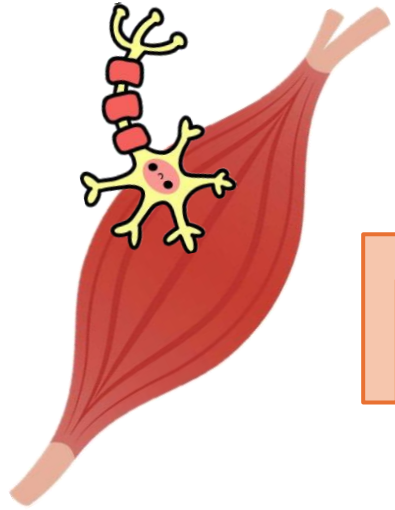




Myasthenia gravis



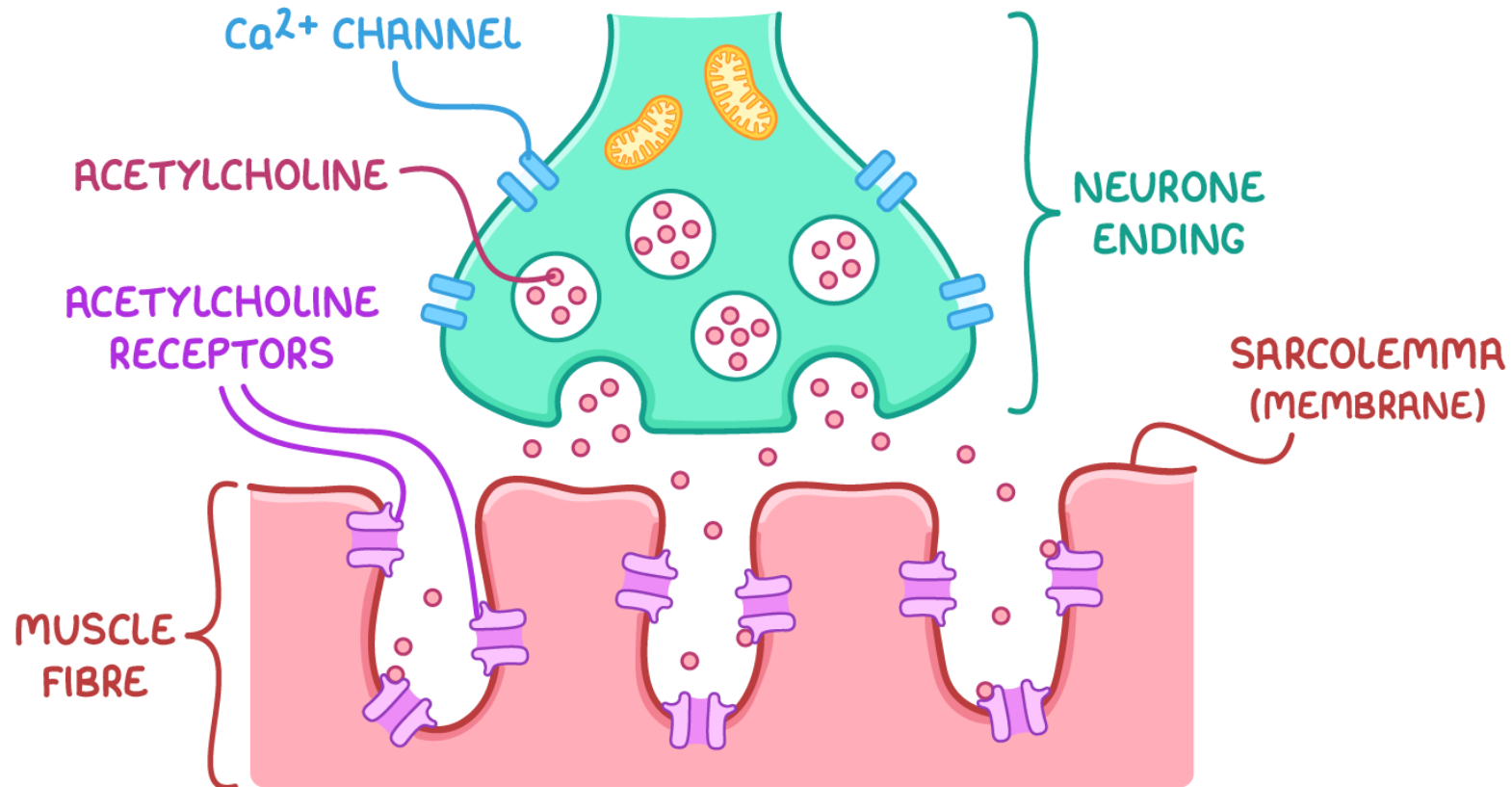
Introduction



Sara Altaweel

Neuromuscular junction (NMJ)

is the synapse or connection point between a motor neuron and a muscle fiber. It plays a crucial role in transmitting signals from the nervous system to initiate muscle contraction.



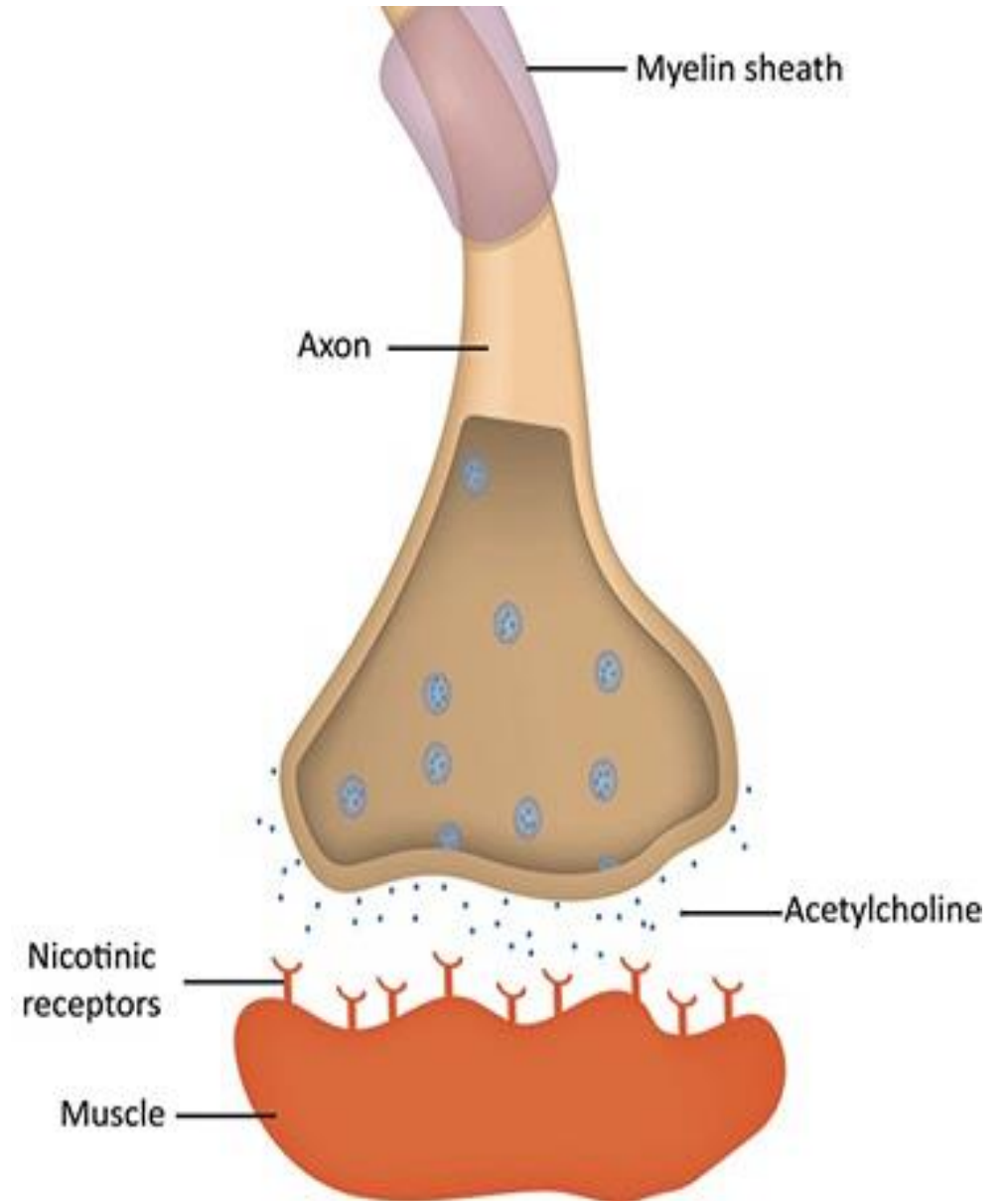
Neuromuscular junction (NMJ)

- **Components:**

Presynaptic Terminal: The end of the motor neuron that contains synaptic vesicles filled with the neurotransmitter acetylcholine (ACh).

Synaptic Cleft: The small gap between the presynaptic terminal and the muscle fiber where neurotransmitter release occurs.

Postsynaptic Membrane: The muscle fiber membrane that contains acetylcholine receptors (AChRs) which bind to ACh and initiate muscle contraction.



The steps of depolarization at the neuromuscular junction (NMJ) involve several key processes:

1.Action Potential Arrival: An action potential travels down the motor neuron to the presynaptic terminal.

2.Calcium Influx: The action potential causes voltage-gated calcium channels to open, allowing calcium ions (Ca^{2+}) to enter the presynaptic terminal.

3.Neurotransmitter Release: The influx of calcium triggers synaptic vesicles to fuse with the presynaptic membrane, releasing acetylcholine (ACh) into the synaptic cleft.

4.ACh Binding: ACh diffuses across the synaptic cleft and binds to acetylcholine receptors (AChRs) on the postsynaptic membrane (muscle fiber).

5.Ion Channel Opening: Binding of ACh causes ion channels to open, allowing sodium ions (Na^+) to flow into the muscle fiber.

6.Depolarization: The influx of sodium ions depolarizes the muscle membrane, creating an end-plate potential (EPP).

7.Action Potential Generation: If the EPP is strong enough to reach the threshold, it triggers an action potential in the muscle fiber, leading to muscle contraction.

8.Termination: Acetylcholinesterase breaks down ACh in the synaptic cleft, stopping the signal and allowing the muscle membrane to repolarize.

Acetylcholine (ACh)

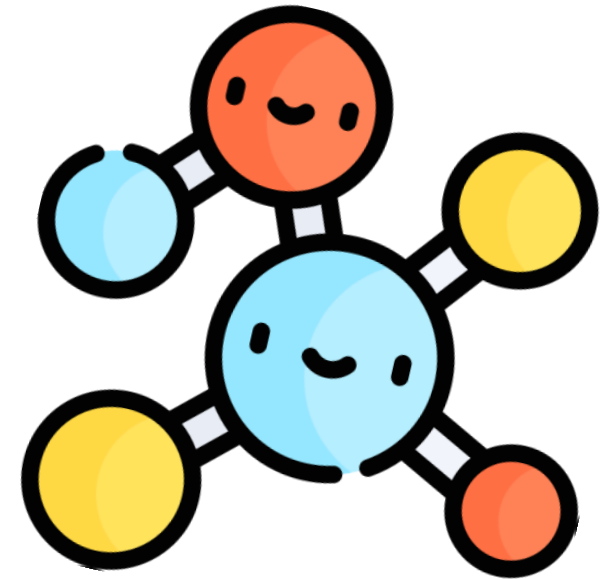
Acetylcholine (ACh) is a neurotransmitter that plays a key role at the neuromuscular junction. When a motor neuron releases ACh, it binds to receptors on the muscle fiber's membrane.

Neuromuscular Transmission: ACh is essential for transmitting signals from motor neurons to muscle fibers, facilitating voluntary muscle contractions.

Autonomic Nervous System: ACh functions in both the sympathetic and parasympathetic divisions, influencing various involuntary functions, such as heart rate and digestion.

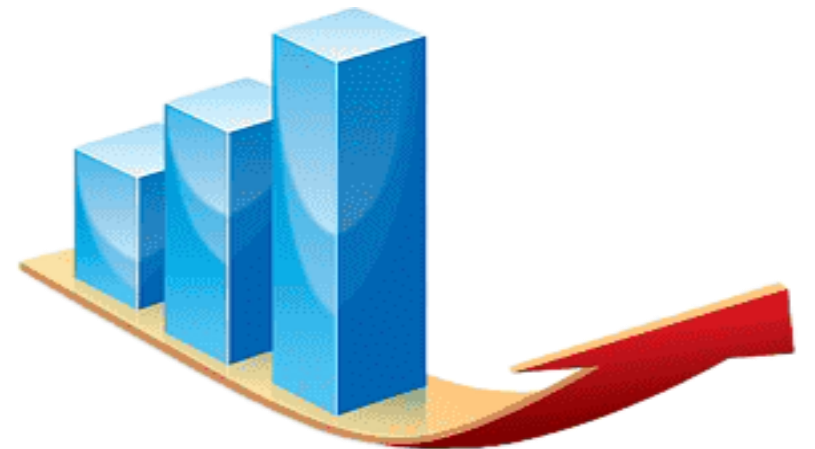
Cognitive Function: In the brain, ACh is involved in memory, attention, and learning. It plays a role in processes related to arousal and alertness.

Regulation of Glands: ACh stimulates the secretion of certain glands, including salivary and sweat glands.



Epidemiology

Hexham yassin



Prevalence:

★ Myasthenia gravis is the most common neuromuscular junction disorder, but still rare with a prevalence rates ranging from 100 to 200 cases per million people worldwide.

Age distribution:

★ MG tends to affect people in two age groups (Bimodal age distribution)

1- Early onset MG: More common in women between 20-30 years old.

2- Late onset MG: More common in men between 50-70 years old.

★ While it's rare but MG can also occur in children (juvenile MG) presents between 10-16 years old.

Gender distribution:

★ MG is more common in Females.

Racial and geographic differences:

★ There may be some variation in the subtypes and severity of MG across populations, but the disease occurs globally

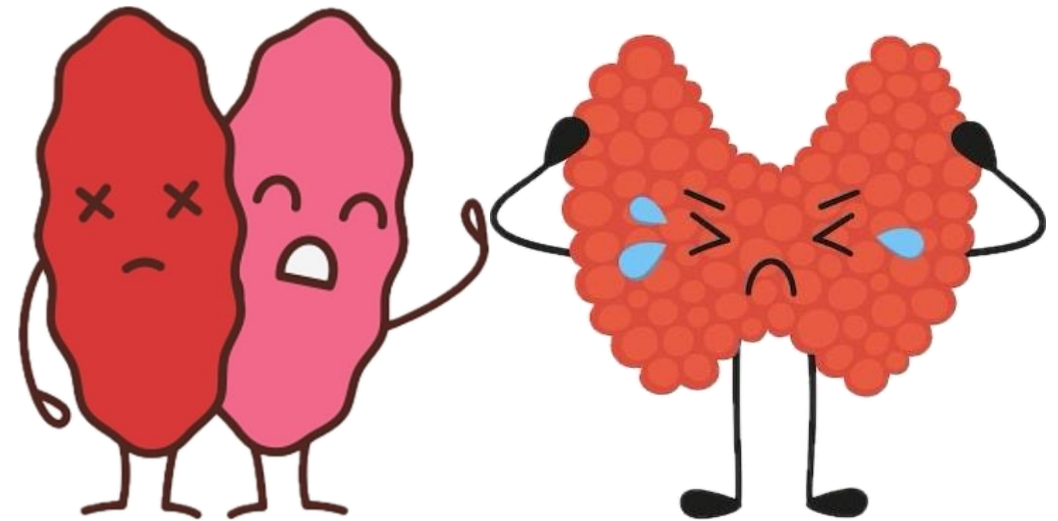
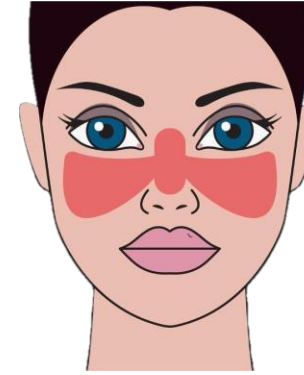
Myasthenia Graves is associated with different types of diseases, including:

Thymus pathology (Thymic hyperplasia & Thymoma, Strong Association).

Thyroid disease (Hashimoto's thyroiditis, Most common).

Systemic lupus erythematosus (SLE, Rare).

Rheumatoid arthritis (RA, Rare).





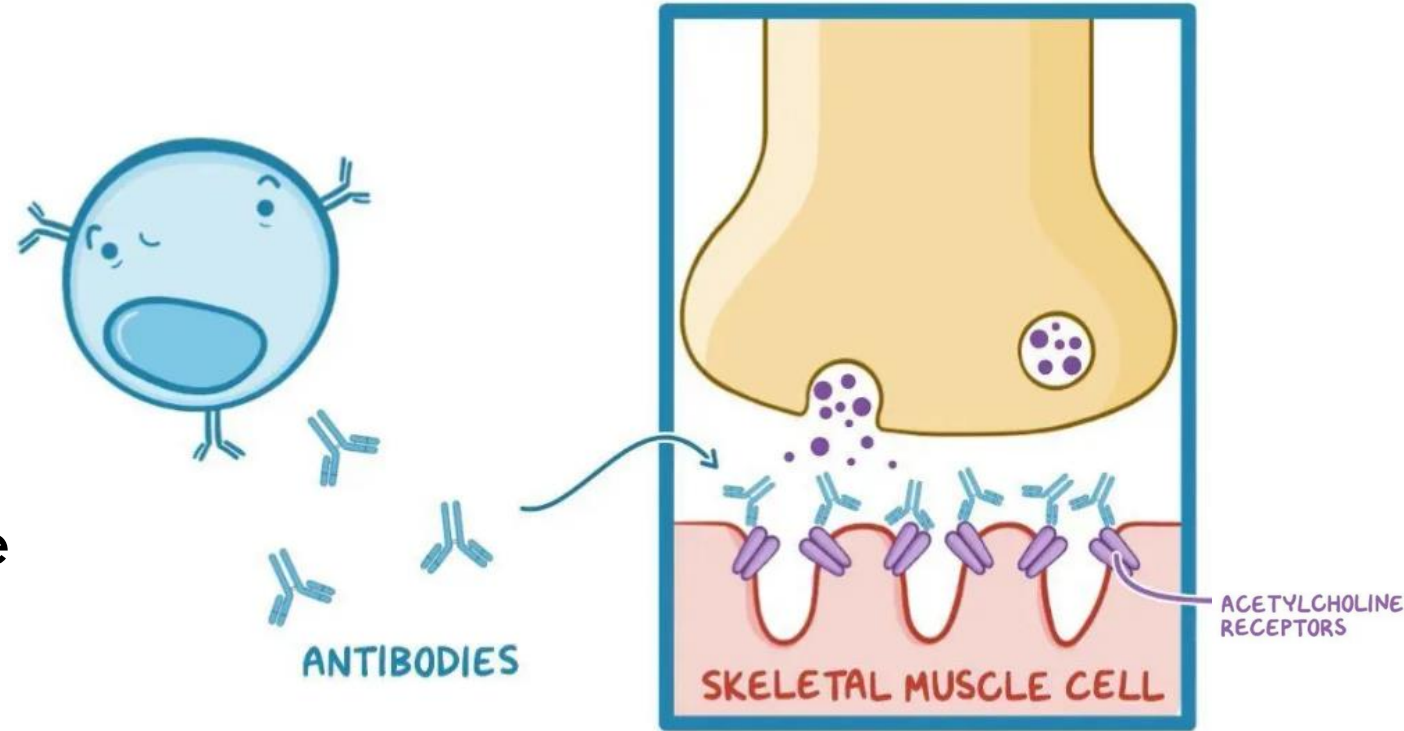
Pathology & cause

Ahmad Edwan

Pathophysiology

→ It's an autoimmune disease, categorised as a type II hypersensitivity reaction (Cytotoxic). B cells inappropriately make antibodies that bind to nicotinic acetylcholine receptors on the muscle cells.

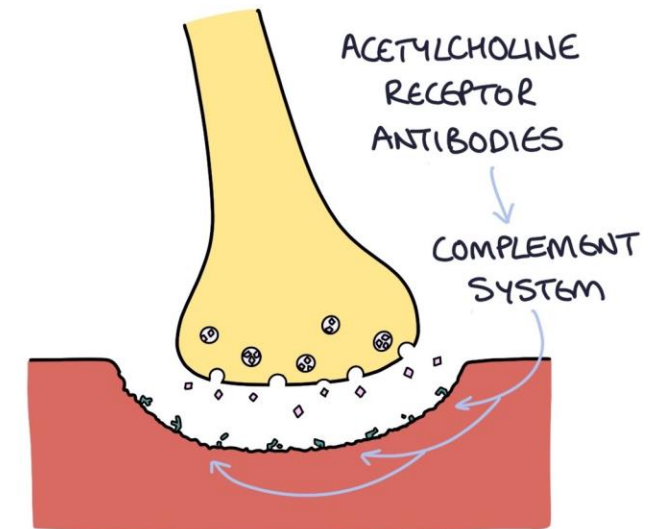
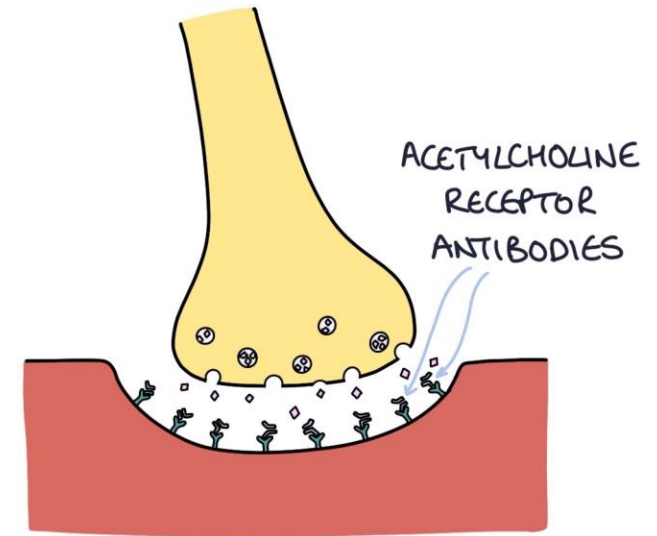
→ Once acetylcholine receptors are bound by the antibody, they are unable to bind to acetylcholine, and therefore don't respond to the "contract" signal from the central nervous system.



Pathophysiology (cont.)

→ Anti-acetylcholine activate the receptor classical antibodies pathway can also of the complement system**.

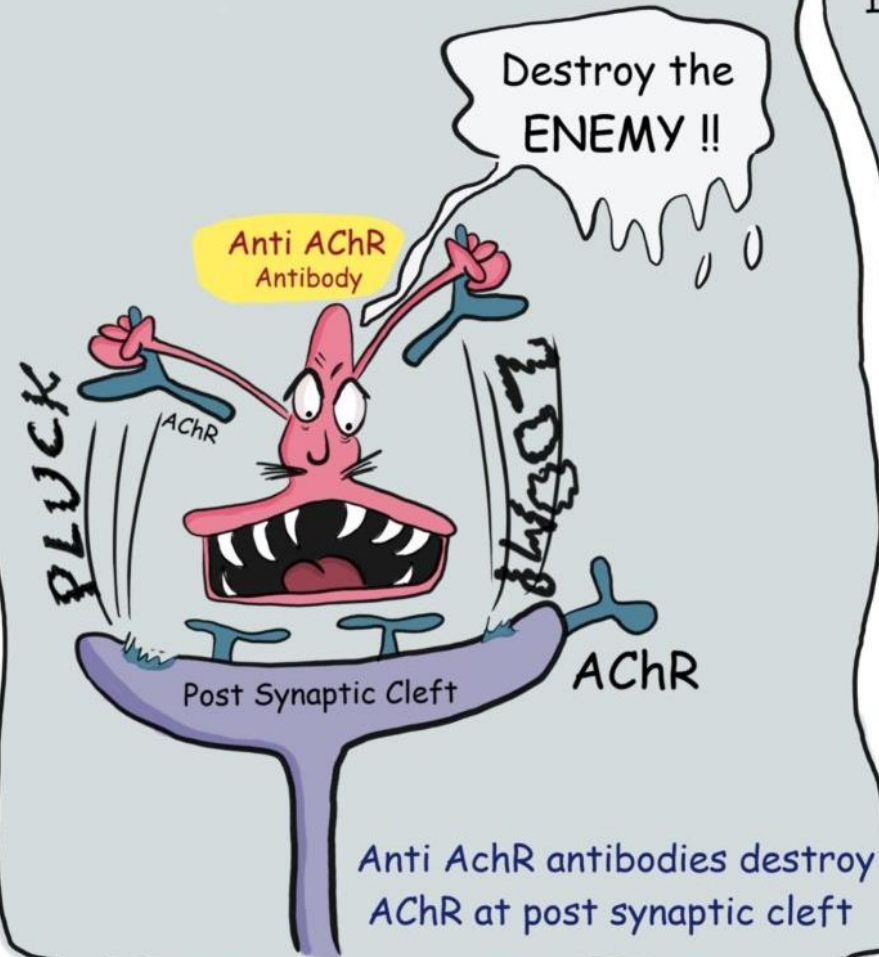
→ The activation of complement causes inflammation and destruction of the muscle cells, reducing the number of acetylcholine receptors on the muscle cell surface, which impairs contraction even more.



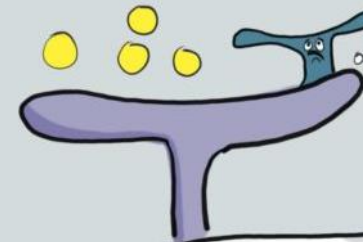
Pathophysiology (cont.)

- Now a minority of people with myasthenia graves, the disease produce another types of harmful antibodies called Muscle-specific tyrosine kinase (MuSK) antibodies, and Low-density lipoprotein receptor related protein 4 (LRP4).
- MuSK and LRP4 are important proteins for the creation and organisation of the acetylcholine receptor .Destruction of these proteins leads to inadequate acetylcholine receptors.
- These antibodies attack proteins inside of muscle cells instead of nicotinic acetylcholine receptors on the muscle cell surface, but they similarly lead to destruction of healthy cells.
- Seropositive MG (80–90% of cases): Positive assays for antibodies (in blood) against the acetylcholine receptor (AChR-Ab).
- Seronegative MG (10–20% of cases): Negative for AChR antibodies, but may be positive for muscle-specific tyrosine kinase antibodies (MuSK antibodies).

Tough Day at NMJ of Myasthenia Gravis



It decreases available AChR at Post Synaptic cleft



Creative-Med-Doses



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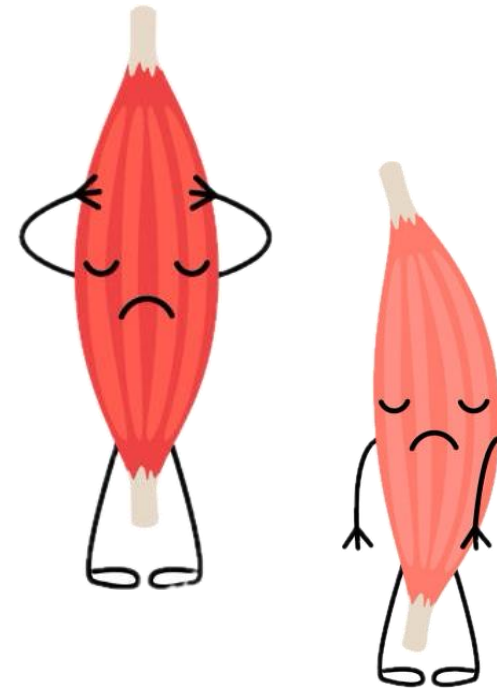


Summary ---

There is inefficient neurotransmission at Neuromuscular junction in MG because of autoimmune AChR destruction.

Symptoms

Batool Abu Shreikh



Symptoms

- Symptoms vary between patients, ranging from mild to life-threateningly severe.
- Symptoms are typically best in the morning and worst at the end of the day.
- The characteristic symptom is “**fatigable weakness**,” a loss of power that becomes more pronounced with the use of the affected muscles.



Symptoms (cont.)

- affects different muscle groups, leading to a variety of symptoms.
- Myasthenia Gravis is classified clinically into:

1. Ocular Myasthenia: some patients have symptoms limited to the ocular region.

2. General Myasthenia: All skeletal muscles may be involved Especially Ocular, Bulbar, Limb, and Respiratory muscles

Bulbar muscles:

These muscles control activities like swallowing and speech, weakness here can cause dysphagia and dysarthria

Symptoms (cont.)

- Signs & Symptoms

On exam, patients may have diplopia asymmetric ptosis or extraocular abnormalities, nasal voice, limited palate elevation, impaired gag reflex, slurring of speech, head drop, proximal weakness, or combinations of these.

There are several ways to check for fatigability in clinical settings:

1) test sustained up-gaze: the examiner asks the patient to look upward at a fixed target for about 60 seconds, Findings supportive of MG include the subjective experience of double vision or the objective development of ptosis, eye misalignment over time, or both. If there is detectable ptosis at baseline, ice can be applied to the affected eye for at least 2 minutes, as tolerated; a transient decrease in the degree of ptosis suggests MG.

Symptoms (cont.)

2)Checking neck muscle strength: is also important, because weakness there may be accompanied by diaphragmatic weakness; nerve roots C3, 4 , and 5 serve both neck and diaphragmatic muscles , the latter through the phrenic nerves.

Asking the patient to count as high as possible during a single exhalation can also provide a rough idea of respiratory function; an inability to count to 40 should raise concern, as should shortness of breath that increases in the supine position (when the mechanical advantage of gravity is lost).

Symptoms (cont.)

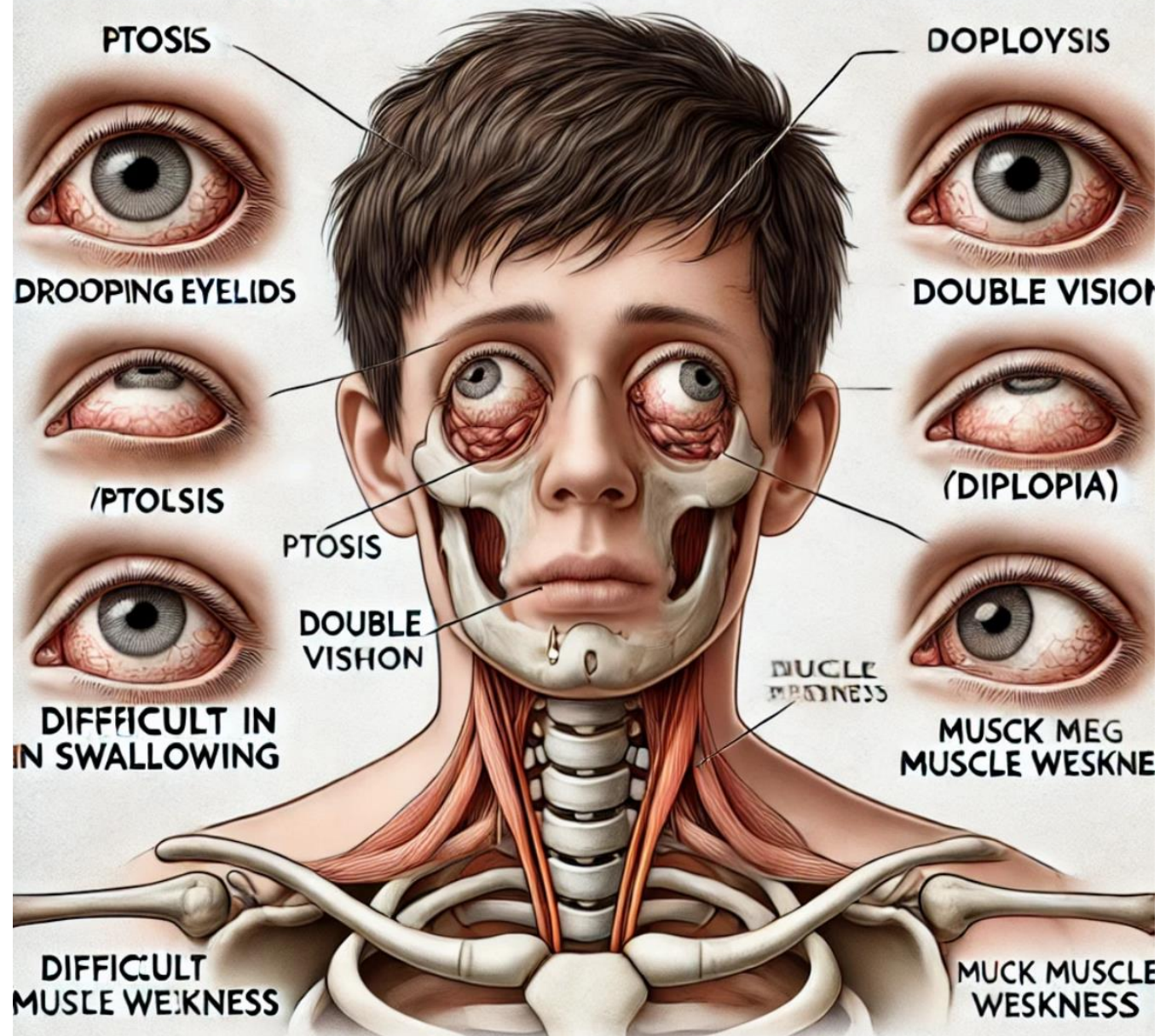
3) Limb strength can be checked before and after

a brief exercise task. For instance, after checking deltoid strength, have the patient perform 20 “arm pumps” in which the arm is repeatedly abducted to shoulder level and

then adducted to the torso. A subsequent reduction in deltoid strength indicates fatigable weakness.

Myasthenia Gravis (MG) can become life-threatening when it leads to a condition called **myasthenic crisis**. This occurs when the muscles that control breathing weaken to the point that a person may need mechanical assistance to breathe. Without prompt medical intervention, it can be fatal.

MYASTHENIA GRAVIS SYMPTOMS

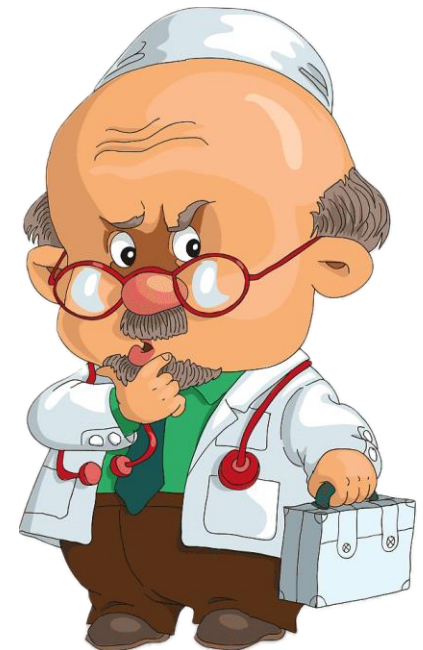




Diagnosis



Omar baha



Diagnosis

1. Laboratory Studies:

★ **AChR antibody test (Most specific serological test):**

- 80 – 90% of patients with generalized Myasthenia Graves have antibodies.
- 100% of patients with thymoma have antibodies.

★ **Other associated antibodies: anti-MuSK (Muscle-specific kinases).**

★ Can be used to monitor response to treatment (Not really used for this purpose, because of its cost)

★ **thyroid function test** (for associated thyrotoxicosis)

2. Chest CT Imaging:

★ Done for Every newly diagnosed patient to rule out thymoma

Diagnosis (cont.)

3a. Electrophysiologic Studies (Repetitive nerve stimulation studies):

- ★ Repetitive nerve stimulation (RNS) studies are performed in patients with suspected NMJ disorders.
- ★ It involves using an electrical stimulus where an electrode needle is applied to the skin overlying the nerve, the nerve then activates and sends the signal to the muscle supplied by that nerve (Painful).
- ★ The above procedure is repeated, if there is an increase or decline of the action potential in the first four to five responses of more than 10%, this means it is a disorder in neuromuscular transmission.
- Low-frequency RNS (e.g., 2–3 Hz) identifies postsynaptic disorders (e.g., myasthenia gravis).
- High-frequency RNS (e.g., 40–50 Hz) identifies presynaptic disorders (e.g., Lambert–Eaton myasthenic syndrome).
- ★ In Myasthenia Gravis, progressive decline in muscle action potential amplitude (decremental response).
- ★ In Lambert-Eaton Myasthenic Syndrome, progressive increase in muscle action potential amplitude (incremental response).

Diagnosis (cont.)

3b. Electrophysiologic Studies (Single-fiber electromyography “EMG”):

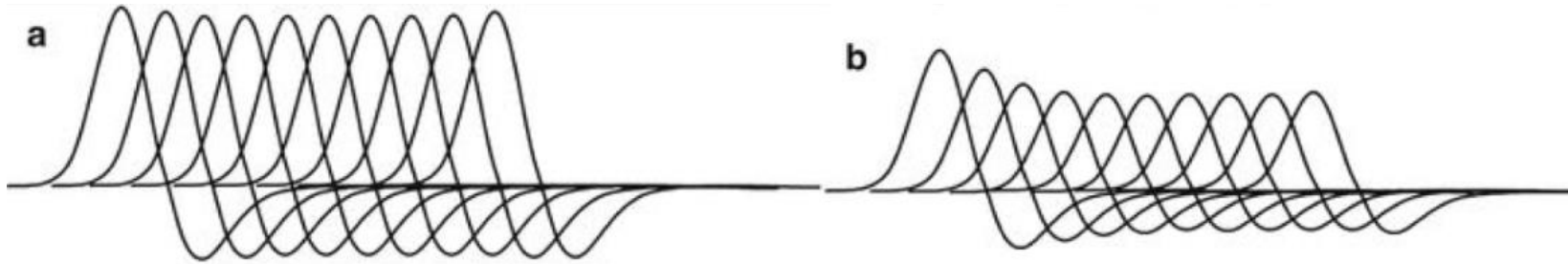
★ The single fiber electromyography (SFEMG) study is a technique developed to aid in the diagnosis of neuromuscular junction (NMJ) transmission disorders, especially myasthenia gravis (MG). It is particularly useful in cases where other test results are not sufficient for diagnosis. The goal of SFEMG is to measure impairment in NMJ transmission (manifested by increased jitter and/or blocking) which can be seen in 95–99% percent of patients with myasthenia gravis.

★ Single Fibre EMG (SFEMG) is a more sensitive test of neuromuscular transmission where a small needle is inserted within a single muscle fibre. Extension or blocking of the action can mean a disorder but can be also seen in other neuromuscular diseases.

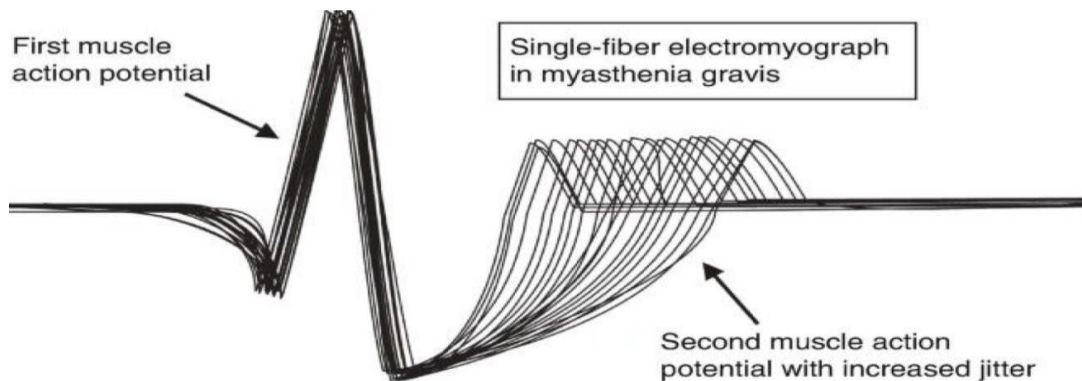
★ The single fiber electromyography (SFEMG) demonstrates increased jitter in virtually all patients with myasthenia gravis (MG) (not specific , can be seen in other conditions including LEMS.)

Diagnosis (cont.)

3a. Electrophysiologic Studies (Repetitive nerve stimulation studies):



3b. Electrophysiologic Studies (Single-fiber electromyography “EMG”):



Diagnosis (cont.)

Tensilon Test (Edrophonium Test):

- ★ Patients are given intravenous edrophonium chloride (or neostigmine). Normally, cholinesterase enzymes in the neuromuscular junction break down acetylcholine.
- ★ Edrophonium blocks these enzymes, reducing the breakdown of acetylcholine.
- ★ As a result, the level of acetylcholine at the neuromuscular junction rises, temporarily relieving the weakness. A positive result suggests a diagnosis of myasthenia gravis.
- ★ This test is not used that much these days due to high false positives



Before Edrophonium test



After Edrophonium test

Treatment

Aya Alquran



Treatment

1. AChE inhibitors-for example pyridostigmen

- a.** Inhibiting AChE increases concentration of acetylcholine at the synapse by decreasing the breakdown of acetylcholine
- b.** This is a symptomatic benefit only.
- C.**increasing doses may develop muscarinic cholinergic side effects, including increased salivation, vomiting, abdominal pain and diarrhoea. In extreme cases, weakness may worsen cholinergic crisis

Treatment (cont.)

2. Thymectomy

- Why thymectomy?

Thymoma MG accounts for around 15% of all MG cases. The immune response against an epitope expressed on thymoma cells spills over to neuromuscular junction components sharing the same epitope.

- a. This provides a symptomatic benefit and complete remission in many patients, even in the absence of a thymoma.

- b. Although usually benign, thymoma is an absolute indication for thymectomy.

Treatment (cont.)

3. Immunosuppressive drugs.

a. Use corticosteroids for patients with a poor response to AChE inhibitors.

- Note: Steroids should be gradually increased from a low dosage as symptoms may initially worsen. Hospital admission is generally advisable for starting steroids in patients whose disease is not purely ocular. Once control has been achieved, the dose may be tapered back in accordance with symptoms.

b. Azathioprine and cyclosporine are alternative third-line agents

Treatment (cont.)

4. Plasma exchange removes antibodies to acetylcholine receptors. Use it if all else fails or if the patient is in respiratory failure.

5. IV immunoglobulin therapy is now sometimes used for acute exacerbations

- With pronounced respiratory distress potentially requiring intubation, intravenous immunoglobulin (IVIG) and plasmapheresis are indicated because they act much more quickly

Treatment (cont.)

6. Monitor serial forced vital capacities.

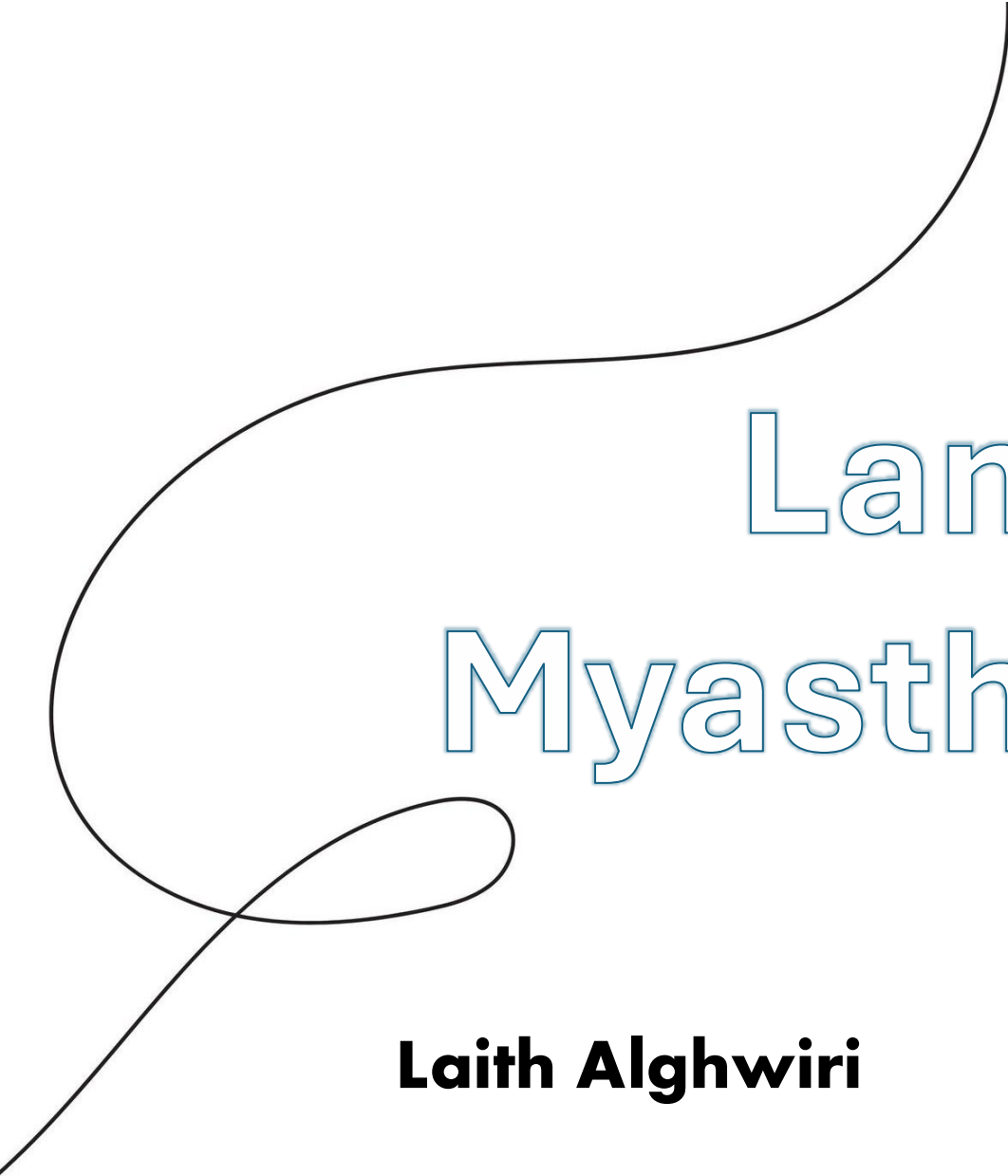
A forced vital capacity of 15mL/kg (about 1 L) is generally an indication for intubation. Patients in myasthenic crisis have a low threshold for intubation-do not wait until the patient is hypoxic

Treatment (cont.)

Quick HIT

Medications that exacerbate symptoms of myasthenia graves :

- Antibiotics-aminoglycosides, fluoroquinolones, and others
- β -Blockers
- Antiarrhythmics-quinidine, procainamide, and lidocaine

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Lambert-Eaton Myasthenic Syndrome

Laith Alghwiri

Lambert-Eaton myasthenic syndrome is an autoimmune neuromuscular disease caused by defective release of ACh due to autoantibodies directed against presynaptic voltage-gated calcium channels.

→ The key presenting features are:

★ Proximal muscle weakness, difficulty climbing stairs, standing from a seat or raising the arms overhead.

★ Autonomic dysfunction, causing dry mouth, blurred vision, impotence and dizziness.

★ Reduced or absent tendon reflexes.

	Myasthenia gravis	LEMS
Nature	Autoantibodies against postsynaptic Ac	Autoantibodies against presynaptic voltage-gated Ca^{++} channels
Weakness	Worsens with use	Improved with use
Associated with	Thymoma	Small cell lung cancer
Muscle involved	Distal	Proximal
Deep tendon reflex	Normal	Decreased or absent
Autonomic symptoms	Absent	Common
Tesilon test	Symptoms improvement	Mild improvement
Treatment	Mention above	Guideline: inhibit K^{+} channels.

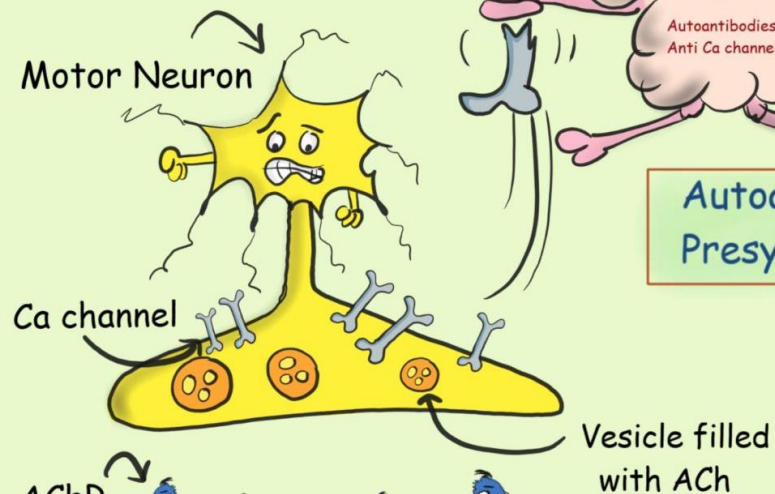
Lambert-Eaton Syndrome

Lamb eating Lamb
Who hated calcium
Channels at NMJ

I dislike calcium
and it's products..

...just lay lazy
and... Weak

don't get up
from chair and
don't climb stairs



Autoantibodies Calcium channels
Presynaptic motor neuron NMJ

No ACh release
from vesicles

AChR has no
ACh to attach

No depolarisation

No muscle contraction

Someone
Please open
Calcium channel
and get me ACh..

Creative-Med-Doses

Proximal
Muscle weakness

Tendon reflexes
depressed or absent

Autonomic symptoms
Dry mouth, impotence

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Resources

- 1. Blueprints Neurology 5th Edition**
- 2. Lecture notes**
- 3. step up to medicine**



Thank you