INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

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Myasthenia Gravis

Severe (Gravis) - **Muscle** (My) **- Weakness** (Asthenia)

It is an **autoimmune disease**, which means that the immune response is turned against the host.

In rare instances, the specific adaptive immune system can produce **antibodies** that are active against **self-antigens** on cell surface or in extracellular matrix causing a hypersensitivity reaction.

This reaction can activate the complement system leading to cell-lysis and extracellular damage, this type of reactions is known as **type II hypersensitivity reaction** (antibody mediated).

An example of type II hypersensitivity reactions is **Myasthenia Gravis**, which is caused by autoantibodies against **acetylcholine receptors** which are present in the neuromuscular junction.

Other examples of type II hypersensitivity reactions:

Some common type II autoimmune diseases caused by antibody against surface or matrix antigens		
syndrome	**Antigen**	**Consequence**
Autoimmune hemolytic anemia	Rh blood group antigens (antibodies against RBCs)	Destruction of RBC by complement system and phagocytes, causing anemia
Autoimmune thrombocytopenic purpura	Antibodies against platelets	Abnormal bleeding
Goodpasture's syndrome	Antibodies against glomerular basement membrane proteins (anti-GBM)	Glomerulonephritis Pulmonary haemorrhage
Pemphigus vulgaris	Epidermal cadherin	Blistering of skin
Graves' disease	Thyroid-stimulating hormone receptor (agonist)	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycaemia, ketoacidosis
Hypoglycaemia	Insulin receptor (agonist)	Hypoglycaemia

The discovery of this disease as an autoimmune disease:

This disease was first identified as an autoimmune disease when an immunologist immunized rabbits with purified acetylcholine receptors to obtain antibodies against this receptor. He noticed that the rabbits developed floppy ears, like **the droopy eyelids (ptosis)** that are the most characteristic symptom of myasthenia gravis in humans. Subsequently, patients with this disease were found to have antibodies against the acetycholine receptor.

In addition, pregnant women with myasthenia gravis transfer the disease to their new-born infants. As **IgG** is the only maternal serum protein that crosses the placenta from mother to fetus, neonatal myasthenia gravis is a clear evidence that myasthenia gravis is caused by **an IgG antibody** (remember that type I hypersensitivity is IgE mediated), the new-born will display the symptoms **for 1-2 weeks** until the **clearance of maternal IgG** from the circulation.

Myasthenia Gravis affects young women (20s-30s) and older men (60s-70s), but the cause of this distribution is unclear.

The disease causes weakness **in skeletal muscles**, the weakness is well noted with repetitive movements, this can be explained by **the decreased release of acetylcholine with repetitive nerve stimulation**. In normal conditions this shouldn't be a problem. But in myasthenia gravis, the combination of the pathological reduction of functional acetylcholine receptors with the physiologic decrease in neurotransmitter release results in muscular weakness.

The disease is known for causing weakness in the **ocular muscles**, mostly affected probably due to their small size:

-> when it affects the muscles that control **the movement of the eye**, it causes **double vision (diplopia)** as well **as a limitation in the ocular movement** of the eye.

-> when it affects the muscles that control the **movement of the eyelids**, it causes **droopy eyelids (ptosis),** which is the most characteristic symptom of the disease.

*Young patients usually present with ocular symptoms of this disease (diplopia and ptosis), this is a common type of myasthenia gravis called the oculobulbar form.

*Older myasthenia gravis patients usually present with generalized muscle weakness as a first symptom.

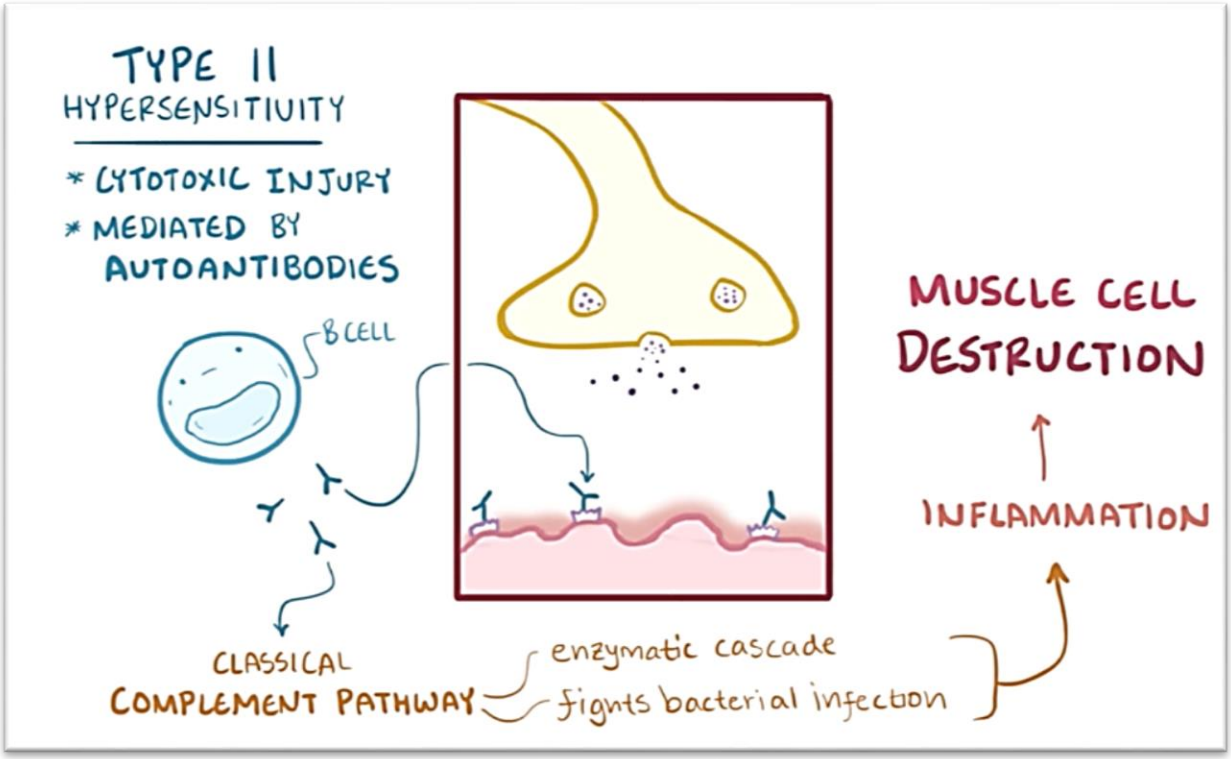
Diagnosis of this disease is not always easy if the patient doesn't present with the typical case.

The pathogenesis of the disease:

In normal conditions, motor neurons release acetylcholine to the neuromuscular junction which will bind to **nicotinic acetylcholine receptors** on the muscle membrane causing muscle contraction.

In myasthenia gravis, B-cells will secrete **autoantibodies against acetylcholine receptors which will:**

1- **Compete against and so impede the binding of acetylcholine and stimulate the internalization and degradation of the receptors** (less binding, weakening/relaxation of muscle).
2- **Antigen-antibody complexes will initiate complement-mediated lysis of the muscle end plate and damages the muscle membrane** (inflammatory reaction causing the destruction on the muscle membrane).



In rare cases of the disease, the autoantibodies are not directed against acetylcholine receptors, but against another type of receptors called **muscle-specific kinase (MUSK)**, MUSK is a tyrosine kinase receptor involved in clustering acetylcholine receptors; therefore, these autoantibodies also inhibit signalling through the neuromuscular junction.

Myasthenia gravis can also be associated (in rare cases) with **a paraneoplastic syndrome as a result of a tumour (usually in the thymus gland, but can occur anywhere)**; this is because the tumour can sometimes secrete proteins that mimic acetylcholine receptors, which will be detected by the adaptive immune system, and so antibodies against acetylcholine receptors will be formed, causing myasthenia gravis.

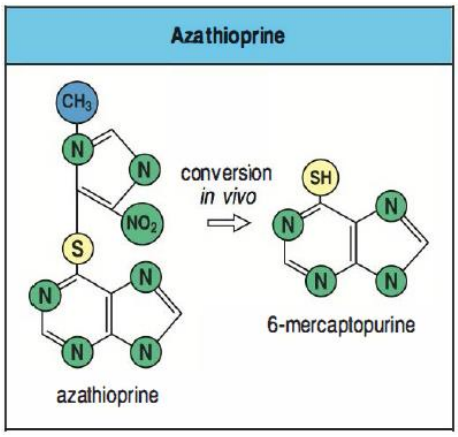
Tumours in the thymus are also associated with **decreased expression of the AIRE gene.** This will cause impaired negative selection in the thymus gland and more activity against self-antigens.

Note: Chest radiographs of younger people with myasthenia gravis frequently reveal enlargement of the thymus gland. However, an association between myasthenia gravis and tumors of the thymus (thymomas) is more common in adults (it is better to check old patients who present with myasthenia gravis for underlying tumours).

Treatment of myasthenia gravis:

1- **Acetylcholine esterase inhibitors (Pyridostigmine):**
Pyridostigmine is an ideal drug for the treatment of myasthenia gravis. It inhibits the enzyme cholinesterase, which normally cleaves and inactivates acetylcholine. In this way, Pyridostigmine prolongs the biological half-life of acetylcholine. Unfortunately, it also causes diarrhea by increasing the amount of acetylcholine in the intestine. Acetylcholine binds to the muscarinic receptors in the intestinal smooth muscle and increases intestinal motility.

2- **Immunosuppressors (Azathioprine):**
Reduces the amount of autoantibodies by inhibiting the immune system. When using this drug for prolonged time, there is a higher risk of infections and tumour formation (especially lymphomas) because of its immunosuppressive effect. This drug is mostly used as an alternative if the patient cannot tolerate Pyridostigmine.



Mechanism of action:

Folds in vivo forming a purine-like structure (purines are building blocks for DNA), it contains -SH group which won't be able to bind to more nuclear acids, causing the termination of DNA replication.

Note: this drug is also used in organ transplants and other autoimmune diseases like rheumatoid arthritis and lupus.

3- **Surgical removal of the thymus gland:**
Patients with enlarged thymus gland have shown some improvement when the gland is removed. Although the mechanism is unclear, it is most probably because B-cells are dependent on helper T-cells in their differentiation.

4- **Plasmapheresis:**
Used in **Myasthenic Crisis** > when the muscle weakness is too severe that it causes difficulty in swallowing and weakness in the respiratory muscles, some food particles might be aspired into the lungs causing impaired breathing which might be fatal. This case requires clearance of the antibodies, and this can be done through Plasmapheresis (the filtration and removal of plasma from whole blood).

-> The case of Mr Weld:

- He is a **71 years-old** retired engineer.

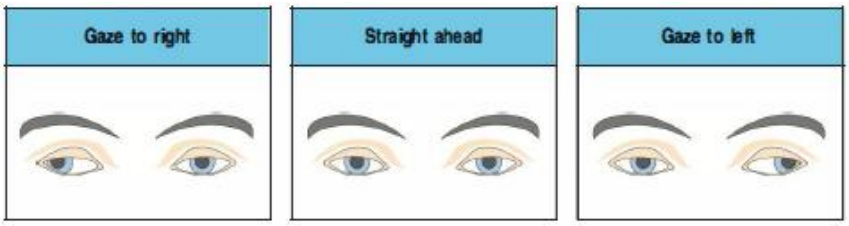
- Has been in a good health and active his whole life.

- Started to develop **diplopia** (double vision), but didn't go to see a physician because he thought it will improve by its own.

- His diplopia kept worsening for 4 months, so he finally decided to see a physician.

- The doctor noticed **ptosis** of both his eyelids (his eyelids where covering the upper third of his irises).

- The doctor asked him to look to the left and then to the right, he noticed a **limitation in his ocular movement**.



- The rest of the neurological examinations showed no other abnormalities; no other muscle weaknesses were noted.

- A radiological examination of the chest was done to see if the thymus gland was enlarged, but it wasn't, so the patient will probably not benefit from thymectomy.

- A blood sample was taken from Mr Weld, and his serum was tested for **antibodies against the acetylcholine receptor**. The serum contained **6.8** units of antibody against the acetylcholine receptor (normal less than **0.5** units). From here the doctor knew it was **myasthenia gravis**.

-Mr Weld was told to take **pyridostigmine**. His double vision improved steadily but he developed diarrhea from the pyridostigmine, and this limited the amount he could take.

Three years later:

- Mr Weld developed **a severe respiratory infection**. Soon afterward, his **ptosis** became so **severe** that he had to lift his eyelids using an adhesive tape. His **diplopia** recurred, and his **speech became indistinct**. He developed **difficulty in chewing and swallowing food.** He could only tolerate a diet of soft food and it would take him several hours to finish a meal.

- On examination the neurologist noted that Mr Weld now had **weakness of the facial muscles and the tongue, and the abnormality in ocular movements became apparent again.**

- Because of the diarrhea Mr Weld was only able to tolerate one-quarter of the prescribed dose of pyridostigmine.

- He also developed **difficulty in breathing**. His **vital capacity** (the amount of air he could exhale in one deep breath) was low, at **3.5** liters.

- He was admitted to hospital and treated with **azathioprine (Imuran).** Thereafter he showed steady improvement. His ptosis and diplopia improved

remarkably, and he was able to eat normally. His vital capacity returned to normal and was measured to be **5.1** liters.

End of the case

What can mimic the symptoms of myasthenia gravis?

Infection with **Clostridium botulinum bacteria**, which produces **Botulinum toxin.** This toxin inhibits acetylcholine release from the motor neuron, causing some sort of an "acute" myasthenia-gravis-like attack.

Note: Botulinum toxin (Botox) is also used in cosmetic field.

Mr Weld had a severe relapse of myasthenia gravis after **a severe respiratory infection.** How can an infection cause a severe relapse of an autoimmune disease?

Besides the necessary **genetic factor**, **faulty selection of lymphocytes in the thymus**, **failure of peripheral tolerance** and **an inflammation to provide cytokines and co-stimulatory signals**, there needs to be a trigger for the autoimmune disease, infections provide this trigger via several mechanisms:

Mechanism	Effect	Example
Molecular mimicry	Production of cross reactive anti-bodies or T-cells	Rheumatic fever Diabetes Multiple sclerosis
Distribution of cell or tissue barrier	Release of sequestered self-antigen, activation of non-tolerized cells	Sympathetic ophthalmia
Infection of antigen presenting cells	Induction of co-stimulatory activation	Experimental Autoimmune Encephalomyelitis
Binding of a pathogen to self-protein	Pathogen act as a carrier to allow anti-self-response	Interstitial nephritis
Superantigens	Polyclonal activation of autoreactive T-cells	TSS (toxic shock syndrome)

Further details:

- **Molecular mimicry ->** In Rheumatic fever the streptococcus has an antigen on its surface that looks like -mimics- antigens on the heart valves, if not quickly treated there will be an autoimmune attack on the valves.

- **Distribution of cell or tissue barrier ->** One way we protect ourselves from autoimmune disease is to have some antigens in privileged sites, not seen (or seen very little) by the immune cells, so even if we do have autoreactive cells against them, there will be no interaction and no immune response. In **sympathetic ophthalmia**, a trauma to the eye could cause the release of antigens from the melanocytes in the uvea, those antigens are usually not seen by the immune system, but with their increase due to the damage, there will be an immune response against them causing uveitis which causes a severe decrease in vision. Those antibodies and T-cells will also circulate and go to the other eye > **bilateral uveitis**. If not treated those patients could go blind.

- **Infection of antigen presenting and immune cells ->** Some viruses are known to trigger autoimmunity (EBV, CMV, HPV, etc.); those viruses can insert certain parts of their genome into the host's DNA and force the cell to abnormally proliferate. So, if they infect autoreactive cells there will be a huge number of those cells that can cause autoimmunity.

- **Superantigens ->** Superantigens are antigens that, due to their structures, allow binding of several T-cells in an MHC-independent manner, causing T-cells to become polyclonal (rather than the usual monoclonal) producing autoimmune reactions. In this case the patients don't have a T-cell response against a specific antigen, but rather a storm of immune cells. An example of this is TSS which is cause by staphylococcus aureus or group A streptococcus and is very common with unhygienic tampon use and could be life threatening.

Thank you