

Immunological aspects of neurological disorders

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Roba ❤️

Malak Alshaikhali

MD, Al-Quds University

MSc Integrated Immunology, University
Of Oxford.

The neuro-immune interaction

- The immune system plays a crucial role in maintaining the brain's health and function.
إنه الجهاز المناعي يلعب دور مهم جدا في الحفاظ على صحة الدماغ حتى يتمكن من القيام بوظائفه على أكمل وجه
- The immune cells within the nervous system and the blood-brain barrier (BBB) are essential for maintaining the brain's health and protecting it from potential threats.
- The neuro-immune systems are connected through the BBB that regulates the passage of cells and molecules into the CNS.

ينفصل ويتصل الدماغ عن الجهاز المناعي بواسطة الـ BBB الذي ينظم مرور المواد والخلايا من وإلى الدماغ

The neuro-immune interaction

- Dysregulation of the neuro-immune communications can lead to inflammation and damage within the nervous system- participates in the onset and progression of autoimmune neurological disorders.

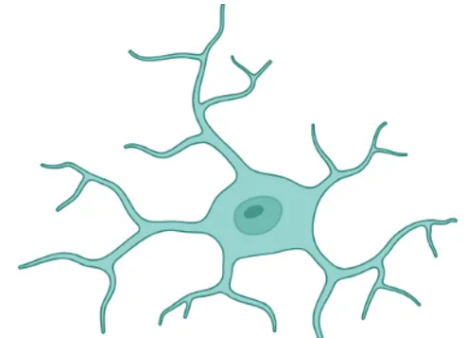
الذي يلحق الضرر يمكن أن يحدث نتيجة التنشيط الخلايا المناعية الفطرية والتكيفية داخل الجهاز العصبي المركزي
الذي يحتاجه هنا كمان شوي يلحق الضرر هي التصلب المتعدد أو الـ production of Ab الذي ما يحصل في الـ myasthenia gravis

- The types of immune cells in close relation with the nervous system include: microglia, macrophages, neutrophils, T-&B-cells.

بالتالي مهم نحافظ على العلاقة ما بين الـ 2 systems ، وعلى الـ balance فيما بينهم

Types could be innate or adaptive immune cells, also could be resident within the CNS like (microglia)

The neuro-immune interaction



Microglia

Origin, function and genetic profile of Microglia of the CNS differs from macrophages of other systems

- Microglia are the resident immune cells of the CNS, “the brain's macrophages”.

حيث كل system يحتوي على macrophages خاصة فيه،
تختلف بخصائصها ما بين جهاز و آخر

- About 10-15% of all cells in the brain.
- **Function:** monitor the brain's microenvironment, the first responders to any injury or infection, regulates synaptic pruning in childhood and immune-synaptic surveillance in adulthood.
- They become activated when infection or signs of damage- they release pro-inflammatory molecules to help clear pathogens and produce anti-inflammatory signals to limit inflammation.

يعني هاي الوظيفة بتكون في ال early life، حيث معنى synaptic pruning إنها تساهم في تكوين ال synapses.
و later في ال adulthood يحصل لوظيفتها shifting إنه بتتغير تحافظ و تحمي هاي ال synapses

حيث ال **origin of microglia** هو **fetal origin**, حيث يبدأ إنتاجها من ال yolk sac of fetus , و later يحصل production من many sites , لكن ال production تتبعها يبدأ من ال yolk sac و ال population وأكبر عدد منها يتم إنتاجه في ال fetal life

بينما ال other macrophages الموجودة في أماكن عديدة زي ال meninges وال choroid plexues أو around the blood vessels , هاي ال origin تتبعها بيكون من ال bone marrow (من ال monocytes يلي بتطلع من ال bone marrow)

بالنسبة لل microglia (كما يظهر بالصورة يلي فوق) هي عبارة عن خلايا لها تشعبات تساعد في وظيفتها

توضيح النقطة الرابعة/ إنه بعض هاي الخلايا بتكون inactive ويحصل الها تنشيط في حالات ال infection و زيها زي باقي خلايا ال innate cells, لما يصير لها تنشيط هتعمل upregulation لل antigen presenting molecule زي ال MHC, بالإضافة إلى إنها تحفز ال production of proinflammatory cytokines, حتى تساعد ال microglia في وظيفتها

The neuro-immune interaction

Perivascular Macrophages:

It differs from microglia genetically and phenotypically
حيث صحيح إنه ال microglia من ضمن ال macrophages
لكنها زي م حكيها لها خصائصها الخاصة فيها

- Found around blood vessels within the brain and contribute to the immune surveillance of the CNS.
Also may be found in the choroid plexuses and in the meninges
- They help regulate immune cell trafficking across the BBB and assist in maintaining the integrity of the BBB.
يعني تلعب دور مهم جداً في عملية تنظيم مرور ال molecules بين ال blood و ال CNS
إضافة إلى أنها تحافظ على ال integrity و ال continuity of BBB من خلال إنها تتخلص من
ال harmful substances و ال toxic mediators

The neuro-immune interaction

Neutrophils

مش موجودة بكثرة داخل ال natural healthy CNS

- Not abundant within the healthy CNS.
- They can infiltrate the brain to aid in immune responses during inflammation or infection.

تزيد وتظهر بكثرة في حالات ال infection وال inflammation, يعني هي مش من ال resident cells, وتتواجد داخل ال CNS فقط في ال abnormal situations أو لما يصير عنا مشكلة في ال BBB لكن بنفس الوقت لو تواجدت بكثرة أو حتى ضلت موجودة حتى بعد انتهاء ال infection, هادا ممكن يكون harmful لل CNS

The neuro-immune interaction

تأثيرات ال infection أو حالات ال autoimmune diseases, علماً أن وجودها في ال CNS رح يكون له effect
neurons, زي إنها بتعمل damage for neuron axons and myelin sheath, حسب طبيعة ال disease,
ث كل autoimmune disease هيكون فيه خلل معين, يلي بيساهم في حدوث ال diseases manifestations

T Cells and B Cells

Its adaptive immune cells, its not highly abundant in the CNS naturally
ووجودها بكثرة معناها صار عنا مشكلة

- T cells and B cells are among adaptive immune cells that can cross the BBB under **certain conditions**, especially when the BBB is compromised.
- In autoimmune neurological disorders like **multiple sclerosis**, activated T cells recognize myelin as foreign, leading to inflammation and demyelination.
- B cells can produce antibodies that target specific antigens within the CNS and contribute to autoimmune responses.

B cells may be activated peripherally(PNS) or within the CNS, and in the 2 states it will produce Ab inflammatory responses in ال neurons, وممكن تساهم في حدوث ال autoimmune diseases

Blood-Brain Barrier (BBB)

ال BBB موجود بشكل أساسي في ال CNS لكن برضو ممكن يتواجد في ال PNS,
يعني بشكل عام ال CNS محمي من ال contents of blood بواسطة ال Barrieres الموجودة

- The BBB is a term used to describe the highly specialized and selective barrier that separates the bloodstream from the brain and spinal cord.

حيث ال BBB هو collective term يعني هو شامل لأكثر من barreier يفصل ال brain وال spinal cord عن ال outer environment.

حيث ال hydrophobic molecule زي ال O_2 و ال CO_2 عادة بيغوتوا بشكل freely يعني diffusion لل membrane

- It is semipermeable membrane that prevents solutes in the blood from crossing into the ECF of the CNS.

ال blood vessels الموجودة في ال Brain يغلفها Endothelial cells, وهاي ال Endothelial cells
Tight junctions يلي بتساهم في تكوين ال Bbb, ويشترك معه في التكوين ال Processes of astrocytes

يعني مع بعض يعملوا على تشكيل physical and chemical barrier

يعني يسمح بمرور بعض المواد لكن بحذر ومش بكميات فارطة

Tight junction

يعني لا يسمحوا بدخول و تمرير ال hydrophilic molecule إلى داخل ال blood

Note :

أغلب ال nutrient تحتاج إلى special transporter حتى تخترق و تدخل عبر ال BBB

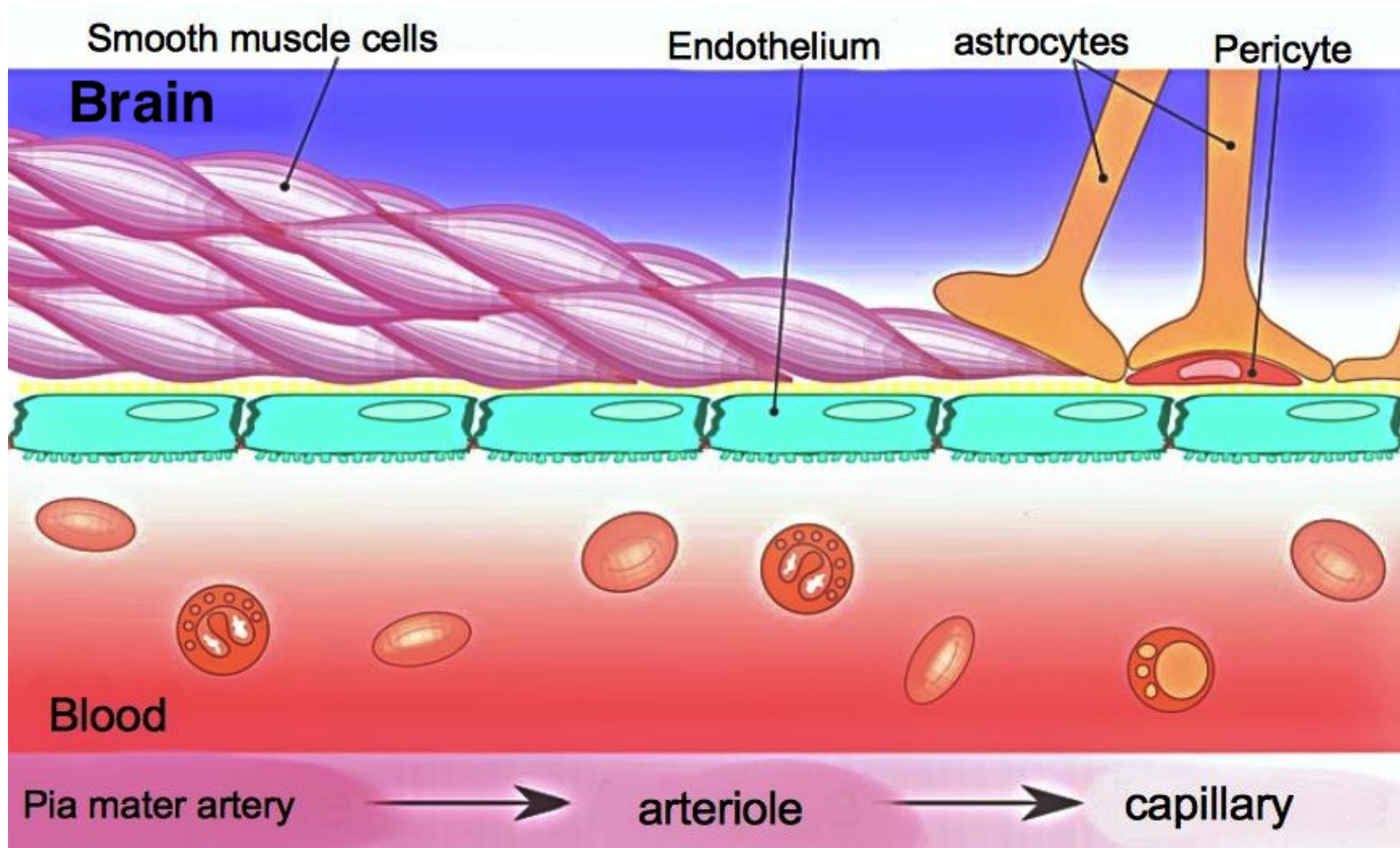
Blood-Brain Barrier (BBB)

هَذَا يَلِي اسْمَهُ ال proper BBB

- It is composed of endothelial cells lining the brain's blood vessels, astrocytes processes that surround the blood vessels, and pericytes (cells that wrap around the endothelial cells).
- Together, they create a physical and chemical barrier to control the entry of substances into the CNS.

لكن يوجد بعض ال sites التي تفصل ما بين ال blood circulation وال extracellular fluid of CNS زي ال choroid plexuses حيث ال tight junctions الموجودة ما بين ال epithelial cells of choroid plexuses حيث هادي بتشارك في المصطلح يلي بنحكي عنه ال bbb بالإضافة إلى ال tight junctions الموجودة بين ال epithelial cells of pia matter هادا كله يمثل أجزاء من ال bbb

Blood-Brain Barrier (BBB)



حكيانا لا تسمح بمرور معظم ال **solutes into the CNS** ويوجد **selective passage** لأغلب ال **solutes** و ال **molecules** حيث عامةً ال **large molecules** ما بتفوت من خلال ال **bbb** بينما تتمكن ال **small** من ذلك زي ال **nutrients** عن طريق **transporter** و **mechanisms** خاصة فيها.

Blood-Brain Barrier (BBB)

Functional and physical characteristics:

- **Tight Junctions:** The endothelial cells in the BBB are tightly connected through tight junctions, forming a continuous barrier that restricts the passage of most large molecules and immune cells from the bloodstream into the brain.
- **Transport Mechanisms:** The BBB employs various specialized transport mechanisms to selectively allow essential nutrients and molecules to pass through while preventing potentially harmful substances from entering the CNS.

في حال حصل **infection** في مكان ما من جسم الإنسان، حينئذ **chemical mediator** حيث هاي ال **mediators** ما رح تنتقل من ال **blood** لل **CNS** بسهولة و ذلك بفضل ال **bbb**

Blood-Brain Barrier (BBB)

- **Efflux Pumps:** The BBB also contains efflux pumps that actively pump certain substances back into the bloodstream, further enhancing its protective function. حيث ال metabolites وال harmful substances الناتجة من ال brain يحصل لها pumping لل blood stream
- **Immune Privilege:** The BBB plays a crucial role in creating an "immune-privileged" environment within the CNS. It helps regulate the entry of immune cells and immune molecules into the brain, limiting immune responses and inflammation and insulating the CNS from peripheral immune events.

يعني ال bbb بيخلي ال immune system كأنه **privilege site**، يعني أماكن بتكون **partially protected from the immune system**، حيث ال bbb يمنع عبور غالبية ال **chemokines** وال **chemical mediators** وال immune system لل CNS tissues يعني هو تقريباً اشتغل كعازل لل CNS من ال **peripheral immune system**

The nervous system and autoimmunity

- Autoimmune neurological disorders are a group of conditions in which the immune system mistakenly targets and attacks components of the nervous system, leading to inflammation and damage.
- They can affect the CNS or the PNS.
- They can be demyelinating or non-demyelinating lesions.

يعني يحصل **attack** على ال **myelin sheath** ويحصل
تعرية لل **neurons**

يعني لا تؤثر على ال **myelin sheath** لكن تؤثر على ال **nerve** مباشرة أو على ال **axons of nerve** مباشرة

The nervous system and autoimmunity

- Common autoimmune neurological disorders include:
 - Multiple Sclerosis- affects CNS
 - Guillain-Barré Syndrome- affects PNS
 - Myasthenia Gravis- Affects PNS (non-demyelinating)

Multiple sclerosis (MS)

- Multiple sclerosis (MS) is an autoimmune neurological disorder characterized by chronic inflammation, demyelination, and axonal damage in the central nervous system (CNS).

حيث كنا حاكين إنه ال myelin يساهم في ال impulse and signal transduction

- This demyelination disrupts nerve signaling and leads to a wide range of neurological symptoms, such as fatigue, muscle weakness, balance problems, and vision disturbances.

Due to affection of optic nerve

بتكون variant, حيث ممكن تيجي ست بhand muscle weakness, ضلت فترة و راحت, رجعت صارت معها بال leg

- It mainly effect females
- Multiple sclerosis is mainly prevelant in white,females, young ages,also in cold weather countries

يعني لو بده يجي سؤال case هيجي إنه ست كانت عايشة في مكان بارد وصار عندها neurological symptoms like muscle weakness, sensory deficit

Multiple sclerosis (MS)

- The characteristic feature of MS is the formation of demyelinated lesions or plaques within the CNS.

White areas with a density that differs from the surroundings' density, can be seen by the MRI

- These lesions can be observed in various regions of the brain and spinal cord and are typically detected by MRI scans.

كيف تكونت ال plaques ؟

هلقيت مع ال inflammation يلي حصل هيصير في عنا demyelination, و في ميزة في ال MS إنه ممكن المرض يروح و يجي يعني relapsing and remitting, في فترات ال relaps يعني لما المرض active رح يصير عنا demyelination وفي فترات ال remission هيحاول الجسم يعمل repair يعني remyelination لكن مهم نعرف إنه قدرة الجسم يعمل remyelination بتكون كثير limited حيث ال myelination بالأساس يحصل early in life وإذا صار demyelination صعب يصير full remyelination لكن يعني يحدث في بعض الحالات و بيغطي على ال neurological weakness يلي بيصير لكن مع التكرار بتقل إمكانية حدوث عملية ال remyelination

Multiple sclerosis (MS)

يمكن تقسيم ال progressive إلى primary و secondary :

Primary : خالص remission من أول ما بدأ وهو في تصاعد و ازدياد وما صار

وهو one of the most serious presentation of multiple sclerosis

بينما secondary يبدأ ك relapsing and remitting ثم يتحول إلى progressive بعد فترة و يصير يتزايد و ما في remission

• The pattern of illness is difficult to predict: chronic and progressive, or relapsing and remitting.

اختفاء الأعراض بعد ظهورها

- The progressive form of the disease leads to disability.
- It affects any age, but predominantly the young.
- Has a 2:1 female predominance.
- Clinical presentations are highly variable and include visual disturbance (optic neuritis), ataxia, weakness, and sensory signs, which usually resolve completely over a few days, at least in initial attacks.

رُي ما حكينا عن ال remission

Multiple sclerosis (MS)

- The exact cause of MS is not fully understood, but it is thought to involve a combination of genetic susceptibility and environmental triggers.
- Infections can be one of the possible triggers.

Multiple sclerosis (MS)

Immunogenetics

- MHC susceptibility loci have been identified, although these differ in different racial groups.
- DR2, DQ1, and DQ6 seem to be particularly important- DRB1*1501 is the strongest HLA association.
- Other genetic susceptibility loci are located on chromosomal regions 19q35 and 17q13.
- Monozygotic twin concordance is only 25–30%.

هدول الجينات الموجودة على ال MHC molecule

مش نسبة عالية

هدول جينات موجودة على كروموسومات و ليس على ال MHC molecule

Multiple sclerosis (MS)- Immunopathogenesis

- The cause of MS is unknown, although there are strong indications that it is triggered by infection.
- The immune system mistakenly recognizes components of the CNS, specifically myelin, as foreign and mounts an immune attack against it.
- The disease seems to involve abnormal T cells reactive to myelin basic protein MBP- a component of the myelin sheath.

يعني هادا البروتين خصوصاً يهاجم من قِبَل الجهاز المناعي، و يُعامل
كأنه antigene

Multiple sclerosis- Immunopathogenesis

T cell من أهمية ال
هان ممكن نحكي عن المرض
T cell mediated إنه
autoimmune disease

Its one of main player in this
condition
يعني هي أهم وحدة تقريباً في ال
pathogenesis of disease

يعني بداية ال activation لل immune
cells تحصل في ال PNS وليس في ال CNS

- Activation of immune cells, such as T cells and B cells, ^{يحصل within} within the peripheral immune system triggers their entry into the CNS across the BBB.
- The exact mechanisms that enable this entry are not fully understood, but it is thought to involve cytokines and chemokines that attract immune cells to the CNS.
- Once within the CNS, these immune cells become activated and initiate a cascade of inflammatory responses.

Multiple sclerosis- Immunopathogenesis

Note:

كان دور ال T cells واضح لما عملوا
animals studies , حفزوا ال MS عند
ال mice , فلما أخذوا ال T cells
الموجودة عند هاي الفئران المصابة
ونقلوها لفئران سليمة، وجدوا إنه
الفئران السليمة بيصير عندهم
manifestations of disease
تأكدوا إنه هادا ال disease بيكون
mediated بواسطة ال CD4+ T cell
وبتلعب دور كبير جداً في ال
pathogenesis تبعه

Role of T cells:

- CD4+ T helper cells play a central role in MS immunopathology.
- Animal studies show that the disease can be transferred with CD4+ T cells.
- Th1 and Th17 cells are considered to be key contributors to the inflammatory response.
- The disease seems to involve abnormal T cells reactive to the MBP.
- Local macrophages and microglia are involved- they release inflammatory cytokines and upregulate MHC class II antigens presentation.

With cytokines released by these cells which will be proinflammatory cytokines which will cause activation of macrophages and other immune cells like microglia and other innate immune cells in CNS, also these activated immune cells will play a role in inflammation by production of other cytokines and upregulation for antigen presenting cells so more presentation of antigens for autoreactive T cells

Multiple sclerosis- Immunopathogenesis

- Th1 cells produce pro-inflammatory cytokines such as IFN- γ and TNF- α , promoting inflammation and activating macrophages.
- Th17 cells produce IL-17 and IL-22, which further promote inflammation and recruit additional immune cells.
- These pro-inflammatory cytokines lead to the recruitment and activation of other immune cells such as B cells and plasma cells.

ال T cells بدورها رح تعمل تنشيط لل B cells، وهاي ال B cells رح تنتج Ab ضد ال myelin components زي ال MBP، أو حتى ضد ل glycoproteins الموجودة في ال myelin، هاي ال Ab مش موجودة في كل الحالات ولو تواجدت فهي تساهم في ال demyelination من خلال إنهم بيعملوا activation لل complements ولل ADCC.

يعني ال ab ترتبط بال cytotoxic cells وبتكون زي المفتاح يلي يعمل على تشغيلها، وال cytotoxic cells بدورها بتعمل damage for nerves
Note: CSF of patient with multiple sclerosis may have brain attack complexes so activation of complement system within the CNS mainly by antibodies so demyelination and damage of nerves will occur

Multiple sclerosis- Immunopathogenesis

- Activated B cells produce antibodies against myelin components, such as MBP and myelin oligodendrocyte glycoprotein (MOG).
- These antibodies can contribute to demyelination through various mechanisms, including complement activation and antibody-dependent cell-mediated cytotoxicity (ADCC)-CSF may contain membrane attack complexes of complement.

Multiple sclerosis- Immunopathogenesis

destruction of signaling due to demyelination and disruption of nerves. ال end result of these processes ال عملية ال متكررة ومستمرة حيصير inflammation

Demyelination and Axonal Damage :

- The immune attack against myelin leads to destruction of the myelin sheath surrounding nerve fibers in the CNS.
- Demyelination disrupts nerve conduction and communication between nerve cells, leading to neurological symptoms such as muscle weakness, coordination problems, and sensory disturbances.
- The inflammatory environment, coupled with the release of toxic molecules by immune cells, can also directly damage axons, leading to axonal degeneration.

Multiple sclerosis (MS)

ما في test معين خاص بال MS

- **Diagnosis:** clinical presentation + investigations.
- There is no specific diagnostic immunological tests.
Its characteristic but not specific
- Helpful tests include: CSF proteins and IgG level, CSF oligoclonal IgG bands, MRI showing typically placed demyelinating lesions. + plaque formation
- **Management:** High-dose steroids in acute attack, immunomodulatory drugs e.g. β -interferon and Glatiramer for relapsing-remitting type. + monoclonal ab

في عنا اشي McDonald criteria يلي هي بتشترط إنه هاي ال lesions يلي شفنائها على ال MRI و ال neurological deficit يلي شفنائها عشان أحكي إنها MS لازم هاي ال lesions تكون disseminated through time and space يعني على ال MRI تكون موجودة في أماكن متفرقة و مختلفة من ال brain وال spinal cord (هادا بالنسبة لل space) أما بالنسبة لل time ف إنه تكون ظهرت هاي ال symptoms في أوقات متفرقة يعني المريض بيجيني مرة عندها weakness in Rt arm ثم يختفي، بترجعلي جايلها في ال left

هدول بيعملوا down regulation for T cell activation، ولل production of inflammatory cytokines
بالتالي تقليل تنشيط ال activation of innate immune cells

Neuromyelitis optica (NMO)

It's one of the rare autoimmune diseases

- Devic's syndrome (neuromyelitis optica) comprises attacks of optic neuritis (optic nerve) and myelitis (spinal cord).

يمكن نتلخبط بينه و بين ال MS لكن الفرق فيما بينهم إنه الأماكن المتأثرة بالمرض تختلف بين المرضين

- Unlike MS, there is no brainstem, cerebellar, or cognitive involvement.

- Seen mainly in Asians and Africans, but not Caucasians.

- Can be triggered by varicella or HIV infection.

With other autoimmune diseases

- Associations: SLE, Sjögren's syndrome, P-ANCA+ vasculitis, or mixed connective tissue disease.
- Autoantibodies to aquaporin 4 (channel for water transport in astrocytes) are frequently found-

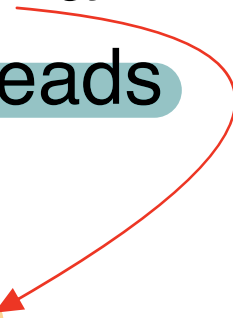
diagnostic. وجود هاد ال ab يعتبر

يلي بيصير إنه الجسم بيعمل ab ضد ال aquaporin 4 channels

Stiff Person Syndrome (SPS)

- SPS is a rare autoimmune disorder that affects the CNS and causes muscle stiffness and spasms, primarily involving the axial muscles of the trunk.
Its manifestation is mainly motor and rarely have sensory or autonomic symptoms
- The immune system produces antibodies that target an enzyme called glutamic acid decarboxylase (GAD), which is involved in the production of a neurotransmitter called gamma-aminobutyric acid (GABA). The loss of GABA leads to increased muscle tone and stiffness.
And spasms

Its important for inhibition



Guillain-Barré syndrome (GBS)

- Guillain-Barré Syndrome is an autoimmune disorder of the PNS characterized by acute inflammation and demyelination of peripheral nerves.
- It is primarily an immune-mediated disease triggered by infections, typically viral or bacterial, and in some cases, it can also be triggered by vaccinations or other factors.
- It frequently follows 1–3 weeks after infection, particularly with *Campylobacter jejuni*.

يعني يلي بيصير فيها هو

بتبدأ تظهر الأعراض خلال ههاي الفترة، مثل ال gastroenteritis , بعدها بأسبوعين ل ٣ أسابيع بيصير عنده weakness على هيئة ascending paralysis, يعني ال weakness بيبدأ من ال lower limb وبيطلع لفوق

Guillain-Barré syndrome (GBS)

يعني خلال ساعات قليلة ممكن يصير عنا paralysis ويوصل لل respiratory muscles و ال bulbar muscles

- Begins with ascending weakness, which may progress with alarming rapidity and involve bulbar and respiratory muscles, including the diaphragm, leading to respiratory failure- **acute Inflammatory Demyelinating Polyneuropathy (AIDP)**.
But it's mainly motor
- Sensory symptoms are mild. *It's the most common classical presentation for the disease, but not the only one*
- There may be marked autonomic instability.
- Demyelination may progress for up to 4 weeks before remyelination begins.

ال disease يمر بمراحل، ال acute phase ممكن يكون خلال ٤ أسابيع ويكون عنا active demyelination of neurons.
بعد هيك بمرحلة ال progression بيوقف ال demyelination لكن ما في recovery, ثم بعدها يبدأ ال recovery.

Guillain-Barré syndrome (GBS)

- There are a number of variants to the classical presentation and progression (AIDP) including:
 - Acute motor axonal neuropathy. AMAN syndrome
 - Acute motor sensory axonal neuropathy. AMSAN syndrome
 - Miller Fisher variant with ophthalmoplegia,
ataxia, and areflexia. ¹
² ³ Less common, it's a triad of symptoms, and it's the most benign variant, which has a high recovery rate

damage mainly in axons not in myelin sheath في هذول ال syndromes يكون ال
guillain barre syndrome لكن الأعراض هتكون مشابهة لل

Guillain-Barré syndrome- immunopathology

Respiratory and gastroenteritis infections (caused
by enterbactericeia)

- The exact trigger for GBS is not always clear, but it is believed to be initiated by an immune response to an infection or other external factors.
- In response to the triggering event, the immune system becomes activated, leading to the production of antibodies and the recruitment of immune cells, such as T cells, B cells, and macrophages, to the peripheral nerves.

And mistakenly attacks its own component or the antigen presented on peripheral nerves

يعني ال immune cells يلي مفترض تهاجم البكتيريا أو ال pathogen بتروح بتهاجم ال antigens الموجودة في أنسجة الجسم

Guillain-Barré syndrome- immunopathology

يعني structerly يوجد تشابه ما بين ال antigens of pathogen و ال components of periphral nerves

Molecular Mimicry is one of the leading theories explaining GBS pathogenesis:

- Infections can produce molecules that share structural similarities with components of the peripheral nerves.
- E.g lipopolysaccharides from C.jejuni cross-reacts with glycolipids from peripheral nerves membranes.
- Antibodies generated against the infecting pathogen can cross-react with nerve components, leading to the immune system mistakenly attacking the peripheral nerves.

Guillain-Barré syndrome- immunopathology

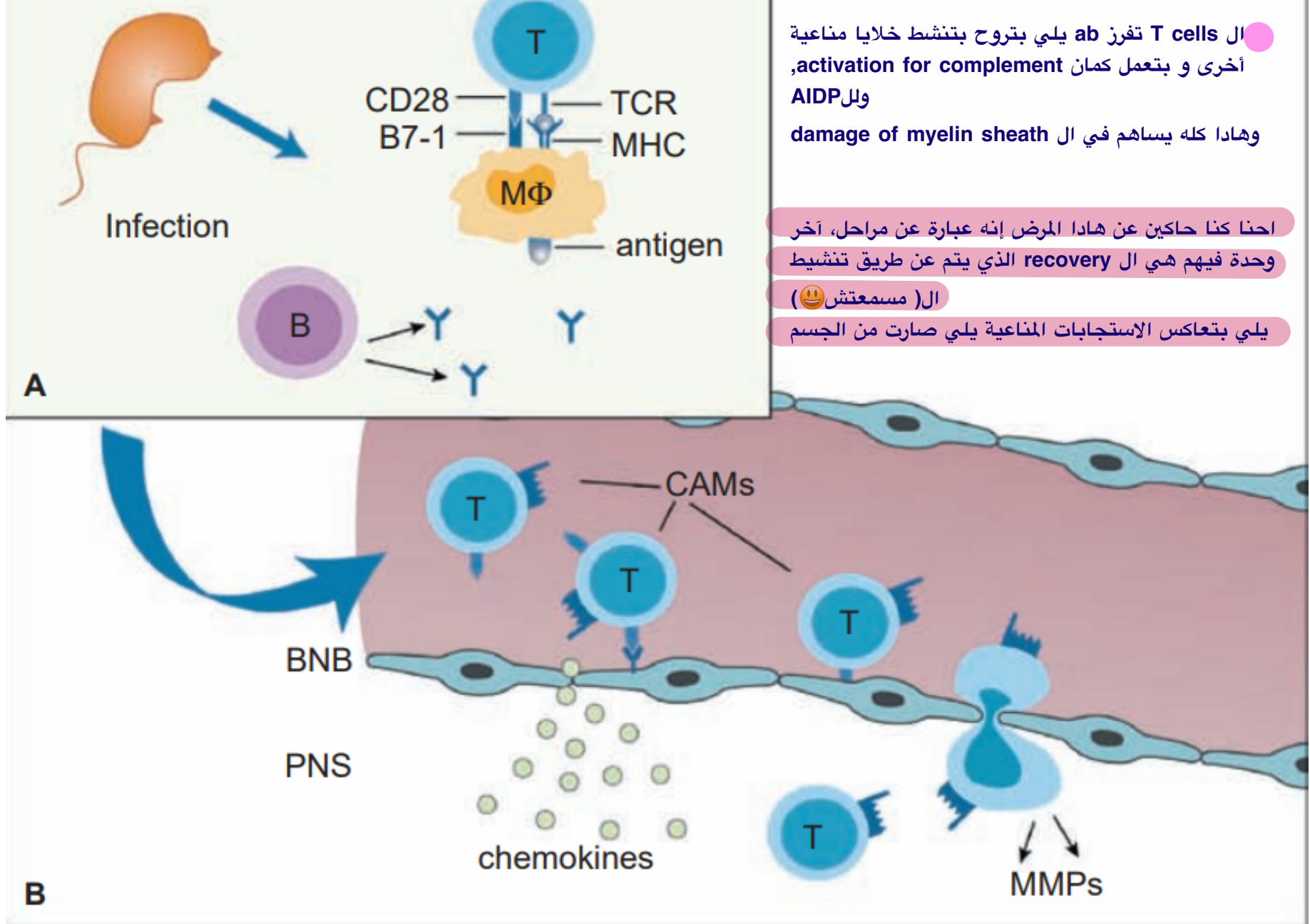
Activation of immune cells:

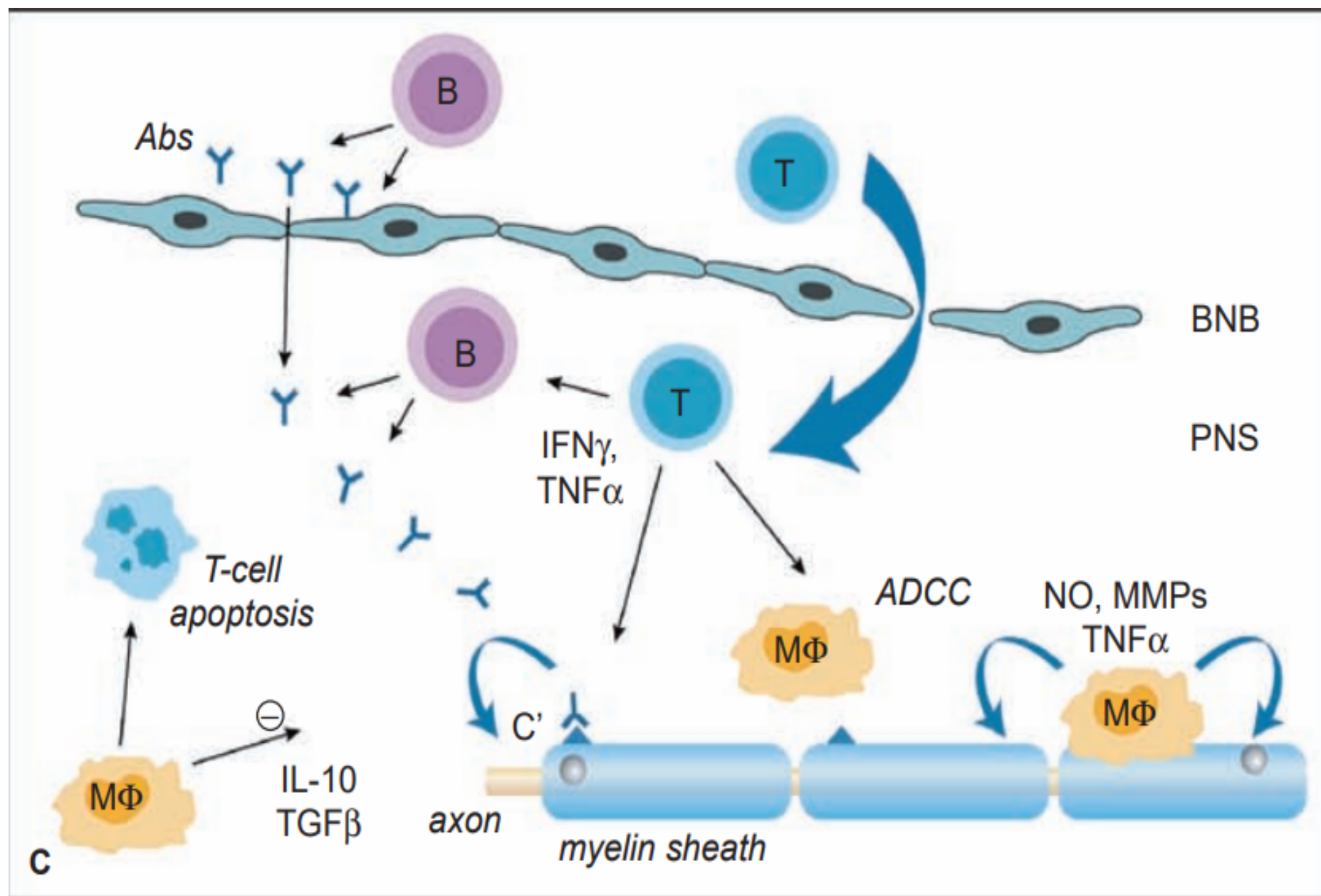
يعني بعد ما يتم تنشيطها رح تروح و تخترقهم

- T-cells becomes activated and infiltrate peripheral nerves.
- They produce pro-inflammatory cytokines (e.g IFN- γ &IL-17), recruit and activate other immune cells including B cells.
- B cells produce antibodies that target the peripheral nerves and contribute to inflammation and nerve damage.

التوضيح:

هلاً صار ال infection, فتم تنشيط ال T cells يلي بدورها نشطت ال B cells, بعدين التنتين بيروحوا بيخترقوا ال barreir of nerves بيدخلوا تحت تأثير ال chemokine على ال receptor, وبورهم رح يعملوا على تنشيط خلايا مناعية أخرى زي ال macrophages يلي بتروح بتعمل phagocytosis لخلايا ال myelin sheath





Guillain-Barré syndrome-immunopathology

Autoantibodies

- Antibodies to membrane gangliosides (glycolipids including GM1, LM1, and GD1b)- found in up to 40% of patients with GBS. Found mainly in non classical variant
- These antibodies interfere with nerve conduction and can activate phagocytes via IgG receptors. Presented on surface of phagocytes
- Anti-GM1 antibodies are known to cross-react with lipopolysaccharides from C.jejuni.
- Other antibodies: Abs to GQ1b are present in 90–100% of cases of the Miller Fisher variant (specific for this condition)- possibly related to the very high expression of this antigen in the third cranial nerve. And diagnostic to it

Guillain-Barré syndrome- immunopathology

Nerve Demyelination and Axonal Damage :

- The immune attack on peripheral nerves in GBS can lead to two main patterns of nerve damage:
 - **Demyelination:** The classical form seen in AIDP variant of GBS, the immune system primarily targets and damages the myelin sheath, leading to slowed nerve conduction and sensory-motor deficits.
 - **Axonal Damage:** In the axonal variants, such as AMAN and AMSAN, the immune attack predominantly affects the axons, resulting in more severe motor deficits.

Guillain-Barré syndrome (GBS)

من الشغل المهمة التي لازم اسألها لمريض جاييني ب weakness وهذا ال weakness كان progressing within few days, لازم اسأله هل كان عندك خلال ال ٤ أسابيع الماضية أي gastrointestinal infection

- **Diagnosis:** clinical evaluation by history and examination and clinical investigations.
- Nerve conduction studies, lumbar puncture, MRI and serological tests for autoantibodies e.g anti-ganglioside and anti-GQ1b antibodies.
- **Management:** plasmapheresis or hdIVIg- equally effective if started early.
- **Prognosis:** favourable, recovery may be very prolonged.

Done for exclusion of other diseases

Must be given as soon as possible to prevent progressive damage

Good prognosis, 75-80% of patients will be full recovered

10-15% of cases will be severe, and the progression is very

rapid

So may have respiratory failure which could be lifethreatning, and if lived they will have many residual deficit (in muscles< bladder, respiratory muscles)

ما بعطي steroids خالص في ال GBS لأنه في الحالات بيزيد الوضع سوءاً وما بيحسن، لكن في حالات ال chronic inflammatory neuropathy هاي تعتبر variant من ال GBS (acute)

هان بيصير relapsing and remitting و frequent attacks وعادةً ما بيكون في

عوامل مسببة و سابقة، هдол بستخدم الها ال steroids.

عوامل مسببة و سابقة، هдол بستخدم الها ال steroids.

Myasthenia gravis (MG)

- Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by muscle weakness and fatigue, especially during repetitive use.

يعني الأشخاص هدول في بداية اليوم وضعهم بيكون تمام، لكن مع الحركة والنشاط و الاستخدام بيصير decline for muscles tone

- It leads to muscle weakness and fatigue, particularly in the muscles controlling eye movements, facial expressions, and swallowing.

So the patient may come with diplopia

هاي الأعراض تظهر مع الحركة و النشاط خلال اليوم

Myasthenia gravis (MG)

- In MG, the immune system produces antibodies that target and interfere with acetylcholine receptors on muscle cells, disrupting nerve impulses to muscles and impairing their function.
- It is a heterogeneous condition with varying ages of presentation. يعني ال presentation تبع المرض بيكون مختلف بين الأشخاص
- Prevalence is 2–10/100 000. إنه ممكن تيجي في أي عمر

Myasthenia gravis (MG)

Immunogenetics

- In younger patients there is an association with HLA-A1, B8, and DR3.
- There is strong female predominance.
- Disease can also be induced by penicillamine, and is mostly found in those who are HLA-Bw35/DR1 positive.

A type of medication

الناس يلي عندهم هادا النوع من الجينات هم الأكثر عرضة
انه يصير معهم المرض لو اخدوا penicillamine

Myasthenia gravis (MG) and the thymus gland

- The cause of MG is unknown but the disease is strongly associated with thymic disorders e.g thymomas, thymic hyperplasia, and other autoimmune diseases such as SLE, polymyositis, haemolytic anaemia, and thyroid disease (especially in those <40 yrs)
- The thymus plays a critical role in MG immunopathology.
- It is involved in the production and maturation of T cells- crucial in the immune response.

By

Myasthenia gravis (MG) and the thymus gland

- The thymus is hyperactive in many MG patients, and in some cases, it contains abnormal structures called thymic follicles, where B cells (that produce the AChR autoantibodies) and T cells interact.
- Approximately 70% of MG patients have thymic abnormalities, and about 10% have a thymoma.

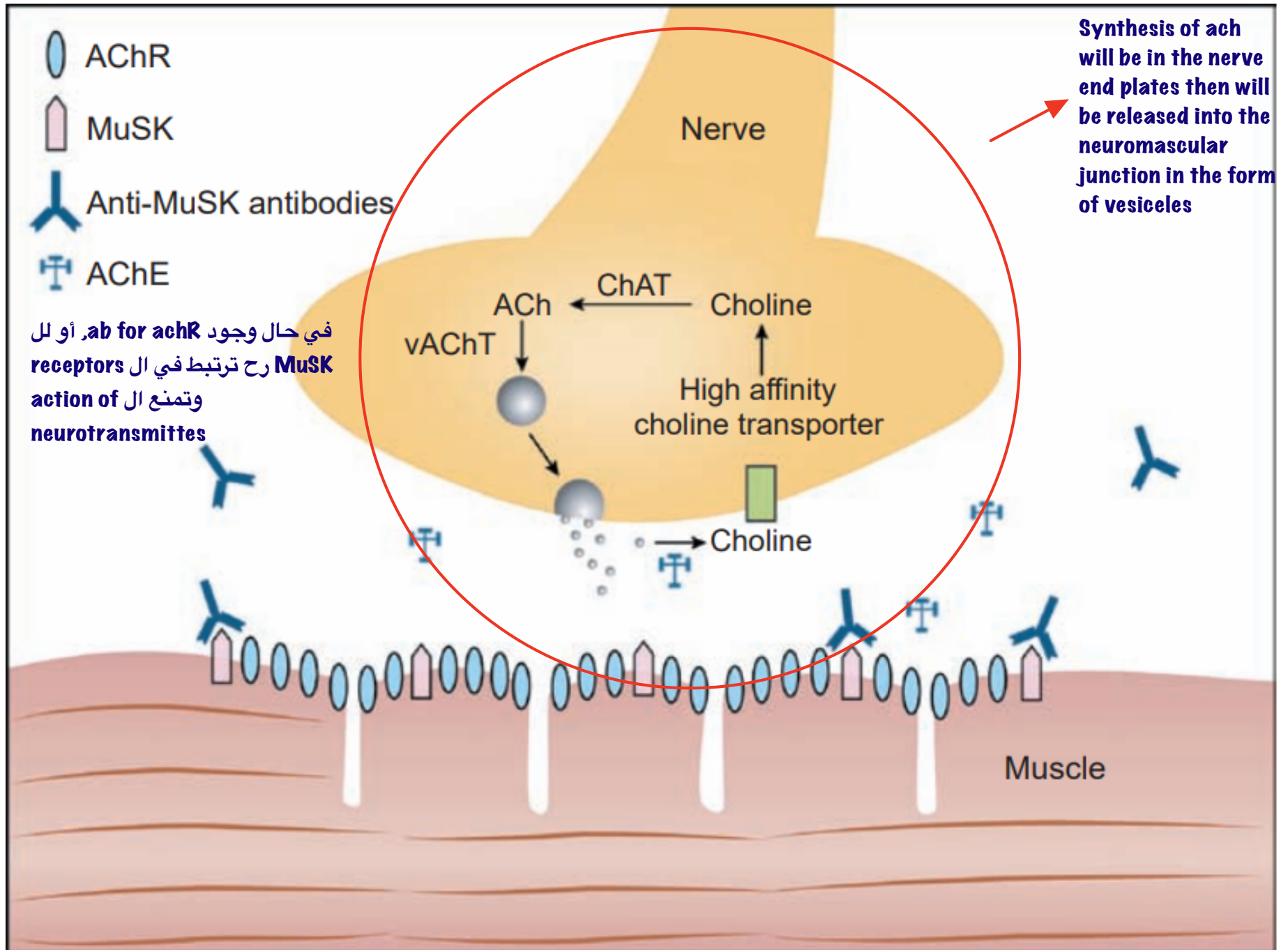
Myasthenia gravis (MG) and the thymus gland

- Patients with thymoma are usually older and both sexes are affected equally.
- Removal of the thymoma does not always affect the course of the disease. يعني لو شلنا ال thyroid من عندهم غالباً ما رح يتحسنوا
- The thymic abnormalities suggest a breakdown in the normal process of T cell selection and regulation, leading to the production of self-reactive T cells that contribute to the autoimmune response against AChRs. في أسباب عديدة لهادا الكلام، أحدها إنه صار تنشيط وخلص للخلايا المناعية، إنه ما هيأثر كثير لو شلتها

Myasthenia gravis- Immunopathology

- The underlying immunopathology of MG involves an abnormal immune response targeting the neuromuscular junction, the specialized region where nerves communicate with muscles.
 - 90% of cases have these antibodies
 - So 10% of cases will be seronegative for these ab, لكن ممكن ab against muscle tyrosin kinase receptors نلاقي عندهم
- Autoantibodies against the Acetylcholine Receptor (AChR) are found in the majority of cases.
 - Ab against other types of receptor within the neuromuscular junction called muscle specific tyrosin kinase receptor
 - هدول ال receptors بيكونوا specific لل neuromuscular junctions وظيفتهم تتمثل aggregation for these receptors support for AchR في ال طريق إنها بتعمل
 - يلي هو لازم حتى تعمل هاي ال receptors وظيفتها

This is a neuromuscular junction



Myasthenia gravis- Immunopathology

نوع ال **ab** غالباً يكون **IgG** ويكون موجود في ٧٥-٩٥٪ من الحالات زي ما حكينا من شوي

Autoantibodies

- IgG anti-ACh-receptor (AChRAb) are detected in 75–95% of patients.
- 10% are seronegative.
- 50% with pure ocular myasthenia are seronegative.
- The disease is caused by direct receptor blockade, complement-mediated endplate damage, and enhanced recycling of the receptor off the endplate surface membrane. **So, Reduction in the number of receptors or destruction and blocadge of it**
- AChRAb levels are variable, but high titres are found in those <40 yrs with thymic hyperplasia.

Myasthenia gravis- Immunopathology

هـيظهر عند ال baby أعراض المرض، لكن مجرد ما تنتهي ال life span of IgG رح تختفي الأعراض، لأنه
هو معندوش المرض، إنما انتقلت الـ IgG من مامته

IgG

- Antibodies can be transmitted across the placenta, causing neonatal myasthenia. **It's a Transiant condition**
- The presence of striated muscle antibodies is a marker for the presence of a thymoma.
- These include antibodies to the ryanodine receptor and titin antibodies.
- Cardiac arrhythmias may occur in the presence of anti-cardiac muscle antibodies. **A Type of muscle weakness caused by myasthenia**



Myasthenia gravis- Immunopathology

- Antibodies to MuSK (muscle-specific tyrosine kinase) are found in 5-8% of MG cases especially patients with AChRAb negative MG.
- MuSK is a receptor tyrosine kinase that is restricted to the neuromuscular junction- it participate in the clustering and stability of AChRs at the neuromuscular junction.
- Antibodies to MuSK interfere with agrin-triggered stimulation of MuSK- thus disrupt the function of MuSK, leading to impaired AChR clustering and reduced neuromuscular transmission.
- Patients with these antibodies are typically female, with bulbar disease, who may be difficult to treat with immunosuppression.

→ Muscle of sawllowing are affected

Myasthenia gravis- Immunopathology

- AChRs are essential for transmitting nerve impulses from motor neurons to muscle fibers, allowing muscle contraction.
- In MG, these autoantibodies interfere with the normal function of AChRs by either blocking the receptor or promoting its internalization and degradation, leading to a reduction in the number of functional AChRs at the neuromuscular junction.

Myasthenia gravis- Immunopathology

- Reduced numbers or dysfunctional AChRs result in weaker nerve impulses reaching the muscle fibers, leading to muscle weakness and fatigue.
- The degree of muscle weakness can fluctuate, ^{Throughout the day} worsening with activity and improving with rest- a characteristic feature known as **fatigability**.
- The binding of autoantibodies to AChRs triggers the activation of the complement system, leading to inflammation and damage at the neuromuscular junction.

في ال tensilon test يعطوا مادة اسمها edrophonium يلي هي anticholinergic يعني يمنع تكسير ال ach بالتالي يزداد تركيز وتواجد ال ach في النوروماسكيولار جنكشن فبيصير زي تنافس بينه ال ach وال ab فبتحسن الأعراض وتقلل ضعف العضلات لكن ما بيعملوا ال test هاد كثير لأنه أعراضه الجانبية كتيرة

Myasthenia gravis (MG)

- **Diagnosis:** Diagnosis of a neuromuscular junction defect can be confirmed by electrophysiological tests and the Tensilon test.
- Tests for diagnosis: Tensilon (edrophonium) test, AchRAb, striated muscle antibodies, MuSK antibodies.
- Test for monitoring AchRAb. الأشخاص يلي بياخدوا علاج بنستخدم الهم هاي الاشبي عشان نشوف هل هناك استجابة للعلاج أم لا
- **Treatment** for MG typically involves immunomodulatory therapies, such as corticosteroids, immunosuppressive agents, and therapies that target B cells, to suppress the autoimmune response and improve neuromuscular transmission.



one day
you'll
see why
God made
you wait