

Immunological aspects of neurological disorders

Malak Alshaikhali
MD, Al-Quds University
MSc Integrated Immunology,
University Of Oxford.

Learning outcomes

Overview of the neuro-immune systems interactions and the blood brain barrier

Understand the mechanism of common autoimmune conditions affecting the nervous system.

Understand the immunopathology of multiple sclerosis, Guillain-Barré syndrome, myasthenia gravis, and other conditions affecting the nervous system.

The neuro-immune interaction

The immune system plays a crucial role in maintaining the brain's health and function.

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.

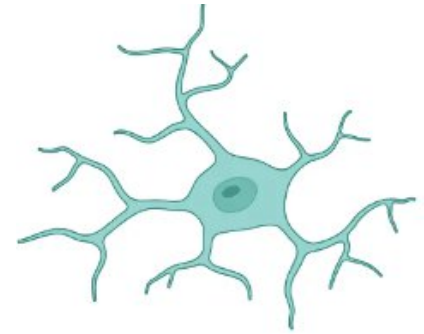
The neuro-immune systems are connected through the BBB that regulates the passage of cells and molecules into

The 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.

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

The neuro-immune interaction



Microglia

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

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.

The neuro-immune interaction

Perivascular Macrophages :

Found around blood vessels within the brain and contribute to the immune surveillance of the CNS.

They help regulate immune cell trafficking across the BBB and assist in maintaining the integrity of the BBB.

The neuro-immune interaction

Neutrophils

Not abundant within the healthy CNS.

They can infiltrate the brain to aid in immune responses during inflammation or infection.

The neuro-immune interaction

T Cells and B Cells

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.

Blood-Brain Barrier (BBB)

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

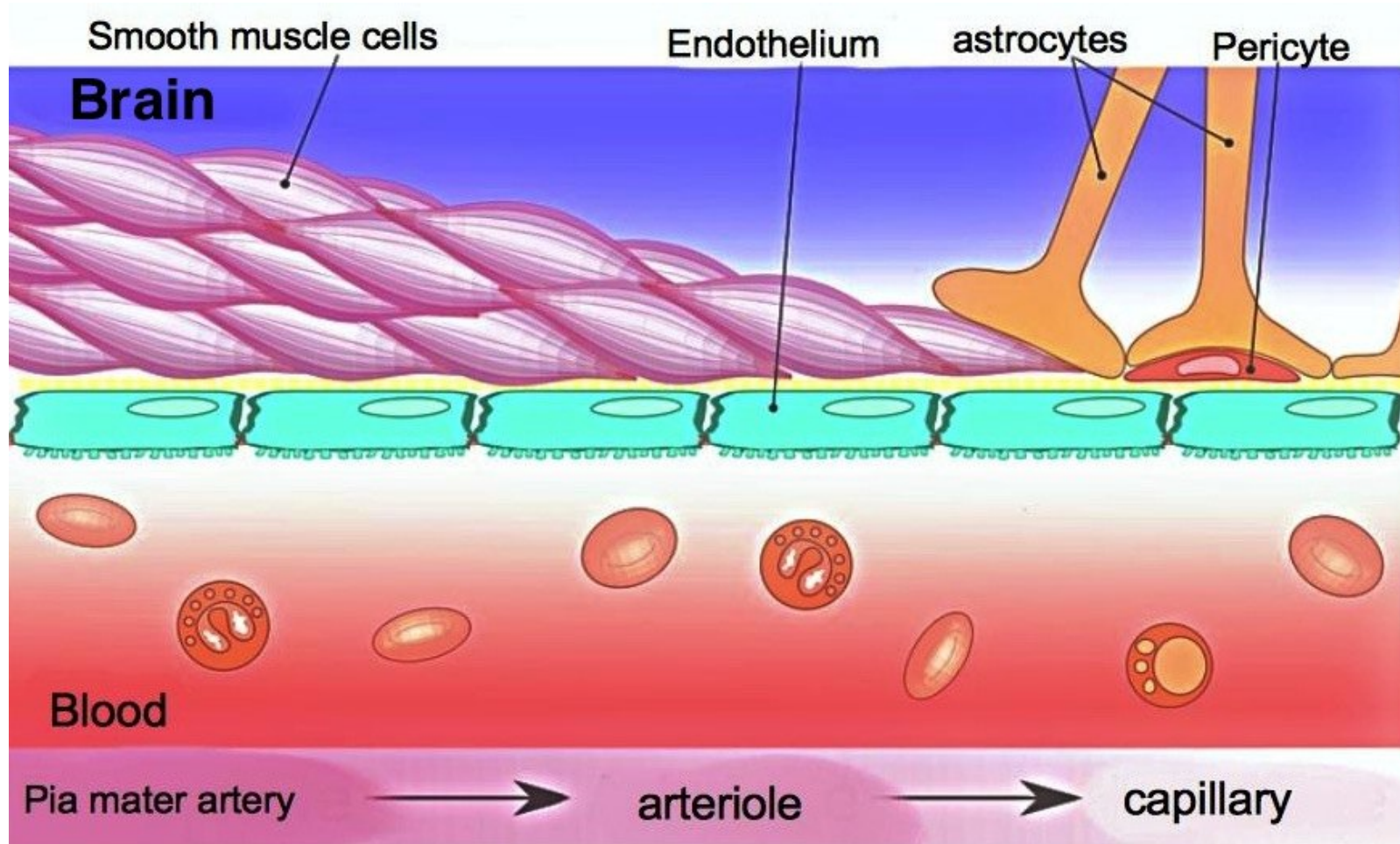
It is semipermeable membrane that prevents solutes in the blood from crossing into the ECF of the CNS.

Blood-Brain Barrier (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.

Blood-Brain Barrier (BBB)



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.

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.

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.

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.

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).

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

Multiple sclerosis (MS)

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

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

Multiple sclerosis (MS)

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

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.

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%.

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.

Multiple sclerosis- Immunopathogenesis

Activation of immune cells, such as T cells and B cells, 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

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.

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.

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

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)

Diagnosis: clinical presentation + investigations.

There is no specific diagnostic immunological tests.

Helpful tests include: CSF proteins and IgG level, CSF oligoclonal IgG bands, MRI showing typically placed demyelinating lesions.

Management: High-dose steroids in acute attack, immunomodulatory drugs e.g. β -interferon and Glatiramer for relapsing-

Neuromyelitis optica (NMO)

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

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.

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.

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.

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.

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*.

Guillain-Barré syndrome (GBS)

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).

Sensory symptoms are mild.

There may be marked autonomic instability.

Demyelination may progress for up to 4 weeks before remyelination begins.

Guillain-Barré syndrome (GBS)

There are a number of variants to the classical presentation and progression (AIDP) including:

- Acute motor axonal neuropathy.

Acute motor sensory axonal neuropathy.

Miller Fisher variant with
ophthalmoplegia, ataxia, and areflexia.

Guillain-Barré syndrome- immunopathology

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.

Guillain-Barré syndrome-immunopathology

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.

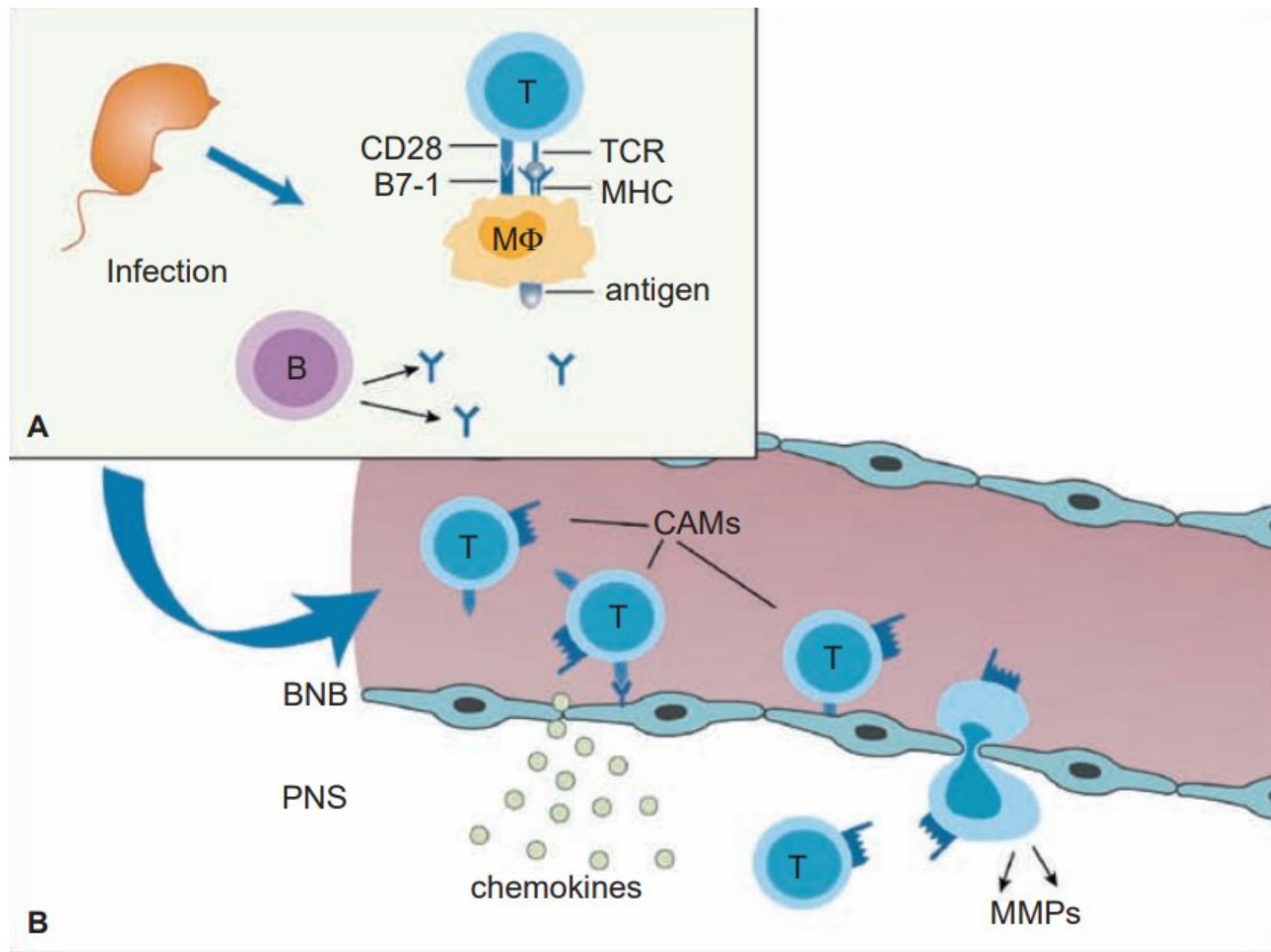
Guillain-Barré syndrome- immunopathology

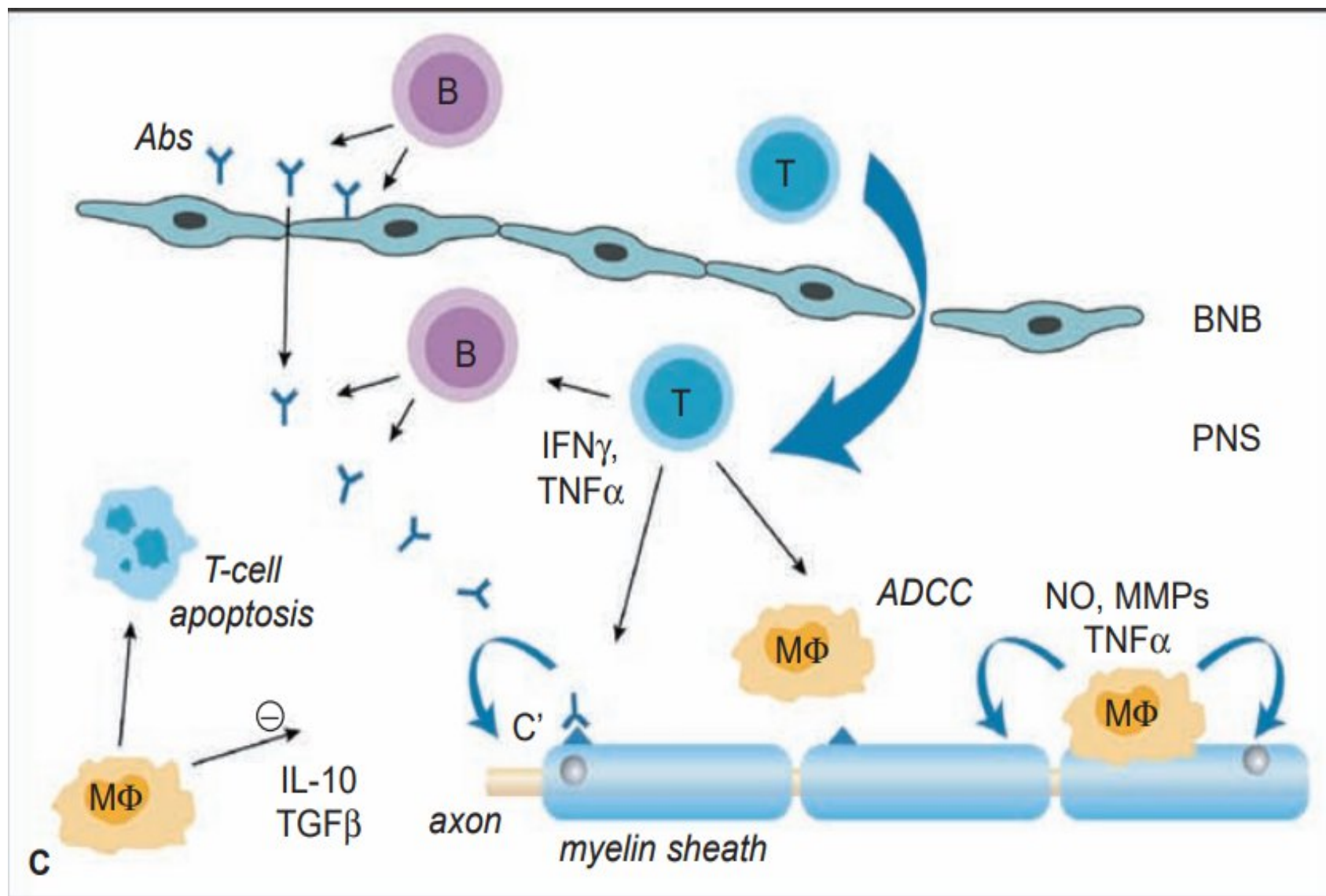
Activation of immune cells:

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.





Guillain-Barré syndrome-immunopathology

Autoantibodies

Antibodies to membrane gangliosides (glycolipids including GM1, LM1, and GD1b)- found in up to 40% of patients with GBS.

These antibodies interfere with nerve conduction and can activate phagocytes via IgG receptors.

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.

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: 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)

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.

Myasthenia gravis (MG)

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

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

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.

Prevalence is 2–10/100 000.

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.

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.

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.

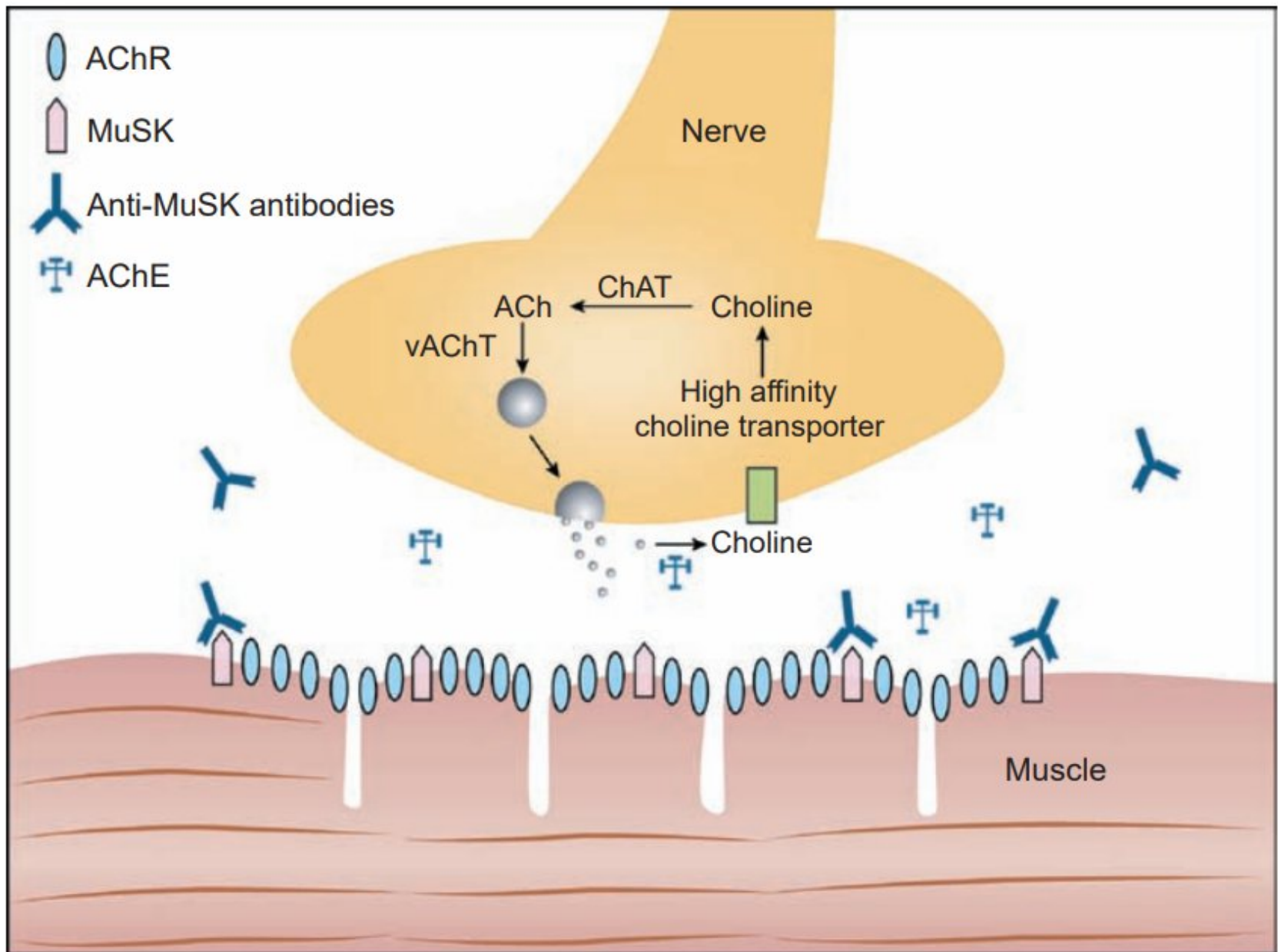
Removal of the thymoma does not always affect the course of the disease.

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.

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.

Autoantibodies against the Acetylcholine Receptor (AChR) are found in the majority of cases.



Myasthenia gravis- Immunopathology

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.

AChRAb levels are variable, but high titres are found in those <40 yrs with thymic hyperplasia.

Myasthenia gravis- Immunopathology

Antibodies can be transmitted across the placenta, causing neonatal myasthenia.

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.

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.

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, 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.

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.

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.