines, as an example measles vaccine , because one of the rare complication of these vaccines in the CNS is demylination . some viral infections also can also cause demylination .

Not due to direct effect of the virus , Pathogen associated antigens cross react with myelin antigens…. Provoke autoimmune response against myelin.

There are two types of this disease :

1-**Acute disseminated encephalomyelitis**:

Symptoms 1-2 weeks after infection (rarely after immunization)
Rapid progression , fatal in 20% of cases, Survivals: complete recovery.
Patients will suffer from Non-localizing symptoms: headache, lethargy, coma.
2-**acute necrotizing haemorrhagic encephalomyelitis** which is more dangerous (hence from the name ,necrotizing haemorrhagic) , permanent disability to the CNS can occur (motor ,cognitive problems).
Children and young adults mostly affected.

So these 2 diseases attack the myelin after a viral infection ,again here Not due to direct effect of the virus , Pathogen associated antigens cross react with myelin antigens…. Provoke autoimmune response against myelin.

2-Neuromyelitis optica:

From its name it affects ***only*** the optic nerve and the optic pathways demylinating them ,it is usually bilateral, *synchronous or mean synchronous* loss of vision. Because it only affects optic pathways; the only symptom is loss of vision.

The problem here occurs because there are antibodies against a protein called **Aquaporin-4**, so again It is an autoimmune disease , these patients are a distinct entity **, not** a subtype of MS .

Aquaporin is an integral membrane protein works as a channel that conducts water through the cell membrane.
It is more common in female, even the ratio F/M is higher than MS .

3-**Central pontine myelinolysis:**

-It affects mainly the Pons but can affect other parts also ,there is lysis to the myelin from its name (myelinolysis),this disease is ***not autoimmune.***
-It is caused by rapid correction of hyponatremia (Iatrogenic which means relating to illnesscaused by medical examination and treatment) .
-The patient suffers from hyponatremia and we wanted to correct his condition by giving Na rapidly so we have changed the whole osmolar balance which may result in **Central pontine myelinolysis** .

-This condition can also be caused by severe disturbances in fluid balance causing the osmolarity imbalance.

- when this happens , edema will form between the myelin and axons affecting the myelin sheath and causing the lysis .This is dangerous and can cause quadriplegia to the patient and can cause what is called **locked in syndrome .**

note : Hyponatremia should be corrected at a rate of no more than 8-12mmol/L of sodium per day to prevent central pontine myelinolysis.

Locked in syndrome:
(**LIS**) is a condition in which a patient is aware but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles in the body except for vertical eye movements and blinking (because the Pons is affected). The individual is conscious and sufficiently intact cognitively (because the cortex is intact) , able to communicate with eye movements.
The brain death: the patient is not intact cognitively nor motor, but here he is cognitively normal .
So if you see a patient with coma ask him "do you hear me? If you do blink " if he blinks or moved his eyes then he is locked in .
Coma: the patient can not move and he is unconscious, but the **condition is reversible but brain death is not** .
There is a case opposite to (LIS) it is called vegetative state, the motor function of the patient is normal but cognitively is not; so in these two cases the patient is alive!!!

The story of man who woke up from coma but developed (LIS).
https://www.youtube.com/watch?v=WQIWc3uE4LU

Leukodystrophies (dysmyelinating disease):

•Inherited dysmyelinating diseases.

•Most are autosomal recessive, some X linked.

•Mutations in : Lysosomal enzymes, perixosomal enzymes, or myelin protein.
So the myelin maybe not produced or there is problem in kinetics ,there is destruction more than production.

End of the sheet the rest the doctor didn't mention but they are from slides

-Several types of dysmyelinating diseases exist.

•Affected children are normal at birth but start loosing developmental milestones during infancy and childhood.

•They might have deterioration in motor skills, spasticity, ataxia…

Morphology:
•White matter: grey and translucent with decreased volume.

•Loss of white matter.. Brain atrophic, ventricles enlarge.

•Several types of diseases exist, each with a specific mutation .

اخر سلايد الجدول مش مطلوب ابدا ابداا

"فتعالوا ننسى أسى الماضي ونعد العدة للآتي

☺ أوَ ليس الله يذكرنا: وأعدوا تلقوا مرضاتي