

Demyelinating diseases:-

- In CNS or PNS some axons are surrounded by myelin to increase velocity and effectiveness of signal conduction (The Action potential jumps from the node of Ranvier)
- myelin sheath produced by

→	oligodendrocyte ^{in CNS}
	Schwann cells ^{in PNS}

Demyelinating diseases are

1. Acquired preferential damage of myelin
2. Axons mostly are preserved (in severe cases they are affected)
3. Initially effect on transmission of impulses along axons and on the action potential velocity and conduction.
4. The size of defect is determined by:
 - A - The limited capacity of CNS to regenerate the myelin
 - B - The degree of 2ry damage to axons.
5. Etiology:
 1. immune mediated destruction (MS)
 2. infection (viral or PML)

3. Inherited (called leukodystrophies)

components

→ Affecting synthesis and turnover of myelin

Multiple Sclerosis (MS)

• Autoimmune demyelinating disorder affect the myelin and the axons are mostly preserved except in ^{severe} cases

• The presentation of disease is that

Symptoms are separated in time and space

يجي المريض بشكله من pins and needles + numbness من لبتفتر في طرف
ويتأخذ منه History بعلامي عنده قبل سنة كان فيه
walking problems وصل في سنة عنده شلل في يمينه اشماله بطه يكون
مرة ومرحبة في كل الأعراض في جهة نيرة ولديها تشدد في كتف من لو ضللت
صوتها في الأعراف

فالمريض يجي ببشيت أنه أه أوقات مرض بس في أوقات راح ال Symptoms
ولما ال Symptoms ملو شت علاقة ببعض

في أوقات مختلفة
Separate in time :

في دماغ ال brain واضح أنه عدة مناطق متأثرة
Separate in space :

على الرغم أنه في areas يتأثره
frequently affected by MS as

→ around Lat ventricles

may affected Corpus Callosum

Any area even the Brainstem and Spinal Cord

So MS has Distinct episodes of neurologic deficits:

- ① Separated in time.
- ② attributed to patchy white matter lesions that are separated in space

• MS primarily affecting **white matter**, Gray matter also be affected

white matter ← MS ← **بنيّة أبيض** ← **axons + myelin**

• MS is the most Common demyelinating disorder (1/1000 in the US and EU)

• vit D deficiency increase the hypothesis of MS

• MS affect any age (more frequently in **20-40**)
(Rare in childhood or after 50)

• **women** are preferred in MS. $F : M = 2 : 1$

Presentation :- Female patient in 20-30 years old with **relapsing and remitting** attacks and the attacks end with **incomplete remission**.

• **ال** attack **ببدا** بعد فترة **لنفسه** بس ما يرجع لـ **base line** **ذاتي** بعد منه
لا **يعزل** **residuals** وبعد **شهر** 6 أسابيع **وتحل** **تجدي** **ال** 2nd attack
فبلا **مقا** أنه **بلا** مرة **عندي** **incomplete remission** فباستمرار **مع** **لور**
الوقت **بلا** **مقا** أنه **ال** **deficit** **يترد**

So MS: clinically relapsing and remitting eprsoods of Variable duration.

• neurological deficits gradually and partial recovery

• Relaps frequency tends to decrease over time

But with steady neurologic deterioration.

Pathogenesis:-

components

① Autoimmune response against myelin

② Genetic factors.



- 15 folds in first degree
- 150 folds in monozygotic twin
- Strong association with HLA-DR (APCs)
- Additional association with IL-2 IL-7 receptors
CK3/receptors genes.

③ Environmental factors.



Geographic variation (مابعد القطب الشمالي، الجنوبي)
(Sun Vit D/equator) (عشر العرض للشمس و Vit D)

* Immune mechanism (self mediated) (type 4 hypersense)



- initiated by Th_1 and Th_{17} cells
- Reaction against myelin
- Secreted cytokines:



1. Th_1 secrete $INF-\gamma$, activates Macrophages
2. Th_{17} ~~secrete~~ → recruitment of leukocytes.



Demyelination by these activated leukocytes and their injurious products. (free radicals)

Lead the CNS to infiltrate in plaques. (CD_4^+
 CD_8^+ T cell + Macrophages)

How the autoimmune reaction is initiated?

The clear cause is unknown but maybe

- 1- viral infection
- 2- Therapy
أنه لا يُعطى علاج على صيد
المريض تحسسه ضياعه كأي حالة
سبب

- 1- Modulation or inhibition of T cell responses
- 2- Blocking of the recruitment of T cell to brain
- 3- Depletion of B cells Ig's.

Morphology: ① is a white matter disease.
(white matter plaques) → active

~~Morphology~~: ② The lesion is firmer than the surrounding white matter (sclerosis)

③ hard lesion (plaque at first are active when remission plaque less active + gliosis)

④ gliosis. (Scar tissue of brain)

⑤ well circumscribed, depressed, Glassy irregularly shaped plaques.

⑥ The area of demyelination sharply defined borders

⑦ variable size

Localization Commonly:

- Adjacent to the Lat ventricles.
- in the Corpus Callosum
- optic nerves and chiasm
- Brain stem
- Ascending and descending fiber tracts.
- Cerebellum + Spinal cord

plaques can extend into gray matter.

morphology: (microscope)

- Ongoing myelin break down
- Associated with abundant foamy macrophages engulfing myelin

- with lymphocytes are perivascular and cutting at the outer edge of the lesion

- Active lesions are often centered on small veins (myelin is completely absent)

blue Luxol stain Luxol stain وبقيته blue

- Axons are relatively preserved.

(axons) (neuron) NF protein IHC (axons) (neuron) NF protein IHC

changes of

- In time, reactive astrocytes

remission

مع انه عدي
limited ability
to repair

As lesion become quiescent, inflammatory cells slowly disappear.

So the inactive plaque formed.

No macrophages / little or no myelin.

reduced oligodendrocytes / Greatly diminished axon in old gliotic

oligode. oligode. بالكل

Proliferation
myelin
بالكثرة
بالكثرة

Diseases of peripheral nerves

Types: (1) axonal neuropathy

primary damage of axons.

Experimental model: Wallerian degeneration

نقص قطع الأعصاب في الحيوانات و يراقب أين حيوان

① distal part of point الـ cutting يبدأ من نقطة الـ start to degenerate and disappear

② proximal part start to grow to replace it

الشروط اللازم هو أن الـ transected ends remain closely approximated.

repair attempts of axon ← **traumatic neuroma** (non neoplastic mass) ← repair attempts of axon
عبر عن axons + Schwann cells + other cells.
Stain with **trichrome** ← تصبغ CT باللون الأزرق

(2) Demyelinating neuropathy:

- primary damage related to myelin and Schwann cell
- relatively preserved axons
- Random degeneration
- Repair attempts to schwann cells (shorter and thinner than original internode)

2 nodes of Ranvier.

المسافة بين

- The electrophysiologic Hallmark is slowed nerve conduction velocity due to loss of myelin

[3] neuropathies:

Axon degeneration 2ry to destruction of neuron (perikaryon)

Examples: • H. Zoster

• Drugs as platinum

↳ in chemotherapy

pins and needles numbness

له عصبه ضيق بعد أول جرعة المرض بقله من

موضوع جديد

• Mononeuropathy Single nerve and its distribution is affected as infection or trauma

• polyneuropathies multiple nerves are affected usually symmetric

Axon are affected in length dependent fashion

• Mononeuritis multiplex: Individual nerves in a haphazard fashion as: vasculitis.

• Polyradiculoneuropathies: Affect nerve roots as well (النسبة تؤثر كل ما يرتبط به ال nerve) as peripheral nerve

inflammatory reaction

• leading to diffuse symmetric symptoms.

1 inflammatory

2 toxic 3 infectious

4 Trauma 5 metabolic (in DM)

6 Genetic 7 Paraneoplastic

Peripheral neuropathies

Clinically:

types (etiology)

• In proximal and distal parts of body

as a result of the products of tumor.

numbness

"Pins and needles" Sensation

Weakness (if related to motor functions)

Inflammatory neuropathies:-

Guillain - Barré' syndrom

- Acute inflammatory demyelinating polyneuropathy.
- is an immunologically mediated demyelinating Peripheral neuropathy, May lead to respiratory Paralysis
- 1 / 100000 year.
- Cause Ascending paralysis (weakness from distal to proximal limbs)
- its injury is Radiculoneuropathy (inflammation and demyelination of Spinal nerve roots and peripheral nerves)

Pathogenesis:

- Acute onset, immune mediated, demyelinating neuropathy
- $\frac{2}{3}$ of cases are preceded by influenza like illness
- as well as association with →
 - C. jejuni
 - CMV
 - EBV
 - M. pneumonia
- no microorganism in the nerves.
- experimentally role of Lymphocyte, macrophages and Abs (if the patient's serum or plasma transmitted to animal → same symptoms appear) so they are transmitted experimentally

Morphology

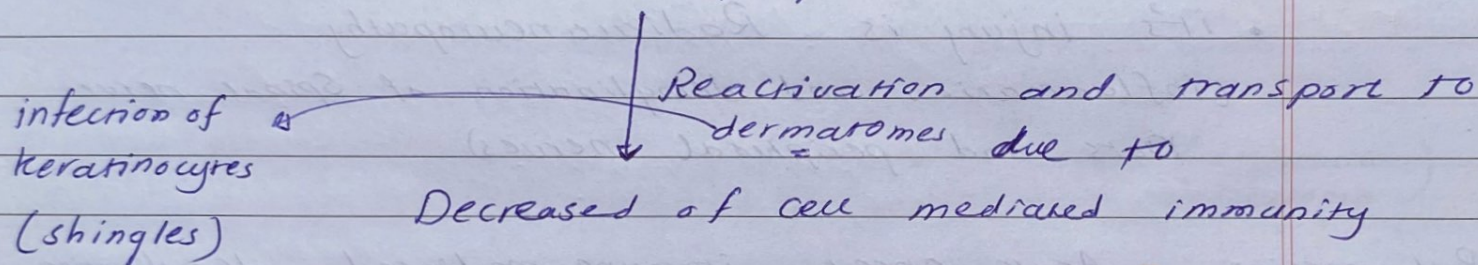
1. inflammation of peripheral nerves.
2. perivenular and endoneurial infiltration
3. segmental demyelination
4. damage to axon (in severe cases)
5. inflammation is more prominent close to nerve roots

as Lymphocyte
Macrophage
Plasma cells

Infectious neuropathies

Varicella - Zoster Virus

- VZV from herpes family
- common, and is latent infection of chickenpox in sensory ganglia



- cause neural death with abundant mononuclear infiltrate then followed by Degeneration of axons.

Metabolic neuropathies

result to (DM)

DM is the most common Cause of peripheral neuropathy overall 50% of Diabetic patients.

Mostly: ascending distal symmetric sensorimotor Poly neuropathy.

Pathogenesis: • complex

→ 1. hyperglycemia. (due to non enzymatic glycosylation of proteins, lipids and nucleic acid)

2. Vascular pathology lead to Ischemia and 2ry will be damaged

in DM Damage to both axons and Schwann cell

Non enzymatic glycosylation of proteins, lipids and nucleic acid will cause (1) Activation of inflammatory signals

(2) Depletion of $NADPH^+$ (anti-oxidant)



injury by free radicals.

Morphology :

- Axonal neuropathy
- Reduced number of axon
- Degenerating myelin sheaths
- Regenerative axonal clusters (amputation neuroma)
- Thickening and hyalinization of endoneurial arterials

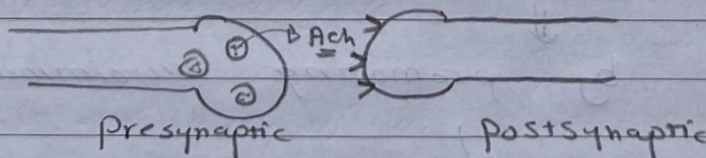
Diseases of neuromuscular ^{NMJ} junctions:

بشكل طبيعي

- motor neuron from Spinal Cord to striated muscle before it reaches it branches to small branches each one ends up with bulb synaps with the membrane of sarcolemma (postsynaptic)

when Action Potential arrives

the presynaptic release Ach



- in this type of disease there's a Painless weakness and fatigue

autoAntibodies is one of the important Causes

Myasthenia gravis:-

- Ab mediated disease of the NMJ
- Autoimmune (auto Abs against Ach receptors)

• incidence: 150 - 200 / 1,000,000

- Bimodal age distribution

Pathogenesis: Auto Abs against Ach receptors ⁱⁿ (post synaptic or sarcolemmal membrane)

- pathogenic Ab (لوظائفها كالأجسام المضادة الضارة)
- passive transfer to animals
- improvement by decreasing these Abs
- leads to aggregation and destruction of receptors
- Damage to postsynaptic membrane through Complement fixation

Ab - Ag $\rightarrow$ Complement fixation $\rightarrow$ Chemical mediators will recruit elements of immune system lead to Destruction

أحد ^{Ach} لفرقة لوسيف. No response to Ach.

Strong association with Thymic abnormalities (10% with thymoma & 30% with thymic hyperplasia)

as a rule $\rightarrow$ triggering autoimmune reaction

$\Downarrow$
by promoting autoimmunity

لأنه $\rightarrow$

The end

☺