Neuromuscular Junction Disorders

Objectives:

- Anatomy and physiology of neuromuscular junction
- Classification of NMJ disorders Based on 1) etiology and 2) location
  - Myasthenia gravis
  - Lambert Eaton myasthenic syndrome
- Other neuromuscular junction disorders

Team Members: Abdulmalik Alhadlaq + lama altamimi + Waled Alaskah + Abdullah Altwerki

Team Leader: Haneen Al Subki

Revised By: Yara aldigi and Basel almeflh

Resources: 435 team + Davidson + 500 Single Best Answers in Medicine +Master the board USMLE + +Step 2 CK Qbook + Case files in Internal Medicine + Stepup to Medicine

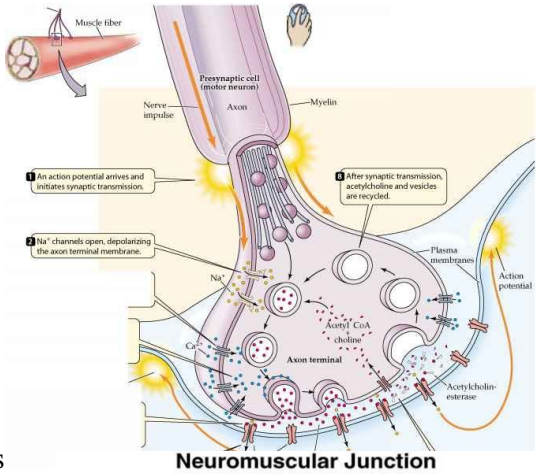
- Editing file
- Feedback

★ Anatomical description of a neuromuscular junction: Video

Each neuromuscular junction (NMJ) consists of the axon terminal of a motor neuron and the motor end plate of a muscle fiber.

The Motor Neuron Part:

- The axon of a motor neuron enters the structure of skeletal muscle and forms many branches called axon terminals.
- There is a swelling called a synaptic end bulb at the end of each axon terminal.
- Each synaptic end bulb contains many synaptic vesicles each of which contains an important neurotransmitter called acetylcholine.



The Muscle Fiber Part:

- The part of the sarcolemma muscle membrane of the muscle cell that is in closest proximity to the synaptic end bulb is called the motor end plate.

The Synapse or Neuromuscular Junction (NMJ):

- The area between the axon terminal and the sarcolemma. It is also called the "synaptic cleft"

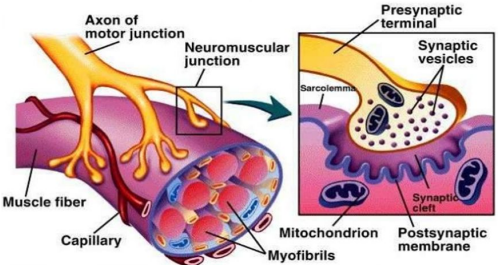
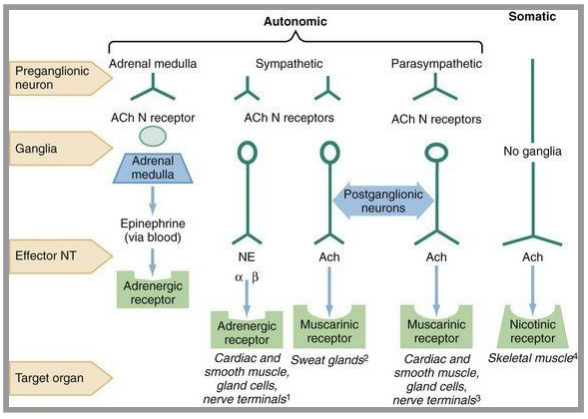
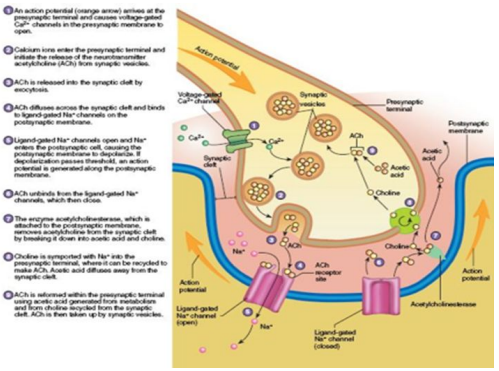


Figure:

Action potential at axon terminal of the motor neuron → Voltage gated Ca^{+2} channels open → Ca^{+2} will enter into the axon terminal → this Ca^{+2} entry will lead to opening of the vesicles that contains Ach and release of ACh by exocytosis → ACh will diffuse across the synaptic cleft and bind to its receptors in the sarcolemma → ACh binding will open ion channels in the receptors and this will lead to the passage of Na and K out of the muscle fiber → end plate potential, which is above the threshold, will open another Na channel in the muscle that will produce an action potential. Muscle contraction will be produced because of the increased Na ion diffusion compared to K → ACh effects are terminated by its breakdown in the synaptic cleft by acetylcholinesterase and diffusion away from the junction.

<table>
<tr><td colspan="3">Recall the anatomy of nerve cell transmission:
The nervous system is divided into</td><td rowspan="5"> 
</td></tr>
<tr><td rowspan="4">autonomic</td><td rowspan="2">Sympathetic</td><td>Preganglionic neuron:
● ACh. to Nicotinic receptors</td></tr>
<tr><td>Postganglionic neuron:
● NE to adrenergic receptors
● ACh. to muscarinic receptors (in sweat glands only)</td></tr>
<tr><td rowspan="2">Parasympathetic</td><td>Preganglionic neuron:
● ACh. to nicotinic receptors</td></tr>
<tr><td>Postganglionic neuron:
● ACh. to muscarinic receptors</td></tr>
<tr><td>Somatic</td><td colspan="2">Neuron directly synapses at the neuromuscular junction, releasing ACh. to nicotinic receptors.</td></tr>
</table>

★ Neuromuscular junction physiology: Release of ACh:



- When a nerve impulse reaches a synaptic end bulb, it triggers the release of the neurotransmitter acetylcholine (ACh) from synaptic vesicles that contain acetylcholine (ACh).
- ACh then diffuses across the synaptic cleft between the motor neuron and the motor end plate it is an electrical-chemical-electrical link.

Activation of ACh receptors:

- The motor end plate contains receptors onto which the free ACh binds after diffusing across the synaptic cleft.
- This binding of ACh to ACh receptors in the motor end plate causes ion channels to open & so allow the sodium (Na+) ions to flow across the membrane into the muscle cell.

Generation of muscle action potential:

- The flow of sodium (Na+) ions across the membrane into the muscle cell generates a muscle action potential.
- This action potential then travels along the sarcolemma,

Breakdown of Ach:

- The ACh that is released is only available to take part for a short time before it is broken down by an enzyme called acetylcholinesterase (AChE). This breakdown of ACh occurs within the synaptic cleft.

★ Classification of NMJ disorders: -According to the mechanism of action or etiology:

I. Immune-mediated disease	II. Toxic/metabolic	III. Congenital syndromes
• Myasthenia gravis • Lambert-Eaton syndrome -one of the best characterized and understood autoimmune disorders.	• Snake venom poisoning • Botulism • Arthropod poisoning • Organophosphates • Hypermagnesemia -the most common category.	• Congenital myasthenic syndromes. -The only disease that is considered presynaptic, synaptic and postsynaptic

According to the location of their disruption:

I. Presynaptic membrane of the motor neuron..
II. The synapse. The problem here is in the transmission of the ACh across the synapse. The disease that acts on the synaptic membrane is congenital myasthenia gravis and Organophosphate.
III. Postsynaptic membrane (the muscle fiber). The highest number of diseases affecting the NMJ are postsynaptic.

I. Presynaptic:

- Different mechanisms:
    a. Decrease in the release of acetylcholine (most often)
    b. Impairment in the calcium channels that induce exocytosis of Ach. vesicles.
    c. Disruption of other ion channels, such as potassium channels, causing inefficient repolarization at the presynaptic membrane as in neuromyotonia.
- Examples:
    a. Autoimmune neuromyotonia.
    b. Lambert-Eaton syndromes.
    c. Congenital myasthenia gravis.
    d. Botulism
    e. Aminoglycosides
    f. Envenomation (venom from animal bites)
    g. Hypermagnesemia and hypocalcemia

II. Synaptic:

- Congenital myasthenic syndromes
- Cholinesterase inhibitors
- Organophosphate

III. Postsynaptic (most common)

- The highest number of diseases affect the neuromuscular junction postsynaptically.
- Immune mediated Myasthenia Gravis is the most common.
- All the diseases that affect the postsynaptic membrane are forms of myasthenia gravis.
- Examples include:
    a. Myasthenia Gravis
    b. Congenital myasthenic syndromes (Neonatal Myasthenia Gravis , several types of Congenital myasthenia)
    c. Drug Induced Myasthenia Gravis (e.g. Penicillamine)

★ Myasthenia Gravis: video

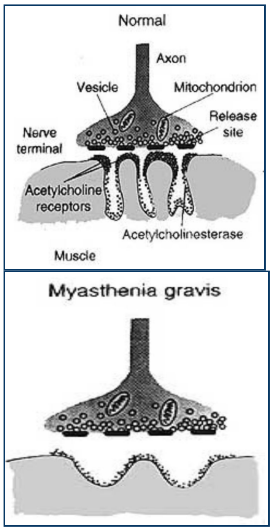
Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission.

Epidemiology:

- Myasthenia gravis is a relatively uncommon disorder with an annual incidence of approximately 7 to 23 new cases per million per year.
- Myasthenia gravis occurs at any age, but there is a **bimodal** distribution to the age of onset:
    a. Early peak in the second and third decades (female predominance) remember autoimmune diseases mostly affect young women
    b. Late peak in the sixth to eighth decade (male predominance)

★ Pathophysiology:

Normal	• With every nerve impulse, the amount of ACh released by the presynaptic motor neuron normally decreases because of a temporary depletion of the presynaptic ACh stores. (a phenomenon referred to as presynaptic rundown) We have two stores of Ach 1) distal and 2) proximal (tertiary) and the one that is released upon stimulation is from the distal stores, so what happens with continuous nerve stimulation is temporary depletion because it takes time to get more Ach from tertiary stores • Normally, when the end plate potential exceeds the threshold it causes an action potential.
Pathophysiology	1. In MG, there are antibodies attacking the ACh receptor by activating the complement system and other antibodies that are just blocking the receptor. The thymus gland has a role in the release of the autoantibodies causing a reduction in the number of ACh receptors (AChR) available at the muscle endplate and flattening of the postsynaptic folds. The flatter the surface (less folds) the higher the severity of symptoms. 2. Even if a normal amount of ACh is released, fewer endplate potentials will be produced, and they may fall below the threshold value for generation of an action potential. The end result of this process is inefficient neuromuscular transmission. Figure: There is a reduction in the number of AChRs at the muscle endplate and flattening of the postsynaptic folds.
	3. Inefficient neuromuscular transmission together with the normally present presynaptic rundown phenomenon results in a progressive decrease in the amount of muscle fibers being activated by successive nerve fiber impulses.The end plate potential in MG patient is less than that of normal people This explains the fatigability seen in MG patients.
	• Patients become symptomatic once the number of AChRs is reduced to approximately 30% of normal. If less, they won't have symptoms .
Reason:	• The decrease in the number of postsynaptic AChRs is believed to be due to an autoimmune process whereby anti-AChR antibodies produced by the thymus (another antibody is anti muscle-specific kinase, MuSK), block the target receptors (nicotinic), causing an increase in the turnover of the receptors, and damage of the postsynaptic membrane in a complement-mediated manner.
special case:	The Cholinergic receptors of smooth and cardiac muscle have a different antigenicity than skeletal muscle and usually are not affected by the disease since it affects **nicotinic** receptors only, THERE IS NO INVOLVEMENT OF GI NOR CARDIAC MUSCLES .



Clinical Features:.

- The hallmark of the disorder is a **fluctuating** (irregularity of the patterns of symptoms from day to day or even hour to hour) degree and variable combination of weakness in ocular, bulbar, limb, and respiratory muscles.
- Most important feature is fatigable weakness.
- It progresses for weeks to months, with maximum severity being usually in the first year. Less pronounced in the morning and improves after rest.
- >50% of patients present with ocular symptoms of ptosis and/or diplopia
- Of those who present with ocular manifestations, about half will develop generalized disease within two years.
- 15% of patients present with bulbar symptoms. These include **dysarthria, dysphagia, and fatigable chewing.**
- <5% present with proximal limb weakness alone usually affects arms more often than legs. When MG is suspected, ask about: breathing, swallowing, chewing, walking in Hx

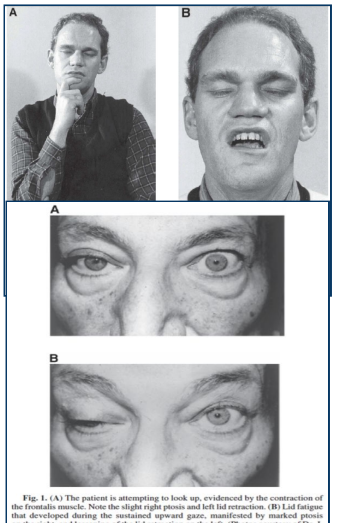


Fig. 1. (A) The patient is attempting to look up, evidenced by the contraction of the frontalis muscle. Note the slight right ptosis and left lid retraction. (B) Lid fatigue that developed during the sustained upward gaze, manifested by marked ptosis

- There are two clinical forms of myasthenia gravis:
  I. Ocular.
  II. Generalized.

I. Ocular myasthenia	II. Generalized disease
• The weakness is limited to the eyelids and extraocular muscles. • Weak eye closure, pupils are spared. • Manifests as binocular diplopia[1] (horizontal or vertical) or ptosis[2].	• the weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles. • Symptoms are typically worse at the end of the day. • Less pronounced in the morning and improves after rest. --- • Breathy nasal speech (palatal weakness). • Dysphagia and difficulty clearing secretions. • Shortness of breath due to diaphragm weakness (orthopnea). --- • Weakness is usually proximal and symmetric (deltoid and triceps). • Proximal muscle involvement. • Specific involvement of extensors of the fingers. • Neck flexors more than neck extensors weakness.

★ Affected Muscles

1. Ocular muscles:

- Weakness of the eyelid muscles can lead to ptosis[2] (fluctuating).
- The ptosis (is usually asymmetric) may start bilaterally then improve in one eye, resulting in unilateral ptosis or alternate.
- BUT the limb has symmetric involvement .
- Variable severity.
- Extraocular muscles involvement (binocular diplopia[1]). It may be horizontal or vertical.

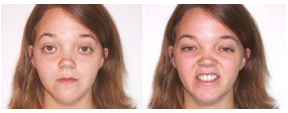
2. Bulbar muscles:

- Muscles of jaw closure more than jaw opening (fatigable chewing).
- Oropharyngeal muscle weakness produces dysarthria and dysphagia.
- Palatal muscle weakness causing nasal speech.
- Nasal regurgitation, particularly of liquids, may occur due to palatal weakness.

[1] Binocular diplopia is diplopia or double vision when BOTH eyes are open, so patients usually complain that they are used to closing one eye in order to see things and people around them as one.
Weakness in which muscles cause diplopia? Any of the extraocular muscle group (medial, superior or inferior recti..). In MG there's a predilection to affect the medial rectus

[2] Weakness in which muscles cause ptosis? Levator palpebrae superioris and superior rectus.

3. Facial muscles weakness, not facial nerve injury! (nerves are intact)



- Frequently involved and causing expressionless face looks like parkinson's face
- Transverse smile may be evident on examination (myasthenic sneer) where the mid-lip rises but the outer corners of the mouth fail to move.
- Orbicularis oculi weakness causing incomplete eye closure (the two pictures). Orbicularis oculi is the muscle in the face that closes the eyelids. When it's affected the patient won't be able to close their eyes and you'll see the sclera when they attempt to. This is called bell's phenomenon.

4. Neck and limb muscles (severe disease only)

- Neck extensor and flexor muscles are commonly affected. (flexor being weaker than extensor)
- Dropped head syndrome (due to extensor weakness). Caused by severe weakness of the neck extensor muscles in the severe cases (very rare) → progress to cause kyphosis and inability to lift the head up.
- Proximal limb weakness (the arms > the legs). proximal more than distal
- Wrist and finger extensors and foot dorsiflexors. This sign is always misdiagnosed with radial nerve injury.

5. Respiratory muscles

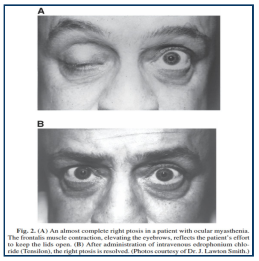
- Respiratory muscle weakness can lead to respiratory insufficiency and pending respiratory failure (myasthenic crisis). Occurs in 15% of patients. sometimes they require intubation .
- It may occur spontaneously during an active phase of the disease or may be precipitated by a variety of factors including surgery, infections, certain medications, or tapering of immunotherapy.
- Restrictive pattern on PFTs

★ Differential Diagnosis

Muscle Disease	NMJ Disorder	Motor Neuron Disease
• Thyroid ophthalmopathy. • Oculopharyngeal Muscular Dystrophy (OPMD). • Myotonic Dystrophy. • Progressive External Ophthalmoplegia.	• Lambert Eaton Myasthenic Syndrome • Botulism and Tick Paralysis • Congenital MG • Penicillamine induced Myasthenia	• Amyotrophic Lateral Sclerosis (ALS) The difference is; ALS is distal, Asymmetric and its extremely rare to have eye involvement. • Progressive Muscular Atrophy (PMA)
Peripheral Nerve	**Brainstem Pathology**	**Others**
• Oculomotor Cranial Nerve pathology. • Guillain Barre Syndrome (GBS) The difference is; GBS is acute and peripheral with sensory symptoms and Areflexia. • Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). • Cavernous Sinus pathology.	• Stroke • MS • Tumours • Infections	• Isolated ptosis • Isolated Dysconjugate Gaze (Decompensated strabismus)

★ Diagnosis:

I. Bedside tests:

1. Edrophonium (Tensilon) test: IV injection of small amount of tensilon either in the arm or the back of the hand depending on the reason behind the test.	It should be used only in those patients with obvious ptosis or ophthalmoparesis, in whom improvement after infusion of the drug can easily be observed. (used to monitor the disease as well). • Edrophonium chloride is an acetylcholinesterase inhibitor with rapid onset (30 to 45 seconds) and short duration of action (5 to 10 minutes).that is why you see the effect immediately • It prolongs the presence of acetylcholine in the neuromuscular junction and results in an immediate increase in muscle strength in many of the affected muscles. • +ve in more than 90% of patients with MG. • Limitations: Not available, time consuming, and has many complications including: bradycardia and respiratory depression, that is why we prefer doing other tests. 
2. Ice pack (ocular cooling) test: low temperatures increase ACh. release → enhancing transmission across NMJ.	It can be used in patients with ptosis, particularly when edrophonium is -ve or contraindicated. • A bag (or surgical glove) is filled with ice and placed on the closed lid for two minutes (and wait for symptom improvement) The ice is then removed and the extent of ptosis is immediately assessed.  Fig. 1 : Bilateral ptosis (more marked in right eye) Fig. 2 : Ice Pack application on right eye Fig. 3 : Improvement in ptosis of right eye after ice pack application • The sensitivity appears to be about **80%**. High sensitivity and specificity for MG. • This is the most common test used in patients with ptosis because it's simple, non invasive, and the diagnosis can be made based on it. The limitation in this test is that it can't be applied to all patients, only patients with ptosis.
3. Fatiguing Maneuvers	(sustained upgaze, sustained abduction of the arms, sustained elevation of leg while lying supine and counting loud) To test eye fatigability, tell the patient to look up for 1-2 minutes without closing their eyes eventually they'll develop ptosis (medial rectus affected more than lateral rectus) To test arm fatigability, tell the patient to raise his arm for 2 minutes after the 2 minutes the arm will be weak. To test the vocal fatigability, ask the patient to count to 50 out loud and you will notice vocal fatigue.

II. Serological Tests:

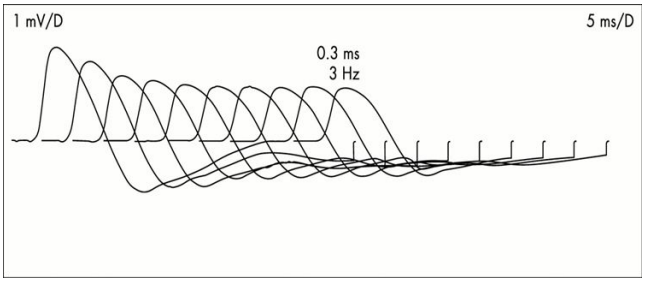
- **Best Initial Test:** Acetylcholine receptor binding antibodies (AChR-Ab) found in in 80-90% of those with generalized disease and in 40-55% of those with ocular myasthenia. If the antibody is negative that doesn't exclude the disease.
- MuSK (muscle specific kinase) antibodies are present in 38-50% of those with generalized myasthenia gravis who are AChR-Ab negative. Very important test for young females with obvious **bulbar, respiratory symptoms or tongue atrophy less involvement eye and limb .**
- If both tests are negative that is called double seronegative
- So if we order AchR-ab and it appears negative but we still have high suspicion we order MuSk-Ab

III. Tests:

- CBC,RFT,LFT,muscle enzyme,TSH , "I want to know the patient"

IV. Electrophysiologic Confirmation:

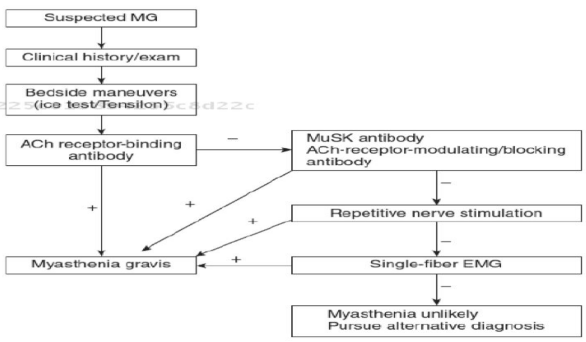
1. **Repetitive nerve stimulation:** No need to memorize the details of this procedure just know the name and pattern .
   - The nerve is electrically stimulated 6 to 10 times at low rates (2 or 3 Hertz) to deplete the Ach. The compound muscle action potential (CMAP) amplitude is recorded from the electrodes over the muscle after electrical stimulation of the nerve.
   - In normal muscles:
     - there is no change in CMAP amplitude with repetitive nerve stimulation.
   - In myasthenia:
     - there may be a progressive decline in the CMAP amplitude with the first four to five stimuli.
   - An RNS study is considered positive (abnormal) if the **decrement is greater than 10 %.**
   - RNS studies are positive in more than 75% of patients with generalized myasthenia.



   - 50-100% sensitivity for Generalized MG whereas, 10-50% sensitivity for Ocular MG.
   - Figure: At the beginning, when we start we will have good action potential but with repetitive stimulation what will happen? the action potential will decrease because there is depletion of ACh (decremental sign/response) leading to a decrease in the action potential.
2. Single fiber electromyography: 📍 Most Accurate Test and sensitive. We insert a needle in the NMJ to record its activity .
   - It is positive in greater than 90% of those with generalized myasthenia.

     -if it's negative it excludes Myasthenia Gravis but it's rarely done due to difficulty of the technique. Ordered only when other tests are negative.

How to approach the patient:



Box 1 Factors exacerbating weakness in myasthenia gravis and potentially triggering myasthenic crisis

- Infections
- Stress—trauma, postoperative
- Withdrawal of cholinesterase inhibitors (when symptoms not fully controlled)
- Rapid introduction or increase of steroids
- Electrolyte imbalance—hypokalaemia, hypophosphataemia
- Anaemia
- Medications: most are rarely implicated, except those highlighted
  - Antibiotics
    - Aminoglycosides: **gentamicin**, amikacin, **telithromycin**, etc
    - Quinolones: ciprofloxacin, norfloxacin, etc
    - Tetracyclines: doxycycline, minocycline, etc
    - Antimalarials: **chloroquine**
  - Antirheumatic drugs: **penicillamine**
  - Anaesthetic agents: **succinylcholine**
  - Antiarrhythmic drugs: quinidine, procainamide
  - Antihypertensives: β blockers and calcium channel blockers
  - Neuropsychiatric drugs: lithium, chlorpromazine, phenytoin
  - Chemotherapy: cisplatin
  - **Botulinum toxin**

V. CT Mediastinum:

- In AChR antibody positive myasthenia gravis, >75% of patients have thymic abnormalities.
- Thymic hyperplasia is most common 85% common in young pts. who are most probably females.
- Thymic tumors (primarily thymoma) is found in up to 15%. (50% of people with thymoma have MG) common in old pts who are most probably males. **Resection is necessary.**

VI. Autoimmune disorders: autoimmune disorders tend to present in association with each other

- Autoimmune thyroid disease[3] is common (3-8%) in patients with myasthenia gravis.
- Screening for thyroid abnormalities should also be part of the initial evaluation.

★ Treatment:

Symptomatic treatment	• Anticholinesterase (Cholinesterase inhibitors): pyridostigmine (mestinon). • It enhances the communication between nerves and muscles. It doesn't cure the underlying condition, but may improve muscle contraction and muscle strength.
Chronic immunotherapies (Immunosuppressive therapy)	• glucocorticoids/immunosuppressive drugs • Used in significant proximal muscle weakness, respiratory or bulbar symptoms. it provides the body with normal antibodies, which alters your immune system response. it may take a week to start working, and the benefits usually last no more than three to six weeks. ➢ Prednisone. ➢ Azathioprine (Imuran). ➢ Methotrexate. ➢ Cyclosporine.
Rapid immunotherapies for myasthenia crisis	• plasma exchange (plasmapheresis) • Intravenous immune globulin [IVIG] ➢ (Used in significant proximal weakness or respiratory/bulbar symptoms)
Thymectomy	• **Done to all patients with thymoma** and for any patient with +ve Ach receptor antibodies except for those who are above 65. If they are above 65 and have thymoma then thymectomy is performed. • It may eliminate the symptoms or improve it. • Improvement is seen in 20% of the patients within the first year. Improvement rates of 70% over 5-7 years. • Not a cure, but increases the chance for control and for lowering cortisone dose • If they present with hyperplasia in the first year of symptom onset then perform thymectomy, but that doesn't mean that that remession will be immediate. it may take up to 10 years .

[3] always check thyroid function, Don't screen for every autoimmune disease unless signs are present, only thyroid function is routine in these patients.

★ Lambert Eaton Syndrome video

Lambert-Eaton myasthenic syndrome (LEMS) is a rare presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine (ACh) is impaired.

Epidemiology:

- The true incidence of LEMS is unknown, but the condition is uncommon and occurs much less frequently than myasthenia gravis.
- The incidence and prevalence of LEMS in patients with SCLC is estimated to be approximately 3%
- Nearly 50% of LEMS cases are associated with a malignancy, mainly small cell lung cancer (SCLC)
- The other tumors associated with LEMS are lymphoproliferative disorders (Hodgkin lymphoma)

Pathophysiology:

1. An autoimmune attack directed against the voltage-gated calcium channels (VGCCs) on the presynaptic motor nerve terminal results in a loss of functional VGCCs (which is responsible for vesicle release) at the motor nerve terminals.
2. The number of quanta[4] released by a nerve impulse is diminished.
3. Because presynaptic stores of ACh and the postsynaptic response to ACh remain intact, rapid repetitive stimulation or voluntary activation that aids in the release of quanta will raise the endplate potential above threshold and permit generation of muscle action potential. with activity they improve , because activity helps release the Ach! unlike myasthenia gravis.

- Clinically, this phenomenon is noted by the appearance of previously absent tendon reflexes following a short period of strong muscle contraction by the patient.
- **Parasympathetic, sympathetic, and enteric neurons are all affected.** Unlike myasthenia gravis
- **Number of vesicles and concentrations of ACh remain normal (very imp).**

★ Etiology:

Autoimmune (inflammatory):

- antibodies directed against the voltage-gated calcium channel (VGCC).
- These antibodies interfere with the normal calcium flux required for the release of acetylcholine.

Paraneoplastic:

- The expression of functional VGCCs in the surface membrane of small cell lung cancer (SCLC) cells (among numerous other neural antigens) is responsible for most cases of paraneoplastic LEM. Small cell lung carcinoma has VGCC expressed on its surface. Since the body wants to attack and fight the tumor, it generates antibodies against all VGCC in the body .

- SO LES may indicate malignancy! That's why we always check for malignancies .

[4] the unit quantity of acetylcholine released at a neuromuscular junction by a single synaptic vesicle, contributing a discrete small voltage to the measured end-plate potential.

Clinical manifestations (Features):

- Most patients with LEMS present with slowly progressive proximal muscle weakness, **particularly involving the legs. (**unlike myasthenia particularly the arms)
- Deep tendon reflexes are typically decreased or absent.
- Occasionally, paresthesias and myalgia
- Recovery of lost deep tendon reflexes or improvement in muscle strength with vigorous exercise, brief muscle activation is a unique aspect of LEMS **(Post exercise facilitation/excitation phenomenon)**

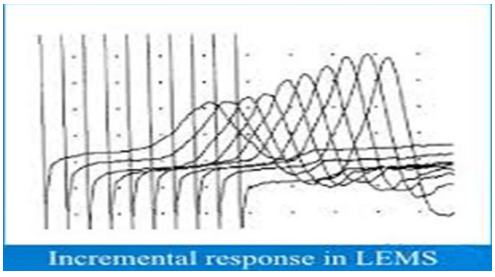
- Ocular symptoms, especially ptosis and diplopia, may occur with LEMS but are rarely the presenting or dominant feature of the illness.
- Eye is typically spared

- Autonomic system involvement
- Dry mouth is the most common autonomic symptom, while erectile dysfunction is common in men.
- Most patients do not have significant respiratory muscle weakness.
- Respiratory symptoms are very rare (if present, they come late)
- Always look for SCC in old people presenting with LEMS (usually male)

Diagnosis:

- On exam:
  - ➢ Proximal muscle weakness
  - ➢ improvement after few seconds of contraction
  - ➢ Poorly reactive pupils
  - ➢ Hyporeflexia or areflexia

- **What is the most important single test in LEMS? CT chest to rule out SCC.**
- The diagnosis of LEMS is usually made on clinical grounds and confirmed by the presence of antibodies to voltage-gated calcium channel (VGCC) and by electrodiagnostic studies which are diagnostic .
- Antibodies against the P/Q-type VGCC are present in approximately 85-95% of patients with LEMS.
- High frequency (10 to 50 Hz) repetitive nerve stimulation (RNS) or brief (eg, 10 seconds) maximal isometric muscle activation results in significant increment with a marked increase in the CMAP amplitude. (hence, EMG is great at distinguishing between LEMS and MG).


Incremental response in LEMS

★ Treatment

- Search for and treat the primary underlying malignancy in patients with any risk factors for small cell lung cancer. i.e. old and smoker. It can significantly improve the symptoms of LEMS
- Symptomatic therapies for LEMS include medications that increase the amount of acetylcholine available at the postsynaptic membrane.
  - ➢ These are: **guanidine**, aminopyridines such as **3,4-diaminopyridine (3,4-DAP)**, and acetylcholinesterase inhibitors such as pyridostigmine.
- Immunologic therapies include intravenous immune globulin (IVIG) and oral immunosuppressive agents.

Other neuromuscular junction disorders:

★ Botulism

What is Botulism?

- It is an uncommon and life-threatening disease caused by bacteria in the Clostridium family.
- Organisms of the Clostridium genus are commonly found in soil and include C.botulinum, C baratii, and C. butyricum.
- They are all gram-positive, anaerobic, spore-forming rods, which have evolved to produce a potent neurotoxin

---

- All forms of the toxin block Ach release from presynaptic motor nerve terminals as well as the sympathetic and parasympathetic nerve ganglia
- In high enough doses, botulinum neurotoxin is considered the most potent lethal substance known.
- The intracellular target is the SNARE proteins[5] of the presynaptic membrane.
- Neuromuscular symptoms usually begin 12-36 hours after ingestion of contaminated food, symptoms usually preceded by nausea and vomiting.
- An average of 110 cases of botulism is reported each year in the United States.
- Approximately 72% of these cases are infant botulism, 25% are food borne botulism, and 3% are wound botulism.

It occurs in 4 forms, differentiated by the mode of acquisition:	1. Food borne botulism (Classic): ● occurs after ingestion of food contaminated by preformed botulinum toxin. ingested through improperly stored foods (e.g. homemade canned food). ● Found in honey, That's why we avoid giving honey to babies <1 year → causes infant botulism.
	2. Infant botulism: ● occurs after the ingestion of clostridial spores that then colonize the host's gastrointestinal (GI) tract and release toxin produced in vivo. That's why we don't feed babies honey. Honey contains botulism spores.
	3. Wound botulism & IV drug abuse: most common ● occurs after infection of a wound by Clostridium botulinum with subsequent in vivo production of neurotoxin.
	4. Adult enteric infectious botulism (or adult infectious botulism of unknown source): ● is similar to infant botulism in that toxin is produced in vivo in the GI tract of an infected adult host.
other forms:	**5. Hidden** 6. **Iatrogenic** if too much botulinum toxin is injected for cosmetic or medical purposes like migraine .

[5] Proteins that mediate the fusion of vesicles with their target membrane bound compartments.

Clinical Features **-Acute onset of bilateral cranial neuropathies associated with symmetric descending weakness.**	
• Cranio-ocular symptoms begin soon after initial GI symptoms after ingestion. • Pupils dilated and fixed in 50-75%. • Ptosis, symmetrical EOM[6] weakness (may improve with tensilon). • Very acute with one to 2 days, descending weakness with pupil abnormality	❖ **Key features of botulism syndrome!** • Absence of fever. • symmetrical neurological deficits. • Normal or slow heart rate and normal blood pressure. • The patient remains responsive. • No sensory deficits with the exception of blurred vision.why? because it's a disease of the NMJ !!

★ Diagnosis:

The diagnosis is usually clinical as routine lab tests are nonspecific, and specific laboratory confirmation may take up to days.

-Electrodiagnostic studies are helpful in the diagnosis of botulism:

- Repetitive nerve stimulation (RNS) at low frequencies of 2 to 5 Hz causes decremental response.
- RNS at high frequencies stimulation or exercise causes incremental response, or postactivation facilitation (in 60% of adult botulis).
- The amount of facilitation[7] seen with botulism (40-100%) is usually less than that seen in Lambert-Eaton myasthenic syndrome (200%).

★ Treatment:

Any patient with clinical signs, symptoms, or history suspicious for botulism should be hospitalized immediately and monitored for signs of respiratory failure and provided with supportive management.

1. There are two botulism antitoxin therapies available (Prevents the toxins from causing further damage):
    a. Bivalent (A and B).
    b. Trivalent (A, B and E) antitoxin.
    - Equine serum heptavalent botulism antitoxin is used to treat children older than one year of age and adults.
    - Human-derived botulism immune globulin is used for infants less than one year of age.
2. Antibiotics are recommended for wound botulism after antitoxin has been administered:
    a. Penicillin G (3 million units intravenously [IV] every four hours in adults) provides effective coverage of other clostridial species and is frequently used.
    b. Metronidazole (500 mg IV every eight hours) is a possible alternative for penicillin allergic patients.

[6] "Extraocular muscle".
[7] the enhancement of the response of a neuron to a stimulus following prior stimulation.

★ Tick Paralysis uncommon (male doctor didn't explain)

The ticks involved include:	1. The Rocky Mountain Wood Tick (Dermacentor Andersoni), 2. The American Dog Tick (Dermacentor Variabilis), 3. The Lone Star Tick (Amblyomma Americanum), 4. The black-legged tick (Ixodes scapularis)	
General	• Several tick species produce a toxin that inhibits transmission at the neuromuscular junction by **blocking influx of sodium ions.** • This prevents presynaptic terminal axon depolarization and inhibits release of acetylcholine at the nerve terminal.	
Symptoms	• onset occurs three to seven days after attachment of the tick • include anorexia, lethargy, muscle weakness, nystagmus, and an ascending flaccid paralysis.	
Diagnosis	• Diagnosis of tick paralysis usually relies on the finding of a tick attached to the patient. • Unexposed areas such as the scalp, genitalia, and external meatus should be inspected carefully. The most common spots are on the scalp especially the neck hairline. Ticks also attach to the armpit, between fingers and toes and around the genital area and rectum, so it's very important to check these areas.	
Treatment	• **Removal of the tick is the primary treatment of tick paralysis.**	

★ Snake Venom

The toxins produce their effect either on the presynaptic or postsynaptic junction.

presynaptic-acting toxins	postsynaptic-acting toxins
• include beta-bungarotoxin (krait), notexin (tiger snake), taipoxin (Taipan), and crotoxin (Brazilian rattlesnake) • The exact mechanism of toxicity is undefined, but initial fusion of synaptic vesicles with the presynaptic membrane is induced, followed by inhibited reformation of the vesicles after exocytosis. Further neurotransmitter release is therefore prevented. • Presynaptic toxins have no response to antivenom.	• The postsynaptic-acting toxins bind **irreversibly** to the acetylcholine receptor site, and prevent the opening of the associated sodium channel (an example is alpha-bungarotoxin). • The postsynaptic toxins produce findings on electrodiagnostic studies identical to those seen in myasthenia gravis, since the mechanism of disease is similar. • Repetitive nerve stimulation produces a decremental response. • Antivenom is available and effective for postsynaptic neurotoxins. It accelerates dissociation of the toxin from the postsynaptic receptor.

★ Organophosphate & Carbamate Toxicity

- Organophosphates and carbamates are potent inhibitors of acetylcholinesterase, causing excess acetylcholine concentrations in the synapse.
- commonly used as pesticides.
- Exposure routes include:
  - ➢ Oral ingestion
  - ➢ Inhalation.
  - ➢ Dermal contact.

Clinical manifestation:

- Both sympathetic and parasympathetic systems are involved.
- Symptoms of organophosphate and carbamate poisoning include both:
  - ➢ Muscarinic signs (lacrimation, bradycardia, bronchospasm)
  - ➢ Nicotinic signs (mydriasis, tachycardia, weakness, hypertension)
- Increased depolarization at **nicotinic neuromuscular synapses results in muscle weakness and flaccid paralysis**
- CNS symptoms may be present, with suppression of central medullary centers resulting in anxiety, confusion, seizures, and coma.
- 10-40% of patients develop a distinct neurologic disorder 24-96 hours after organophosphorus agent poisoning, referred to as the "intermediate syndrome."
- The diagnosis of organophosphate or carbamate poisoning is made on clinical grounds; the clinical features of **cholinergic excess** should indicate the possibility of organophosphate poisoning.

Treatment:

- Emergency management of organophosphate or carbamate poisoning often requires endotracheal intubation and volume resuscitation.
- All cases require aggressive decontamination with complete removal of the patient's clothes and vigorous irrigation of the affected areas.
- **Atropine :**
  - ➢ is used for symptomatic relief of muscarinic symptoms.
  - ➢ It does not reverse the paralysis caused by neuromuscular blockade that results from nicotinic receptor stimulation.
  - ➢ dosing should be titrated to the therapeutic end point of the clearing of respiratory secretions and the cessation of bronchoconstriction.

★ Hypermagnesemia & Hypocalcemia

Happens in icu pts. When there is no other explanation of the symptoms, you check the levels!

- Causes inhibition of acetylcholine release so it's pre-synaptic.
- **Magnesium has a calcium channel blocking effect that decreases entry of calcium into cells.**
- It also decreases the amount of acetylcholine released and depresses the excitability of the muscle membrane.

- This produces proximal muscle weakness, which may progress to respiratory insufficiency.
- Ocular muscles are generally spared.
- The diagnosis of hypermagnesemia or hypocalcemia is generally made by demonstrating **elevated serum magnesium levels or decreased calcium levels.**
- Observing clinical improvement as levels normalize.

Summary

Click HERE for more clear organization :)

	Pathophysiology	Clinical Features	Diagnosis	Treatment
Myasthenia Gravis The most common	1) ↓ in the number of ACh receptors available at the muscle postsynaptic folds. 2) Fall below the threshold value for generation of an action potential. 3) Inefficient neuromuscular transmission (symptomatic once the number of AChRs is 30% of normal).	· Ocular symptoms of ptosis and/or diplopia. · Bulbar symptoms dysarthria, dysphagia, and fatigable chewing. · Proximal limb weakness. · Respiratory muscle weakness can lead to respiratory failure (**myasthenic crisis**).	Best Initial Test: Acetylcholine receptor binding antibodies (AChR-Ab) **Most Accurate Test**: Single fiber electromyography	· Anticholinesterase **pyridostigmine.** · Immunosuppressive therapy **Prednisone** · Thymectomy, We do thymectomy for any patient with thymoma.
Lambert Eaton Syndrome rare	1) Autoimmune attack directed against the VGCCs on the presynaptic motor nerve terminal. 2) Loss of functional VGCCs. 3) The number of quanta **released** by a nerve impulse is diminished. Number of vesicles and concentrations of ACh. remain **NORMAL!!**	· Proximal limb weakness. · Ocular symptoms of ptosis and/or diplopia. · Deep tendon reflexes are typically decreased or absent. · Dry mouth · erectile dysfunction. · Respiratory symptoms are very rare.	What is the most important single test in LEMS? CT chest to rule out SCC. Confirmed by: The presence of antibodies to **VGCC** and by electrodiagnostic studies.	· Treat the primary malignancy. · Symptomatic therapies: **Guanidine Pyridostigmine.** · Immunologic therapies: **intravenous immune globulin**
Botulism rare	· life-threatening disease caused by: C.botulinum, C baratii, and C butyricum. · The toxin blocks Ach release from presynaptic motor nerve terminals as well as the sympathetic and parasympathetic nerve ganglia.	· Pupils dilated and fixed. · Ptosis, symmetrical EOM weakness. · Bulbar weakness. · Symmetrical limb weakness. · Respiratory weakness	Electrodiagnostic studies. Repetitive nerve stimulation (RNS)	Botulism antitoxin: **Bivalent** or **trivalent.** Antibiotics for wound botulism: **Penicillin G Metronidazole** Hospitalized immediately!

Questions

1. Which of the following statements concerning the neuromuscular junction is correct?

A. The motor nerve endings secrete acetylcholine
B. The motor nerve endings secrete noradrenaline (norepinephrine)
C. Curare leads to prolongation of neuromuscular transmission
D. The muscle membrane possess muscarinic receptors
E. Nicotine blocks neuromuscular transmission

2. A 55-year-old woman complains of double vision. She finds that she is more tired than usual and has difficulty climbing stairs, especially when they are very long. She has difficulty getting items off high shelves at work and lately even brushing her hair is a problem. During the consultation, her voice fades away during conversations. Reflexes are present and equal throughout. Which sign or symptom is most indicative of myasthenia gravis?

A. Proximal weakness
B. Normal reflexes
C. Diplopia
D. Fatigability
E. Bulbar symptoms

3. A 67-year-old man with lung cancer is seen by the palliative-care team after complaining of severe fatigue and weakness. He is now unable to stand from sitting, has problems chewing and gets occasional double vision. Examination shows normal power in the hands and feet, but weakness of the girdle muscles and an oculomotor nerve palsy on the right with ptosis. The doctor is surprised that the weakness improves after repeated demonstrations to colleagues. Most likely diagnosis is:

A. Isaac's syndrome
B. Horner's syndrome
C. Lambert–Eaton syndrome
D. Myasthenia Gravis

4. A 55-year-old woman complains of double vision. She finds that she is tired all the time and has difficulty climbing stairs. She has difficulty getting items off high shelves at work. Reflexes are absent but elicited after exercise. Shoulder abduction is initially 4−5 but on repeated testing is 4 +/5. What pathology is associated with this female's diagnosis?

A. Thyrotoxicosis
B. Peptic ulcer
C. Diabetes
D. Stroke
E. Lung cancer

5. The bacteria that cause botulism are usually found where in nature?

A. In feces
B. In mold
C. In the soil
D. In the air

Answers: 1: A, 2: D, 3: C, 4: A, 5: D