Team Medicine

Neuromuscular Junction Disorders

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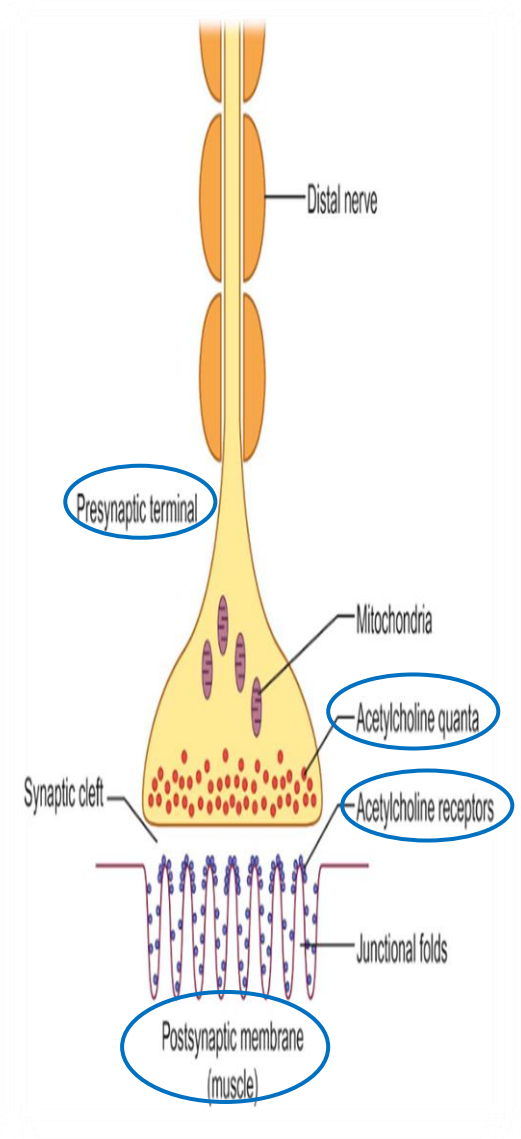
■ Slides ■ Doctor's note ■ Additional

..... = words that we could not hear!!

- What is neuromuscular junction?
- It is the junction between presynaptic terminal of the nerve and the postsynaptic membrane of the muscle.
- Presynaptic membrane contains acetylcholine
- Acetylcholine is the major neurotransmitter for the neuromuscular junction
- Postsynaptic membrane contains acetylcholine receptors.

Definition of NMJ Disorders:

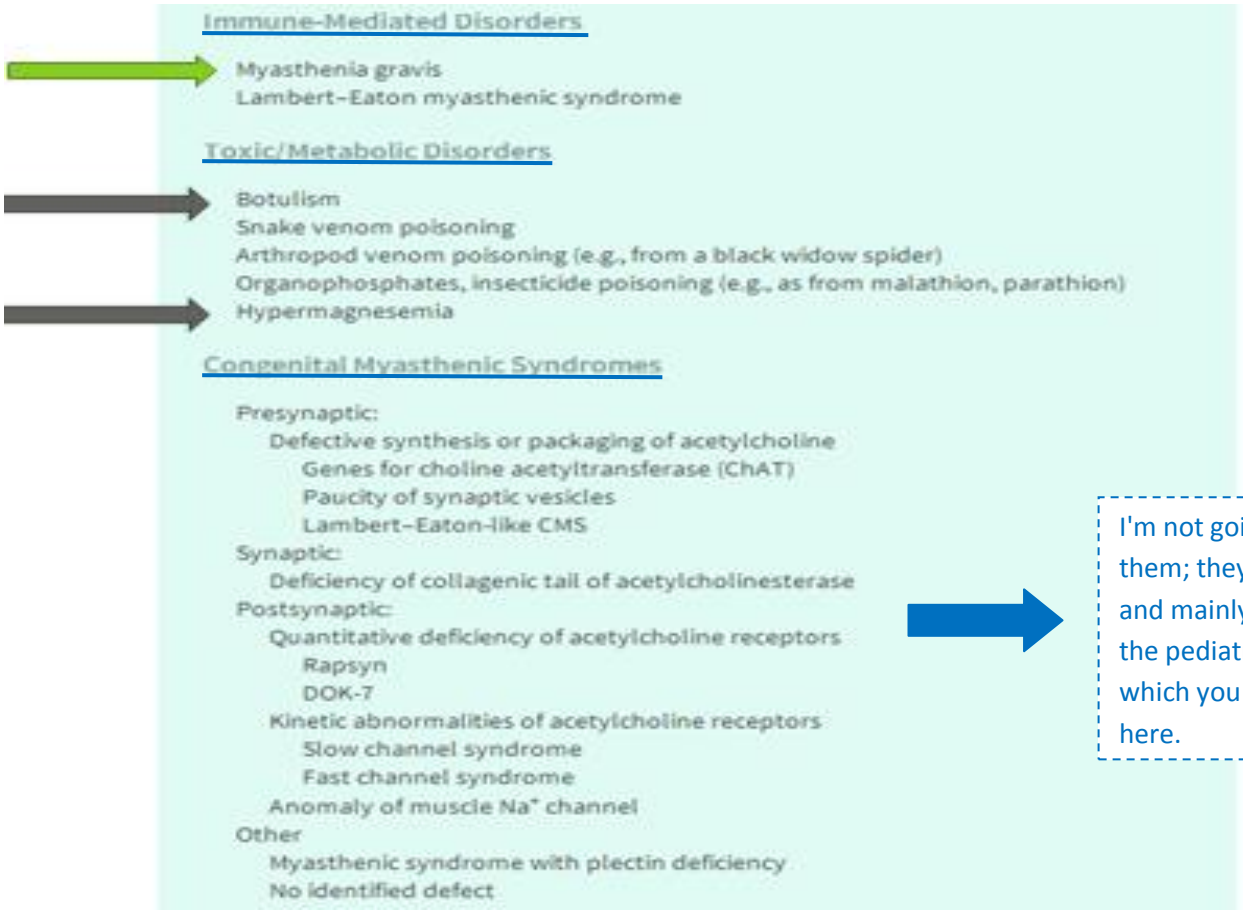


- Disorders affecting the junction between the presynaptic nerve terminal and the postsynaptic muscle membrane.
- Pure motor syndromes. Why?
- It is not because the nerve is not affected because some of the neuromuscular disorders the nerve terminal is affected but it is a neuromuscular junction and the nerve carried impulse to the muscle.
- Preferentially affect proximal, bulbar, or extraocular muscles.

Physiology of NMJ Transmission:

- Chemical neurotransmitter at the NMJ is acetylcholine (ACH).
- ACH is stored in vesicles in the presynaptic terminal in discrete units known as quanta (the single is quantum).
- Each quantum contains 10,000 molecules of ACH.
- The quanta are located in three separate stores (so, we have three levels of storage for ACH). The primary, or immediately available store→ immediately available for release on influx of the calcium, secondary→ up in the axon and a tertiary far from the NMJ in the axon and cell body.
- Action potential invades and depolarizes the presynaptic junction.
- VGCCs (voltage-gated calcium channels) are activated (opened), allowing an influx of calcium into the nerve terminal.
- Release of ACH.
- ACH binds to ACHRs on the postsynaptic muscle membrane.
- This opens sodium channels.
- Leading to local depolarization, the endplate potential (EPP).
- The size of the EPP is proportional to the amount of ACH released, so if we have decreased amount of ACH or damage to the receptor then the EPP will be small and might not have a muscle action potential→ so this will be present as weakness as the syndrome we talked about.
- A threshold needs to be reached for the EPP to be produced and muscle fiber action potential to be generated .
- In normal circumstances, the EPP always rises above threshold, resulting in a muscle fiber action potential.
- In the synaptic cleft, ACH is broken down by the enzyme acetylcholinesterase.
- http://www.youtube.com/watch?v=y7X7IZ_ubg4

NMJ Disorders: we can divide them into:



I'm not going to talk about them; they are very rare and mainly presented in the pediatric age group which you can take a look here.

Myasthenia Gravis (الوهن العضلي الوبيل):

- The most common disorder of neuromuscular transmission and is mediated by the ACH receptor antibody, so it will be an autoimmune disease (as MS, SLE and others).
- Caused by an immunoglobulin G (IgG)-directed attack on the NMJ nicotinic ACH receptor.
- A post-synaptic NMJ disorder this means that the problem is in the postsynaptic membrane and the nerve terminal is intact.
- Hallmark of the disorder is a **fluctuating fatigable** weakness, so the patient sometimes you will examine him and he is perfectly normal and then he comes another visit he has weakness, double vision, and manifestations of ……. movement. "…….= Words we could not hear"

Classification:

- According to onset:

A- Congenital (the one in the table)

B- Acquired (we will be talking about which is the immune mediated)

- According to clinical presentation:

A- Ocular (only involving the eye muscle)

B- Generalized (involving everything)

Epidemiology of MG:

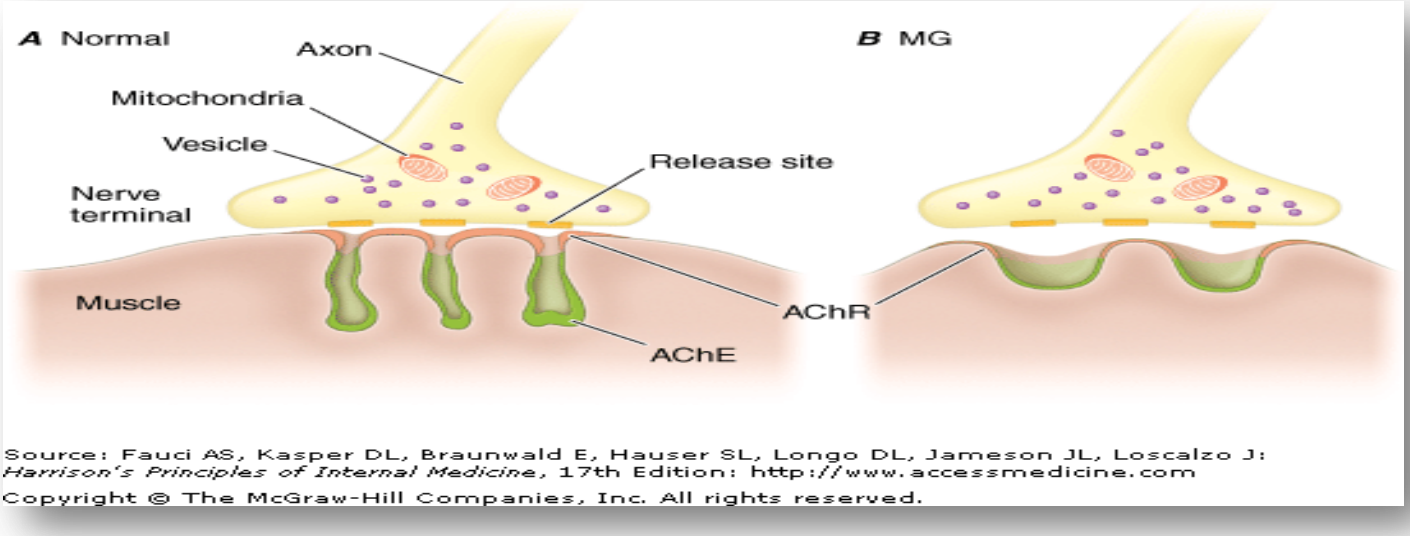
- Prevalence is 200 per million.
- Bimodal distribution:
  - Early peak: 2nd and 3rd decades (female predominance).
  - Late peak: 6th to 8th decade (male predominance).
- Neonatal MG: a transient form it will lasts for weeks or months then it will end and the baby is back to his normal, which affects babies of mothers with MG due to trans-placental passage of maternal antibodies.
- Association with other autoimmune diseases as, autoimmune thyroid disease, SLE, and rheumatoid arthritis, neuromyelitis optica.
- RISK FACTORS :
  - Age > 40
  - Short history of disease
  - Thymoma

Pathogenesis of MG:

- Autoantibodies against the AChR
- Considered a B cell-mediated disease.
- Decrease in the number of active acetylcholine as a consequence of AChR antibody binding (antibodies take the plates of acetylcholine).
- Destruction of receptors occurs via a complement-mediated process
- Destruction of the post-synaptic folds
- Reduces amount of Ach released causing weakness
- Associated with thymus (الغدة الزعترية) pathology.
- 60-70% of AChR ab positive patients have thymic hyperplasia (just enlargement) and 10-12% have **thymoma** which is a tumor, and they think that the thymus is the cause of the antigen for this autoimmune response it produce particles of the acetylcholine receptor, so it will induce the autoimmune reaction. "T-cell mediated"
- Produces AChR subunits that triggers the immune response

consequences of AChR antibodies binding to the receptor

Closer look at the NMJ in MG:



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Clinical features of MG:

- The most important symptom again is fluctuating weakness.
- **Fluctuating**, intermittent symptoms sometimes with periods of spontaneous improvement
- Appearing with repetitive activity and worsening as day progresses → so patient usually complain toward the end of the day they are weak or they have the symptoms double vision,…..
- Muscle fatigue→ usually we mean by fatigue tiredness but here we mean worsening of the contractile force, actual weakness not generally tired of the feet but we are talking about specific group of muscle that are weak and weakness
- No abnormality of mental state, sensory or autonomic function
- Characteristically affects the extra-ocular, bulbar or proximal limb muscles however distal muscles such as or especially wrist extensors, finger extensors, and ankle dorsiflexors are also affected and neck muscles.

Fatigue: worsening contractile force, not tiredness

Types of Presentation in MG:

1. Ocular presentation 50% either double vision or ptosis.
2. Bulbar (oropharyngeal) presentation 15% which means dysphagia or dysartheria.
3. isolated Limb weakness (<5 percent)
4. Isolated neck→ head drop (uncommon)
5. Isolated respiratory weakness (rare)

Ocular-onset MG:

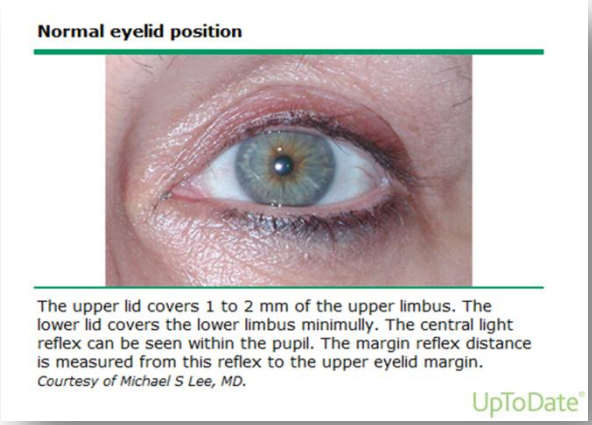
More pictures in the slides.

- the most common
- eventually 90% → in patients with MG will have eye muscle involvement at the end even if they did not start with eye muscle.
- 15% continue to have isolated ocular symptoms
- Extraocular weakness frequently begins asymmetrically presented as double vision.
- Mimics 3rd , 4th , and 6th nerve palsies and, rarely INO is a characteristic of MS.
- Unlike true 3rd nerve palsies MG never **affects pupillary function**. Why? Because the pupil is controlled by autonomic nervous system plus sympathetic parts for constriction and dilation, autonomic nervous system is not affected in MG.
- The picture of ptosis is bilateral symmetrical but commonly it is asymmetrical, sometimes unilateral, or shifting from one eye to another.
- There are three ways to determine that this patient has ptosis or this is the normal shape of eye:
- First we'll measure the distance between the lid crease and the lid margin should be at least 5 to 6

- We'll measure the papillary fissure which is between the upper lid and the lower lid should be 9 to 12 mm.
- We will shine a light in the center of the pupil and then we will measure the distance between the focused light and the upper eyelid, we call this the margin reflex distance and maybe this is the most accurate way and this should be at least 4 or 5 mm.
- If a patient came to the clinic and she told you "I have droopy eyelid and you examined her and you think it is normal and you measured everything and it was ok, so we ask her to look up. Why? To try to fatigue the muscle for 1 to 2 minutes
- That's why in MG sometimes you need to fatigue the muscle not only the eyelid, even the leg in that you have to ask the patient to left the thigh then test him again ask him to do abduction, adduction 10 time and then test the power again.
- Problem in abduction could be sixth nerve palsy or a myopathy affecting which is very unlikely only the lateral rectus muscle ,or a neuromuscular junction disorder.

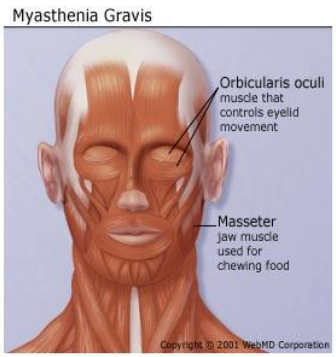
The normal eyelid and palpebral fissure:

- normal eyelid crease is 6 to 7 mm away from the eyelid margin in adults.
- upper eyelid covers top 1 mm of the cornea.
- normal PF measures 9 to 12 mm.
- distance from a central pupillary light reflex to upper eyelid margin is called the margin reflex distance, normally this measures 4 to 5 mm.



Bulbar-onset MG:

- Bulbar muscles weakness is the next most common
- Dysphagia
- a very characteristic symptom is Fatigability and weakness of mastication, with the inability to keep the jaw closed after chewing. at the begging of the meal the patient will have no problem. but when he eats for example steak needs a lot of chewing he cannot complete his meal, because of that sometimes it presents with weight loss.
- Dysarthria: nasal speech → due to weakness of soft palate, slurred → due to weakness of tongue, and lip and hypophonic
- Swallowing may be difficult and **aspiration** may occur with fluids—coughing and choking while drinking.
- Nasal regurgitation



Facial muscles involvement:

- Facial muscles are frequently involved → facial muscle weakness in exam
- Patient appear expressionless
- "myasthenic sneer" on attempting to smile where the mid-lip rises but the outer corners of the mouth fail to move caused by the weakness of the facial muscle.

Sneer: يبتسم باستهزاء

Orbicularis oculi & Masseter are more effected

Limb involvement in MG:

- limbs weakness, usually symmetric and proximal like shoulder abduction for example.
  (Upper limbs more common than lower limbs)
- wrist and finger extensors and foot dorsiflexors are often involved → distal as we said earlier.
- Rare patients present with an isolated limb weakness and never develop eye movement or bulbar muscle weakness
- How do you ask about proximal muscle weakness? ask about combing or washing hair, climbing stairs, also we ask patient in hx "do you have any problem with reaching objects above your head level like a towel in the cabinet", also ask about standing from setting position, proximal thigh muscle, also we can ask him toward the end of the day or while breathing patient have head drop.

Respiratory Involvement in MG:

- Difficulty breathing, SOB
- Obstructive sleep apnea sometimes it is the main presentation and then they are referred from pulmonology to us.
- Difficulty sleeping on flat bed

Diagnosing MG:

It is a clinical diagnosis because it is a unique disease, there are no other diseases other than MG and other neuromuscular disorders can be presented with fluctuating symptoms related to fatigue and weakened muscle.

- **Bed side tests:**
  - Tensilon test: we are not using it much now, injection of edrophonium (acetylcholinesterase inhibitor) in patients with ptosis or ophthalmoparesis (extra ocular muscle limitation) looking for improvement or we can use something else like tablet which are the same of the ones we used in treatment instead of ……. because sometimes it cause problem because it will not only increase the acetylcholine at the nicotinic receptors but also at the muscarinic receptors this can lead to bronchospasm or bradychardia and so on.
  - Ice pack test used in patients with ptosis mainly, not in limb weakness of course.
  - What you do in ice pack test?
  - A pack full of ice put it on the eyelid and see the ptosis will improve. Why?
  - We said acetylcholinesterase break down the acetylcholine, so if I inhibit this enzyme I have more ACH even if I have less receptors but I have more ACH so, power will improve, the ATP increase and the muscle action potential and so on.

- "…….= Words we could not hear"

- **Serologic testing:**
  - *Antiacetylcholine receptor antibodies (AChR-Ab):*
    - 80-90% of generalized MG
    - 50% of ocular MG
    - Test of choice (most specific)

  - *Anti Muscle-specific kinase antibodies (MuSK-Ab):*
    - 38-50% of generalized MG who are AChR-Ab –ve (without)
    - much lower frequency of thymic pathology
    - More common in females
    - Usually present with proximal weakness, severe oculobulbar weakness along or neck, shoulder, and respiratory weakness

- **Electrophysiological studies:**
  - repetitive nerve stimulation studies
  - single-fiber EMG the most sensitive test

- **CT scan of the chest**. Why?
  - To look for thymoma or thymic hyperplasia. Why?
  - Because thymoma has to be removed it's a tumor.

Prognosis:

- Early, the symptoms are often transient, with hours, days, or even weeks free of symptoms
- Symptoms typically worsen and are more persistent months later.
- Maximum weakness is reached within two years in 82 percent of patients
- An active phase with fluctuations and most severe symptoms in the 1st five to seven years. Most myasthenic crises occur in this early period.
- More stable second phase, symptoms are stable but persist. They may worsen in the setting of infection, medication taper, or other perturbations.
- Followed by 3rd phase, the most stable in which remission may occur with or without medication, for occurring better you are treating the patient.
- Usually if they remit they remit after decades after 10 or 20 years all autoimmune diseases tend to improve with age, he is already disabled but the immune system become weaker.

Treatment of MG:

- Crisis: IVIG modulate the immune system and reduce the number of these harmful antibodies or Plasma exchange to washout the antibodies and to get rid of them.
- Symptomatic treatment, the patient is not in crisis suppose he comes to the clinic his breathing is ok : cholinestrase inhibitor "Pyridostigmine" but we still we have to suppress the immunity because it is autoimmune disease.
- Chronic immunomodulatory and immunosuppressive treatment used in cancers: steroids, azathioprine, cellcept….
- Thymectomy is always indicated for patients with thymoma and usually always also in thymus hyperplasia we remove it except if the patient is very old, multiple comorbidities, above 75 and

sometimes the cells are not relaxant to remove the thymus in these people if they have thymoma then we have to remove.

Myasthenic Crisis:

- It is very important, life-threatening condition
- If it is acute disease usually comes with MG crisis
- Definition: weakness from acquired MG that is severe enough to necessitate intubation
- due to weakness of respiratory muscles.
- Severe oropharyngeal muscle weakness leading to severe dysphagia and risk of aspiration often accompanies the respiratory muscle weakness, or may be the predominant feature
- Triggered by simple infections for example cold or UTI especially in elderly or certain medications.
- A list of medications that affect the NMJ transmission should be given to MG patients to avoid or to use with caution. Why? Because there are lots of medication can worse MG. How? Because it affects the neuromuscular junction by mean or another either acetylcholine itself or the receptor.
- Treated with plasma exchange or IVIG.

Drugs that may unmask or exacerbate myasthenia gravis*

Anesthetic agents
Chloroprocaine
Diazepam
Ether
Halothane
Ketamine
Lidocaine
Neuromuscular blocking agents
Propanidid
Procaine
Antibiotics
Aminoglycosides
Amikacin
Gentamicin
Kanamycin
Neomycin
Netilmicin
Paromomycin
Spectinomycin
Streptomycin
Tobramycin
Fluoroquinolones
Ciprofloxacin
Gemifloxacin
Levofloxacin
Moxifloxacin
Norfloxacin
Ofloxacin
Others
Ampicillin
Azithromycin
Clarithromycin
Clindamycin
Colistin
Erythromycin
Lincomycin
Quinine
Telithromycin
Tetracyclines
Anticonvulsants
Gabapentin
Phenytoin
Trimethadione
Antipsychotics
Chlorpromazine
Lithium
Phenothiazines

Antirheumatic drugs
Chloroquine
Penicillamine
Cardiovascular drugs
Beta blockers
Bretylium
Procainamide
Propafenone
Quinidine
Verapamil and calcium channel blockers
Glucocorticoids
Corticotropin
Methylprednisolone
Prednisone
Neuromuscular blockers and muscle relaxants
Botulinum toxin
Magnesium sulfate and magnesium salts
Methocarbamol
Ophthalmologic drugs
Betaxolol
Echothiophate
Timolol
Tropicamide
Proparacaine
Other drugs
Anticholinergics
Carnitine
Cholinesterase inhibitors
Deferoxamine
Diuretics
Emetine (Ipecac syrup)
Interferon alpha
Iodinated contrast agents
Narcotics
Oral contraceptives
Oxytocin
Ritonavir and antiretroviral protease inhibitors
Statins
Thyroxine

* Drugs listed here should be used with caution in patients with myasthenia gravis. Aminoglycosides should be used only if absolutely necessary with close monitoring. Please refer to the text for further information.

UpToDate

Antibiotics are important due to the overuse.

Over the counter drugs also important ,Anything that has magnesium. Why? Because hypermagnesiumia cause neuromuscular junction block

Lambert Eaton Myasthenic Syndrome:

- It is autoimmune and paraneoplastic disorder.
- These people have antibodies to the calcium channel, you remember the what's the role of calcium→ calcium open→ calcium influx→ acetylcholine released but here there is no acetylcholine to be released
- The most important is **Presynaptic** NMJ disorder. Why? Because the affected part is the calcium before the neuromuscular junction.
- Middle age to old people
- **50%** of cases are associated with malignancy (especially lung cancer)
- Fluctuating proximal weakness "proximal muscles of lower limbs most commonly affected"
- Associated with P/Q type voltage gated Ca channels antibodies
- **This type is better on excretion**
- patients with Lambert-Eaton syndrome have depressed or absent reflexes, autonomic changes (dry mouth, impotence) and show incremental responses on repetitive nerve stimulation.
- Majority of patients with this syndrome have an associated malignancy - most commonly small cell carcinoma of the lung

Botulism:

- Very rare now I've never seen any case.
- Presynaptic NMJ disorder→ so MG is unique it is postsynaptic.
- Caused by toxin produced by Clostridium Botulinum
- Inhibits the release of Ach from the NMJ, sympathetic and parasympathetic ganglia → this differentiate botulism from MG and Lambert Eaton. Why? Because you will have also autonomic symptoms the heart rate, the pupils, constipation, or conversely diarrhea.
- Food borne or wound related like infections especially some RTA (road traffic accident) or
- Typically presented with Descending weakness and autonomic disturbance

Summary:

1- Hallmark of the disorder is **a fluctuating fatigable** weakness
2- RISK FACTORS are age > 40,Short history of disease and **thymoma.**
3- Antiacetylcholine receptor antibodies (AChR-Ab) is the test of choice.
4- Lambert Eaton Myasthenic Syndrome is **Presynaptic NMJ** disorder. Why? Because the affected part is the calcium before the neuromuscular junction.
5- The cardinal sign of Lambert Eaton Myasthenic Syndrome is **absence of tendon reflexes.**
6- Botulism **Presynaptic NMJ** disorder caused by toxin produced by Clostridium Botulinum
7- Botulism Typically presented with **Descending** weakness and autonomic disturbance

Qs: **A 30-year-old woman presents to her primary care physician complaining of double vision and fatigue. Her symptoms are absent in the morning but become progressively worse by the end of the day. Physical examination reveals a heart rate of 90/min and a blood pressure of 115/75 mm Hg. Ophthalmologic examination is remarkable for symmetric ptosis and intact pupillary responses bilaterally. Weakness of the muscles of the hand is evident bilaterally, but only after multiple contractions. Sensory exam is completely normal and deep tendon refl exes are intact.**

Q1: What is the most likely diagnosis?
Q2: What is the pathophysiology of this disorder?
Q3: What tests and/or imaging tools could be used to confirm the diagnosis?
Q4: What is the most appropriate treatment for this condition?
Q5: What is a potential complication of this condition and how is it managed?

Answers

A1:Myasthenia gravis (MG). Hallmarks include progressive weakness and fatigability of striated muscles; proximal muscles are most often affected, and weakness in ocular muscles results in ptosis and diplopia. MG can occur at any age, but is most commonly seen in women during the third and fourth decades and in middle-aged men. It is associated with other autoimmune disorders and hyperthyroidism. The differential diagnosis includes Lambert-Eaton myasthenic syndrome(LEMS), an autoimmune disorder that is often a paraneoplastic condition in which antibodies are produced against presynaptic voltage-gated calcium channels; this results in less calcium entry into the presynaptic terminal and thus less release of acetylcholine (ACh) into the neuromuscular junction. Associated symptoms include depressed or absent refl exes and increasing amplitude of responses on repetitive nerve stimulation.

A2: MG is a disorder of the neuromuscular junction (NMJ) in which autoantibodies to the ACh receptor effectively blunt the depolarization of the muscle endplate. The phenomenon of "myasthenic fatigue" is due to the fact that on repeated activation of the NMJ and release of ACh, there are fewer available ACh molecules released and fewer receptors for the ACh molecules to bind. The sensory nerves are unaffected, and deep tendon and pupillary refl exes are preserved.

A3: A rapid diagnosis can be made with the edrophonium test. This fastacting acetylcholinesterase inhibitor will cause a transient resolution of symptoms in the myasthenic patient as more ACh is available in the cleft. Repetitive nerve stimulation tests will demonstrate a characteristic decrement of evoked compound muscle action potential (CMAP) amplitude. Antibody tests can confirm the diagnosis and are used to follow treatment response. Eighty percent of patients with general myasthenia have ACh receptor antibodies, and 5% have antibodies to muscle-specifi c kinase (anti-MuSK). A CT of the chest is recommended, since 15% of MG patients also have an associated thymoma.
A4: Acetylcholinesterase inhibitors (pyridostigmine) are fi rst-line treatment; these medications inhibit the enzyme that degrades Ach (acetylcholinesterase) and allow ACh to build up in the neuromuscular junction. In patients with associated thymoma, thymectomy may be curative. If symptoms persist, immunosuppressive therapy is initiated, primarily with corticosteroids and immunosuppressants.

A5: Myasthenic crisis is a serious complication characterized by severe weakness and respiratory and pharyngeal muscle paresis leading to respiratory failure. It may occur spontaneously or after physiologic stress (infection/surgery). Management consists of early elective intubation, withdrawal of anticholinergic medication, and plasmapheresis or intravenous immunoglobulin.