Neuromuscular Junction Disorders

435 medicine teamwork

[**Important** | **Notes** | **Extra** | **Editing file**]

lecture objectives:

- Recognize the symptoms and signs of neuromuscular junction disorders (e.g. myasthenia gravis, MG)
- Understand the pathophysiology of MG
- List the appropriate workup for MG
- List management options for MG

The doctor mentioned that the slides and his notes are more than enough,

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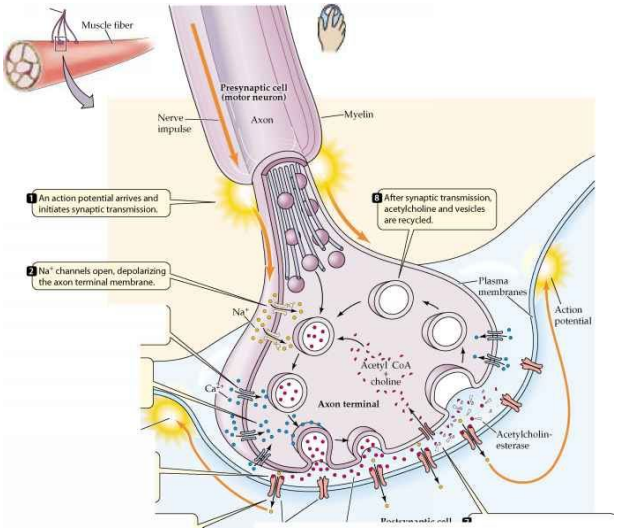
References: Doctors' Slides + Davidson + Master the boards + Step Up

What is Neuromuscular Junction?

Each neuromuscular junction 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 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):

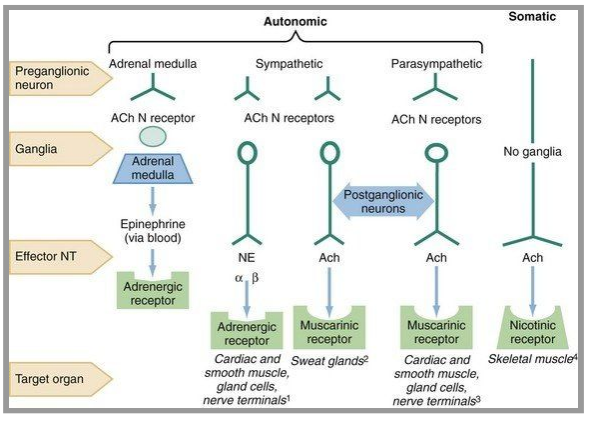
- The area between the axon terminal and the sarcolemma, also called the 'synaptic cleft'

Recall the anatomy of nerve cell transmission:

The nervous system is divided into

1. Autonomic
   → Sympathetic
   - Preganglionic neuron:
     ➢ ACh. to Nicotinic receptors
   - Postganglionic neuron:
     ➢ NE to adrenergic receptors
     ➢ ACh. to muscarinic receptors (in sweat glands only)

   → Parasympathetic
   - Preganglionic neuron:
     ➢ ACh. to nicotinic receptors
   - Postganglionic neuron:
     ➢ ACh. to muscarinic receptors
2. Somatic
   Neuron directly synapses at the neuromuscular junction, releasing ACh. to **nicotinic** receptors



Physiology of NMJ

Release of ACh:

- When a nerve impulse reaches a synaptic end bulb, it triggers 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

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. into the T tubules, allowing the release of calcium from sarcoplasmic reticulum

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:

Immune-mediated disease	Toxic/metabolic	Congenital syndromes
• Myasthenia gravis • Lambert-Eaton syndrome	• Snake venom poisoning • Botulism • Arthropod poisoning • Organophosphates • Hypermagnesemia	• Congenital myasthenic syndromes

According to the location of their disruption:

1. Presynaptic membrane of the motor neuron
2. Synaptic
3. Postsynaptic membrane (the muscle fiber)

- It's important to know which conditions are presynaptic, synaptic or postsynaptic

Presynaptic

- Different mechanisms:
  - ➢ Decrease in the release of acetylcholine most commonly
  - ➢ Calcium channels impairment that induces exocytosis of Ach. vesicles like Lambert Eaton
  - ➢ Disrupted K channels causing inefficient repolarization at the presynaptic membrane as in neuromyotonia
- Examples:
  - ➢ Autoimmune neuromyotonia
  - ➢ Lambert-Eaton syndromes
  - ➢ Congenital myasthenic syndrome
    - It's the only condition that is considered presynaptic, synaptic and postsynaptic
  - ➢ Botulism
  - ➢ Aminoglycosides
  - ➢ Envenomation venom from animal bites
  - ➢ Hypermagnesemia and hypocalcemia
    - They affect calcium channel influx

Synaptic

- Congenital myasthenic syndromes
- Cholinesterase inhibitors
- Organophosphate Dr. **emphasized** that we should know that it is synaptic

Postsynaptic (most common)

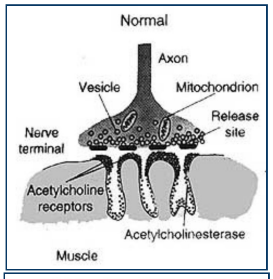
- Immune mediated Myasthenia Gravis is the most common
- All the diseases that affect the postsynaptic membrane are forms of myasthenia gravis
- Examples include:
  - Myasthenia Gravis
  - Congenital myasthenic syndromes
  - Penicillamine
  - Drug Induced Myasthenia Gravis

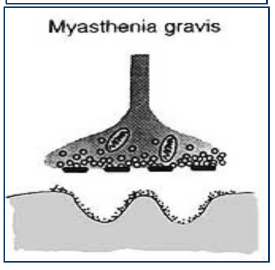
Myasthenia Gravis

Epidemiology

- Myasthenia gravis is a relatively uncommon disorder with an annual **incidence** of approximately 10 to 20 per million per year, and a **prevalence** of 200 per 100 000
- Gender and age influence the incidence of MG
  - Women are affected 3 times more common than men under the age of 40
  - Incidence is higher in males over 50 and roughly equal during and before puberty
- Myasthenia gravis occurs at any age, but there is a **bimodal** distribution to the age of onset:
  - Early peak in the second and third decades (female predominance)
  - Late peak in the sixth to eighth decade (male predominance)

Pathophysiology





- In MG, there is a reduction in the number of ACh receptors available at the muscle endplate and flattening of the postsynaptic folds
- The decrease in the number of postsynaptic AChRs is believed to be due to an autoimmune process whereby anti-AChR antibodies (anti muscle-specific kinase, MuSK), are produced and 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
- Acetylcholine receptor antibodies originate from the thymus gland, why? thymic gland contains myoid cells which are the only extramuscular region where acetylcholine receptors are present
- Patients become symptomatic once the number of AChRs is reduced to approximately 30% of normal
- This will lead to a decline in the amount of ACh released by the presynaptic motor neuron (a phenomenon referred to as presynaptic rundown)
- Both the reduction in AchRs and presynaptic rundown result in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or myasthenic fatigue
- Cholinergic receptors of smooth and cardiac muscle have a different antigenicity than skeletal muscle and usually are not affected by the disease why? Because MG affects nicotinic receptors only

Clinical Features

- Myasthenia gravis is the most common disorder of neuromuscular transmission
- Most important feature is **fatigable weakness**, fluctuating from day to day or hour to hour throughout the day. it is NOT progressive
- It progresses for weeks to months, with maximum severity being usually in the first year
- less pronounced in the morning and improves after rest
- There are two clinical forms of myasthenia gravis:
  - ➢ Ocular in 50%
  - ➢ Generalized in 50%
- Ocular and bulbar are much more common than the others, it rarely affects peripheral muscles

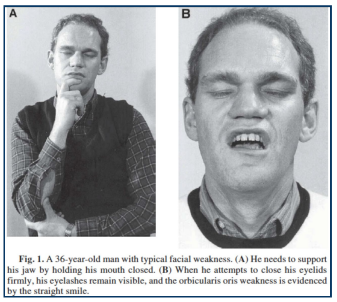


Fig. 1. A 36-year-old man with typical facial weakness. (A) He needs to support his jaw by holding his mouth closed. (B) When he attempts to close his eyelids firmly, his eyelashes remain visible, and the orbicularis oris weakness is evidenced by the straight smile.

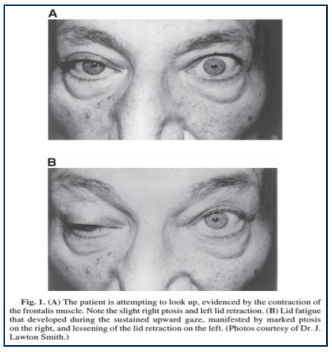


Fig. 1. (A) The patient is attempting to look up, evidenced by the contraction of the frontalis muscle. Note the slight right ptosis and left lid retraction. (B) Lid fatigue that developed during the sustained upward gaze, manifested by marked ptosis on the right, and lessening of the lid retraction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

Ocular myasthenia:

- The weakness is limited to the eyelids and extraocular muscles and usually asymmetric ptosis
- Weak eye closure, pupils are spared
- Manifests as **binocular diplopia**[1] or **ptosis**[2]
- Usually progression (into generalized) is serious in the first two years, after that it's extremely rare (disease remains purely ocular)

Generalized disease:

- 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)
- Of those who present with ocular manifestations, about half will develop generalized disease within two years
- Proximal muscle involvement
- Specific involvement of **extensors of the fingers**
- **Neck flexors** more than neck extensors weakness It also affects triceps more than biceps. Deltoid, finger extensors, hip flexors and ankle dorsiflexors are commonly affected

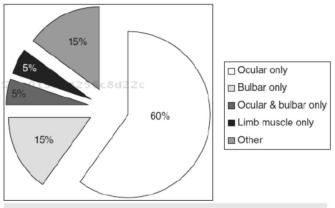


TABLE 1-2 Distribution of Weakness in a Large Cohort of Patients With Generalized Myasthenia Gravis (n = 609)

Distribution of Weakness	Percentage of Patients
Localized ocular	17%
Ocular and generalized	50%
Ocular and bulbar	13%
Ocular and limb	20%

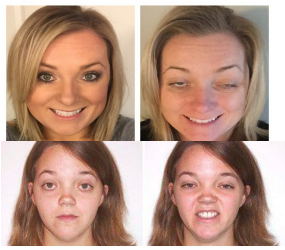
Data from Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37(2):141–149.

[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. Binocular diplopia directs you to neurological disease whereas **monocular diplopia**, if the doubling in vision does not resolve when closing one eye is usually caused by a focal disease. 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] Ptosis can be **unilateral** or **bilateral**, unilateral being more common in MG. If you have a patient with bilateral ptosis that is continuous and **fixed**, question your Dx of MG as it is unlikely to be MG. Weakness in which muscles cause ptosis? Levator palpebrae superioris and superior rectus

Affected Muscles

Ocular muscles



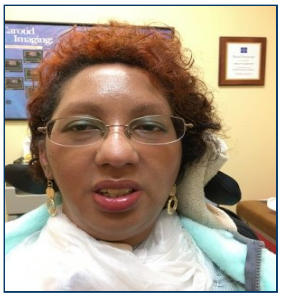
- Weakness of the eyelid muscles can lead to ptosis that is **fluctuating**
- The ptosis is usually asymmetric and may start bilaterally then improve in one eye, resulting in **unilateral ptosis** or alternate
- Extraocular muscles involvement **binocular diplopia** that may be horizontal or vertical

Bulbar muscles

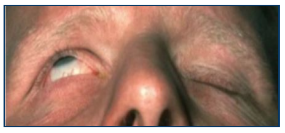
- Muscles of **jaw closure** (fatigable chewing)
- Affects swallowing and speech
- Oropharyngeal muscle weakness produces dysarthria and dysphagia
- Palatal muscle weakness (difficulty in palatal elevation) causing nasal speech or regurg
- Nasal regurgitation, particularly of liquids, may occur due to palatal weakness

NOTE:
Monitoring FVC is vital in patients with severe bulbar weakness

Facial muscles



- Frequently involved and causing **expressionless 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 you can see their sclera when they attempt to close their eyes **(bell's phenomenon)** bottom two pictures



Neck and limb muscles

- Neck **flexor (more common)** and extensor muscles head are affected
- Dropped head syndrome due to extensor weakness
- Proximal limb weakness (the arms > the legs) can be equally affected
- Wrist and **finger extensors** and foot dorsiflexors

Respiratory muscles

- Respiratory muscle weakness can leads to respiratory insufficiency and pending respiratory failure (myasthenic crisis). Occurs in 15% of patients
- 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 PFTs** (NMJ disorders should be in your DDx)

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) • Progressive Muscular Atrophy (PMA)
Peripheral Nerve	**Brainstem Pathology**	**Others**
• Oculomotor Cranial Nerve pathology • Guillain Barre Syndrome (GBS) • Chronic Inflammatory Demyelinating Polyneuropathy (CIDB) • Cavernous Sinus pathology	• Stroke • MS • Tumours • Infections	• Isolated ptosis • Isolated Dysconjugate Gaze (Decompensated strabismus)

Diagnosis

Bedside tests:

1. Edrophonium (Tensilon) test[3]:
    - Edrophonium chloride is an acetylcholinesterase inhibitor with rapid onset, allowing Ach to diffuse more widely throughout the synaptic cleft, increasing the time of its interaction with AchR on the postsynaptic membrane
    - It is most reliable in **patients with obvious ptosis/diplopia or ophthalmoparesis** there has to be an obvious symptom in order to look for improvements during the test
    - +ve in more than 90% of patients with MG

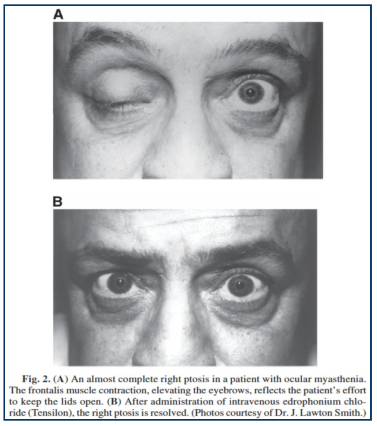


Fig. 2. (A) An almost complete right ptosis in a patient with ocular myasthenia. The frontalis muscle contraction, elevating the eyebrows, reflects the patient's effort to keep the lids open. (B) After administration of intravenous edrophonium chloride (Tensilon), the right ptosis is resolved. (Photos courtesy of Dr. J. Lawton Smith.)

2. Ice pack (ocular cooling) test:
    - Used **in patients with ptosis only**, 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
    - **High sensitivity and specificity for MG**
    - Low temperatures increase ACh. release, enhancing transmission across NMJs
3. Fatiguing Maneuvers (sustained upgaze, sustained abduction of the arms, sustained elevation of leg while lying supine and counting loud)

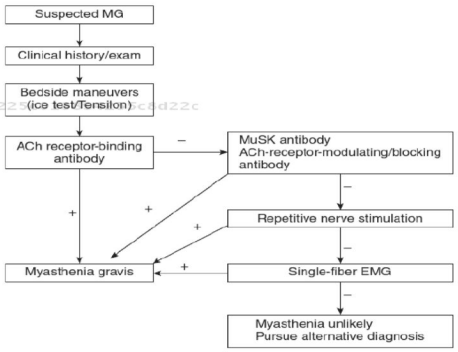
Serological Tests:

- **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
- MuSK (muscle specific kinase) antibodies are present in 50% of those with generalized myasthenia gravis **who are AChR-Ab negative**. This test is **especially important** in **young females** with obvious **bulbar** or respiratory symptoms +/- **tongue atrophy**

Electrophysiologic Confirmation:

1. **Repetitive nerve stimulation[4]:**
    - 50-100% sensitivity for GMG whereas, 10-50% sensitivity for OGM
2. **Single fiber electromyography: Most Accurate Test**
    - If it was negative it excludes Myasthenia Gravis but it's rarely done due to difficult technique

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**

Being an anticholinesterase inhibitor, edrophonium will cause unwanted anticholinergic side effects, our major concern is bradycardia and respiratory depression, that is why we prefer doing other tests (ice cooling, serological and electrophysiological tests)

[4] The nerve is electrically stimulated 6 to 10 times at low rates. 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%

CT Mediastinum: Must be ordered in all MG cases

- In AChR antibody positive myasthenia gravis, >75% of patients have thymic abnormalities
- Thymic hyperplasia is most common 85%
- Thymic tumors (primarily thymoma) is found in up to 15%. (50% of people with thymoma have MG)
- Thymic hyperplasia is typical in **young** MG patients (usually **females**)
- Thymoma is seen in the **elderly** (mostly **men**)

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

- Autoimmune thyroid disease is common (3-8%) in patients with myasthenia gravis
- Screening for **thyroid abnormalities** should also be part of the initial evaluation
- Do not screen for every autoimmune disease unless features are present, only thyroid is routine

Treatment

- Symptomatic treatment:
  - ➢ Cholinesterase inhibitors: pyridostigmine (mestinon)
- Immunosuppressive therapy:
  - ➢ Prednisone
  - ➢ Azathioprine (Imuran)
  - ➢ Methotrexate
  - ➢ Usually Azathioprine and Methotrexate are used
  - ➢ Cyclosporine
- Rapid immunotherapies for myasthenia crisis:
  - ➢ plasma exchange (plasmapheresis)
  - ➢ Intravenous immune globulin [IVIG]
  - ➢ **Used in significant proximal weakness or respiratory/bulbar symptoms**
- Thymectomy
  - ➢ We do thymectomy for any patient with thymoma
  - ➢ We also do thymectomy for any patient with +ve Ach receptor antibodies except for those who are above 65, unless if they have thymoma then we do thymectomy
  - ➢ Symptomatic improvement is seen in 20% of the patients who underwent thymectomy within the first year. Improvement rates of 70% over 5-7 years

NOTE:
Glucocorticoids are given to:
- Those who do not respond to acetylcholinesterase inhibitors
- Patients above 60

Azathioprine/cyclosporine Are alternative 3rd line agents

NOTE:
Myasthenia weakness is often exacerbated by infections and can lead to myasthenia crisis

Lambert Eaton Syndrome

Epidemiology

- The incidence and prevalence of LEMS in patients with SCLC are 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

- 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, impairing Ach quantal release

- 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
- Number of vesicles and concentrations of ACh. remain NORMAL

NOTE:
☆ Myasthenia Gravis
↓
Thymoma
☆ Lambert Eaton Myasthenia Syndrome
↓
Small cell carcinoma of the lung

Etiology

Autoimmune (inflammatory):

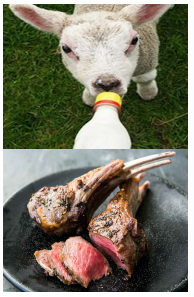
- Autoantibodies directed against the voltage-gated calcium channel (VGCC) typical in a young female
- These antibodies interfere with the normal calcium flux required for the release of acetylcholine

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 carcinoma of the lung (SCC) expresses several characteristics of neuronal cells, including voltage-gated Ca2+ channels (VGCC) the immune system fights off the tumour by producing antibodies against VGCCs

Clinical Features

- Weakness/ fatigue in limb girdle distribution, slowly progressive, proximal, particularly in the **legs**
- Deep tendon reflexes are typically decreased or absent, Reflexes are enhanced after exercise
- Mild ptosis, diplopia and dysarthria 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
- Respiratory symptoms are very rare (if present, they come late)
- Occasionally, paresthesias and myalgia
- **Recovery of lost deep tendon reflexes or improvement in muscle strength with vigorous, brief muscle activation is a unique aspect of LEMS (Post exercise facilitation/excitation phenomenon)**
- Always look for SCC in old people presenting with LEMS (usually male)



MNEMONIC سيئة
The lamb drinks milk, milk is rich in calcium. In Lambert Eaton, antibodies ATE the calcium channels Just like people, other lambs are too cool for milk, so they smoke lots of cigarettes, predisposing them to CSC. Those lambs are smoked.

Diagnosis

- On exam:
  - ➢ Proximal muscle weakness
  - ➢ improvement after few seconds of contraction
  - ➢ Poorly reactive pupils
  - ➢ Hyporeflexia or areflexia
  - ➢ May have mild distal sensory loss in feet
- **What is the most important single test in LEMS? CT chest to rule our 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**
- 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 result in significant increment with a marked increase in the CMAP amplitude. (hence, EMG is great at distinguishing between LEMS and MG)

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
- Guanidine hydrochloride, aminopyridines such as 3,4-diaminopyridine (3,4-DAP)[5], and acetylcholinesterase inhibitors such as pyridostigmine
- IVIG is used initially for treatment until the primary tumour is found and dealt with

Botulism

What is Botulism?

- It is caused by the anaerobic bacterium Clostridium Botulinum gram +ve and spore forming anaerobic found in wounds
- 8 types of botulinum toxin exist, these are A, B, C, D, E, F and G
  - ➢ A and B cause most cases in the US
  - ➢ Transmission of type E is through seafood
- 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 of the presynaptic membrane
- Neuromuscular symptoms usually begin 12-36 hours after ingestion of contaminated food, symptoms usually preceded by nausea and vomiting
- 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 is why we avoid giving honey to babies <1 year (causes infant botulism)
  2. **Infantile botulism** occurs after the ingestion of clostridial spores that then colonize the host's gastrointestinal (GI) tract and release toxin produced in vivo
  3. **Wound botulism & IV drug abuse:** occurs after infection of a wound by Clostridium botulinum with subsequent in vivo production of neurotoxin
  4. **Hidden**
  5. **Iatrogenic**
  6. **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

Clinical Features

- It is described as the acute onset of bilateral **cranial neuropathies** associated with **symmetric descending weakness**

[5] Normally, efflux of K into the presynaptic membrane through K channels will close Ca channels and stop the release of ACh. vesicles. 3,4, DAP will block presynaptic K channels to prolong the opening of Ca channels. We use it in combination with mestinon (pyridostigmine) in order to lower the 3,4 DAP dose why? because 3,4, DAP lowers seizure threshold

- Cranio-ocular symptoms begin soon after initial GI symptoms after ingestion
- Pupils dilated and fixed in 50-75%
- No sensory deficits with the exception of blurred vision
- Ptosis, symmetrical EOM weakness (may improve with tensilon)
- Bulbar weakness: dysarthria, dysphagia, and facial muscles weakness
- Symmetrical limb weakness (proximal > distal)
- Respiratory weakness
- Affects the heart
- Absence of fever
- The patient remains responsive
- Normal or slow heart rate and normal blood pressure

DDx of Botulism
1. Guillain Barre Syndrome (usually ascending but Fischer variant causes descending paralysis)
2. Eaton Lambert Syndrome
3. Myasthenia Gravis
4. Diphtheria
5. Tick Paralysis

Diagnosis

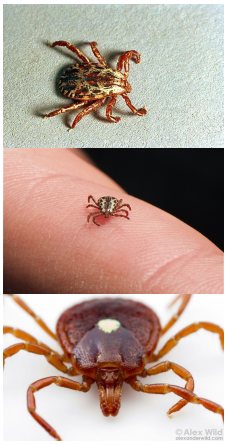
- The diagnosis is usually clinical as routine lab tests are nonspecific and specific laboratory confirmation may take up to days
- RNS at high frequencies stimulation or exercise causes incremental response, or postactivation facilitation that is usually less than that seen in Lambert-Eaton myasthenic syndrome they are both presynaptic

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 Supportive management
- Bivalent (A and B) or 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
- Antibiotics are recommended for wound botulism after antitoxin has been administered
  - ➢ Penicillin G or Metronidazole for penicillin-allergic patients
- Infantile botulism: IV human botulism immune globulin (BIG-IV)

Tick Paralysis

the doctor didn't talk about it at all because it's uncommon in SA



- Several tick species produce a toxin that inhibits transmission at the neuromuscular junction by blocking influx of sodium ions. (Na for Namosa ناموسة)
- This prevents presynaptic terminal axon depolarization and inhibits release of acetylcholine at the nerve terminal
- The ticks responsible include the Rocky Mountain wood tick 1st (Dermacentor andersoni), the American dog tick 2nd (Dermacentor variabilis), the Lone Star tick 3rd (Amblyomma americanum), the black-legged tick 4th (Ixodes scapularis)
- Symptoms include anorexia, lethargy, muscle weakness, nystagmus, and an ascending flaccid paralysis
- Symptom onset occurs three to seven days after attachment of the tick
- 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
- Removal of the tick is the primary treatment of tick paralysis

Snake Venom

the doctor didn't mention this at all

- The toxins produced affect either the presynaptic or postsynaptic junction
- Toxins affecting the presynaptic junction 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
- 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)
- Snake venom neurotoxins affect the cranial nerves first, resulting in ptosis, ophthalmoplegia, dysarthria, dysphagia, and drooling. This progresses to weakness of limb muscles
- Clotting time is also increased
- 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
- Presynaptic toxins have no response to antivenom

Organophosphate & Carbamate Toxicity

the doctor didn't mention this at all

- Organophosphates and carbamates are potent inhibitors of acetylcholinesterase, causing excess acetylcholine concentrations in the synapse, they are commonly used as pesticides
- Exposure routes include oral ingestion, inhalation, or dermal contact
- Both sympathetic and parasympathetic systems are involved
- Symptoms of organophosphate and carbamate poisoning include typical muscarinic signs (lacrimation, bradycardia, bronchospasm) and **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
- Atropine dosing should be titrated to the therapeutic end point of the clearing of respiratory secretions and the cessation of bronchoconstriction

Hypermagnesemia & Hypocalcemia

the doctor didn't mention this at all

- Causes **inhibition of acetylcholine release**
- 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

MCQs

1) 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 conversation. 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

2) 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. Lung cancer

3) The following statements are true regarding botulism except ?

a. Infant botulism is caused by ingestion of preformed toxin
b. Clostridium botulinum A,B,C and F cause human disease
c. The gene for botulinum toxin is encoded by a bacteriophage
d. clostridium baratti may cause botulism

4) Which one of the following is an autoimmune disease affecting the neuromuscular junction?

a. Myasthenia Gravis
b. Parkinson's Disease
c. Multiple Sclerosis
d. All of the above

5)) Which of the following is true with regard to the clinical presentation of Myasthenia Gravis?

a. Weakness worsens as the day progresses
b. Limb weakness is more severe distally than proximally
c. Weakness is not affected by the level of activity
d. Weakness generally starts in the limb muscles and then spread to facial muscles and ocular muscles

Answer key:

1 (d) | 2 (d) | 3 (a) | 4 (a) | 5 (a)