Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Neuromuscular Junction disorders

Objectives :

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

Done by :

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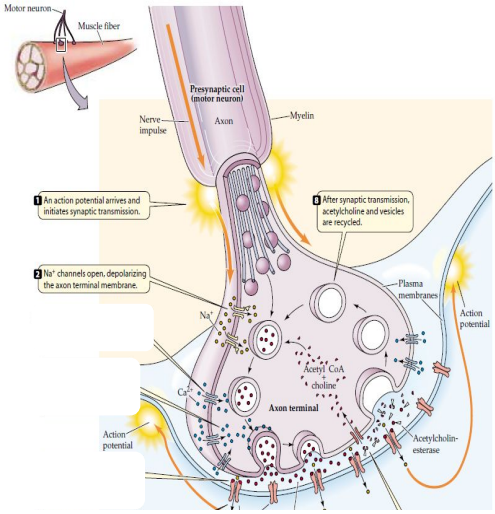
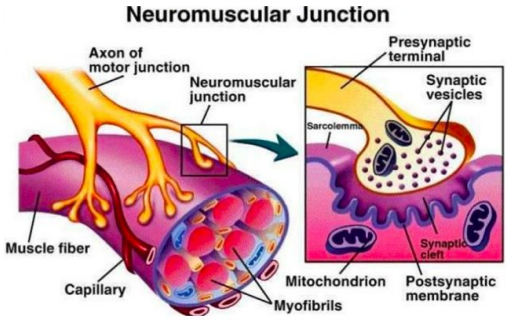
Resources :

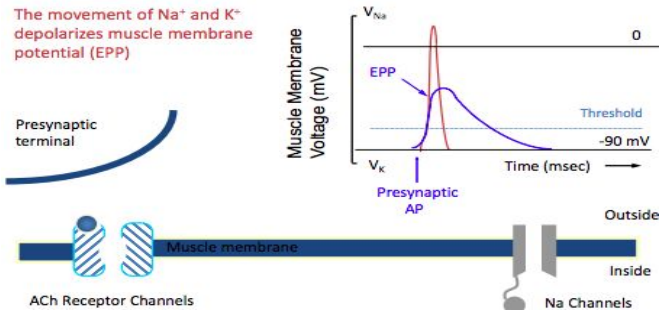
- 437 slides | Same as 436's MALE slides
- Teamwork 436
- Doctor notes | Prof. Muhammed Al Anazy

Physiology





End Plate Potential (EPP)



Classification of NMJ disorders

Presynaptic

- Lambert Eaton Syndrome
- Botulism
- Congenital myasthenic syndrome
- Hypermagnesemia
- Envenomation
- Aminoglycosides toxicity

Synaptic

- Congenital myasthenic syndromes
- Cholinesterase inhibitors
- Organophosphate toxicity

Post-synaptic

- Myasthenia gravis
- Congenital myasthenic syndromes
- Penicillamine

Congenital myasthenic syndrome can affect any of the three classifications depending on the type of gene affected

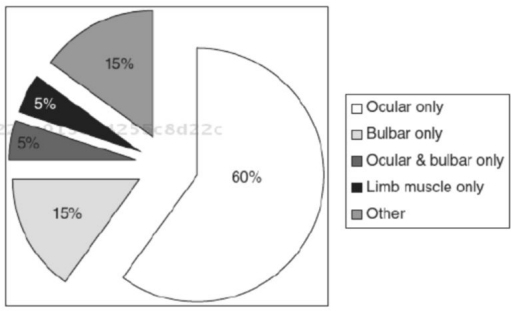
Myasthenia Gravis

Epidemiology

- **Incidence:** 10 – 20 per 1,000,000/year
- **Prevalence:** 20 per 100,000
- **Gender and age influence the incidence of MG**
  - Women are affected nearly three times more often than men before age 40.
  - The incidence is higher in males after age 50 and roughly equal during & before puberty.

Clinical Presentation

- Usually progresses for weeks-months, and maximum severity is usually in first year of disease.
- 80% of ocular MG progress to generalized MG within 2 years.
- After 2 years with no limb Sx, disease usually remains purely ocular. Called ocular MG



- Typically it starts with the ocular or bulbar muscles, then it progresses to occupy the limb muscles.
- Only a minority of patients get limb involvement without ocular/ bulbar.

Figure 15.1. Initial symptoms in 919 patients with myasthenia gravis seen at the Duke University myasthenia gravis clinic (Sanders DB and Massey JM, unpublished data). Seventy percent had ocular symptoms (ptosis, diplopia, or blurred vision) at onset, and these were the only initial symptoms in 60%. Twenty-two percent had bulbar symptoms (dysarthria, dysphagia, or facial weakness), and these were the only symptoms in 15%; 5% had ocular and bulbar symptoms, and these were the only initial symptoms in 4%; and 5% had isolated weakness of limb or axial muscles alone. Twelve percent had initial symptoms of generalized weakness or fatigue, with or without other symptoms.

The picture description is important !

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.

Ocular Myasthenia	Generalized Disease
The weakness is limited to the eyelids and extraocular muscles.	The weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.

- Ocular muscle involvement is very common.
- Diagnosis is questionable if ocular muscles aren't involved.

Clinical Presentation- Cont.

Weakness in MG

- Most important feature is fatigable weakness.
- Fatigable and fluctuates.
- Less pronounced in the morning and improves after rest.
- Asymmetric ptosis and EOM weakness, sparing pupils. Because it's part of the autonomic function.
- Weak eye closure. Due to affected orbicularis oculi muscle.
- Nasal speech (palatal weakness).
- Dysphagia and difficulty clearing secretions.

- NF (neck flexion) > NE (neck extension) weakness.
- Proximal > distal limb weakness, usually symmetric. While oculat are asymmetric.
- Deltoid, triceps, WE (wrist extensors), FE (finger extensors), Ank. DF (ankle dorsiflexors) weaker than other limb muscles.
- SOB due to diaphragm weakness (orthopnea).

TABLE 1-1 Fatiguing Maneuvers in Suspected Myasthenia Gravis

Clinical Fatiguing Maneuver	Manifestation in Symptomatic Myasthenia Gravis	Comments
Sustained upgaze (30 to 60 seconds)	Enhances ptosis and elicits medial rectus weakness Causing divergence of the eyes	Medial rectus muscle is usually most severely involved extraocular muscle
Sustained abduction of the arms (120 seconds)	Patient can no longer hold arms up, or weakness becomes apparent with subsequent manual testing Deltoid muscle	Dysarthria or shortness of breath may be enhanced
Sustained elevation of leg while lying supine (90 seconds)	Patient can no longer hold leg up, or weakness becomes apparent with subsequent manual testing	Dysarthria or shortness of breath may be enhanced
Repeated arising from chair without use of arms (up to 20)	Fatigues after several attempts	Early/mild weakness may cause exaggerated lean-forward and "buttocks-first" maneuver
Counting aloud (1 to 50)	Enhances dysarthria	Nasal, lingual, or labial

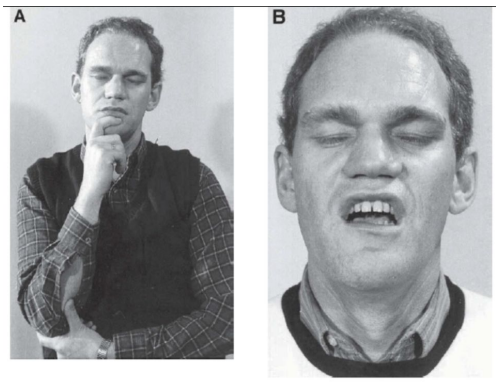


Fig. 1. A 36-year-old man with typical facial weakness. (A) He needs to support his jaw by holding his mouth closed. (B) When he attempts to close his eyelids firmly, his eyelashes remain visible, and the orbicularis oris weakness is evidenced by the straight smile.

(A) And head will drop forward due to weakness of neck muscles

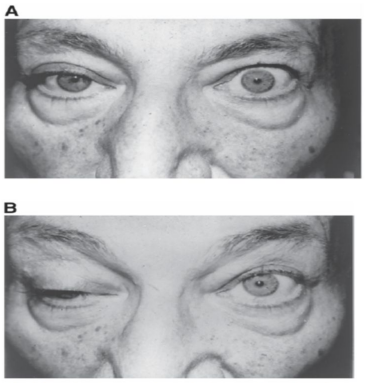
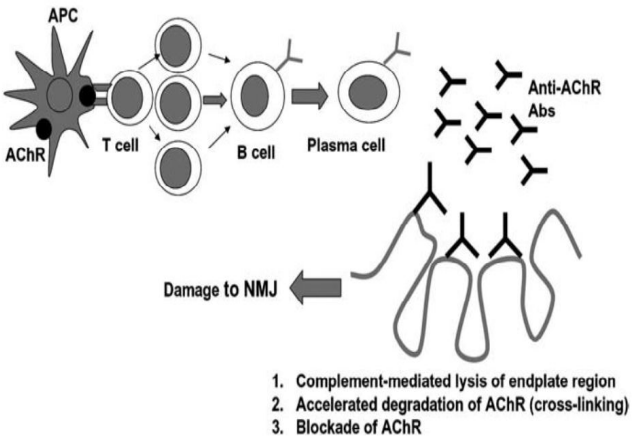


Fig. 1. (A) The patient is attempting to look up, evidenced by the contraction of the frontalis muscle. Note the slight right ptosis and left lid retraction. (B) Lid fatigue that developed during the sustained upward gaze, manifested by marked ptosis on the right, and lessening of the lid retraction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

Frontalis muscle is affected bilaterally

Pathogenesis



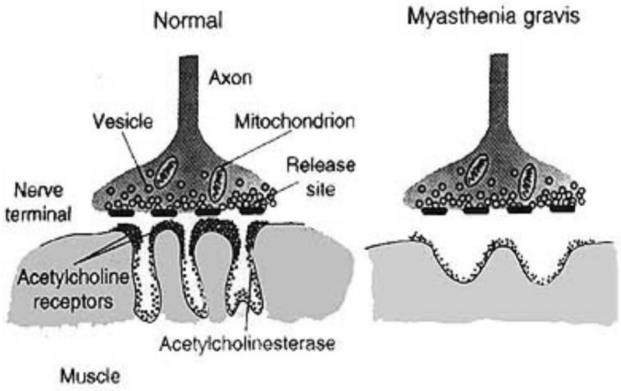
Antigen presenting cells present Ach Receptor peptides to T cells, creating Ach specific T cells.These T cells produce Anti-AChR Abs. These autoantibodies reduce the no. of ACh receptors mainly by:

1. Complement mediated destruction of postsynaptic membrane.
2. Cross-linking the receptors.

This causes enhanced endocytosis & destruction of these receptors. While direct blockade of AChR is less frequent

What Happens in MG:

- Simplified postsynaptic membrane.
- Decreased # of AchR's.
- Remaining AchR's not localized to peaks of the membrane.
- Lower safety factor.



Investigations

- CBC, LFT, RFT, CK, TSH, ESR, ANA.
- Edrophonium Chloride (Tensilon) Test.
- Ocular Cooling/"ice-pack" test.
- Acetylcholine Receptor (AChR) Antibodies.
- Anti-MUSK Antibodies.
- Repetitive nerve stimulation (RNS).
- SFEMG.
- CT chest.

Investigations Cont.

Edrophonium Chloride (Tensilon) Test

- Inhibits the action of acetylcholinesterase, thus allowing ACh to diffuse more widely throughout the synaptic cleft and to have a more prolonged interaction with AChR on the postsynaptic muscle membrane.
- The test is most reliable when the patient has ptosis or diplopia, and is positive in more than 90% of patients with MG.

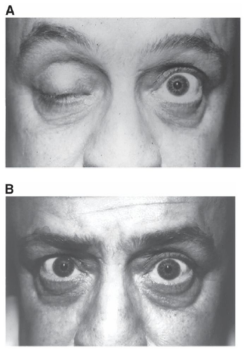


Fig. 2. (A) An almost complete right ptosis in a patient with ocular myasthenia. The frontalis muscle contraction, elevating the eyebrows, reflects the patient's effort to keep the lids open. (B) After administration of intravenous edrophonium chloride (Tensilon), the right ptosis is resolved. (Photos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

Ocular Cooling/"ice-pack" Test

Dr. didn't read this

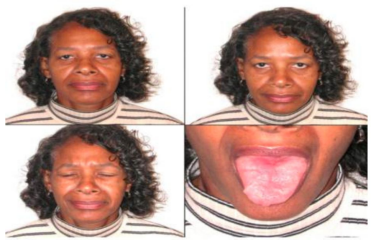
- Place an ice pack over the ptotic eyelid for 2 minutes.
- Positive responses can occur even when edrophonium tests are negative.
- A meta-analysis showed his test to have high sensitivity and specificity in MG, suggesting that it may be useful in patients with lid ptosis, particularly if the edrophonium test is negative or contraindicated.

Acetylcholine Receptor Antibodies

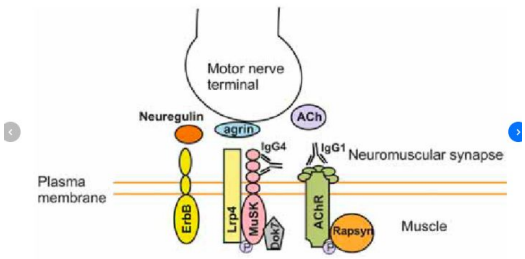
- Sensitivity
  - 85% for GMG
  - 50% for OMG

Anti- MuSK antibodies

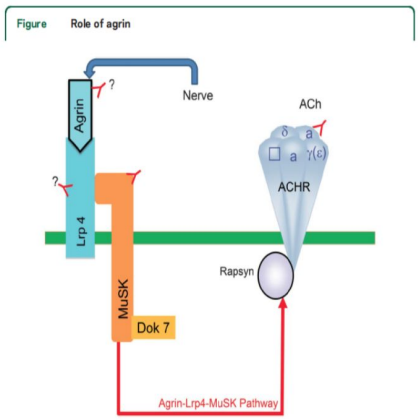
- Present in up to 40 % of GMG patients who are seronegative for AChR antibodies and in some patients with OMG. About 5- 7% of all patients.



Extra



Agrin-MuSK signalling at the neuromuscular synapse. Neural agrin is released from the motor nerve terminal and attaches to MuSK along with its co-receptor Lrp-4. This binding of agrin induces a cascade of phosphorylation on MuSK and then on other intracellular proteins, such as rapsyn, enabling the clustering of AChR. The autoantibodies in MuSK-antibody seropositive MG are mainly of IgG4-subtype and attach to the IgG-like domains in the extracellular domain of MuSK. The autoantibodies in AChR-antibody seropositive MG are of IgG1 subtype and bind to the main immunogenic region of the AChR, blocking the acetylcholine binding and activating complement pathways which destroy AChRs. Another important pathway at the synapse is ErbB with its neurotransmitter neuregulin. In 2001, antibodies against the MuSK (MuSK-Ab) were identified and found to be present in about 40-70% of patients who are seronegative for AChR-Abs (Hoch, McConville et al. 2001; Bartoccioni, Marino et al. 2003; Rostedt Punga, Ahlqvist et al. 2006). MuSK-Abs have also been identified in 14% of patients who have been characterized as having low titers of AChR-Abs; thus, MuSK-Abs are not entirely restricted to the AChR-Ab seronegative MG subgroup (Rostedt Punga, Ahlqvist et al. 2006). While MuSK-antibodies are predominantly of IgG4 subclass, up to 30% of the MuSK-antibodies belong to the IgG1 subclass (McConville, Farrugia et al. 2004). Despite the controversial pathogenicity of MuSK-Abs (Lindstrom 2004; Selcen, Fukuda et al. 2004), their role in disrupting the NMJ and development MG has been evidenced in animal studies with MuSK immunization (Shigemoto, Kubo et al. 2006) and passive transfer of sera from MuSK+ patients (Cole, Reddel et al. 2008). Patient-anti MuSK abs have been shown to inhibit neural agrin-mediated formation of AChR clusters in vitro (Hoch, McConville et al. 2001; Cole, Reddel et al. 2008).

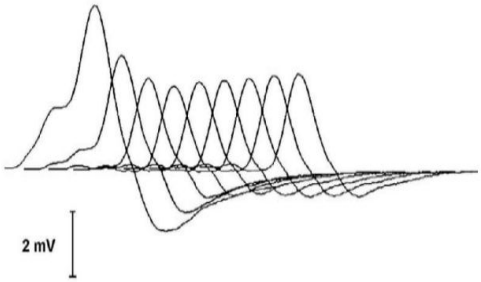


Agrin released from the nerve binds to LRP4, and through a complex with MuSK induces clustering of AChRs, which is further stabilized by rapsyn. Dok7 is required for proper activation of MuSK by nerve-derived agrin. See text re autoantibodies that have been demonstrated to produce myasthenia gravis and those that have yet to achieve requirements for confirmation as pathogenic antibodies. ACh = acetylcholine; AChR = acetylcholine receptor; Dok7 = docking protein 7; LRP4 = low-density lipoprotein-related receptor 4; MuSK = muscle-specific protein kinase.

Investigations Cont.

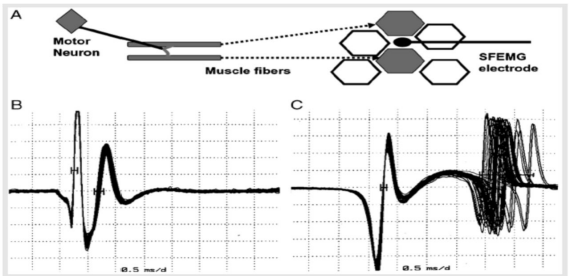
Repetitive Nerve stimulation (RNS)

- The sensitivity of RNS for diagnosing MG reportedly ranges from 53% to 100% in GMG and 10% to 48% in OMG.
- Normal pupils show <10%.
- If >10% it indicates NMJ disorder.
- There is decremental response at low rates of RNS.

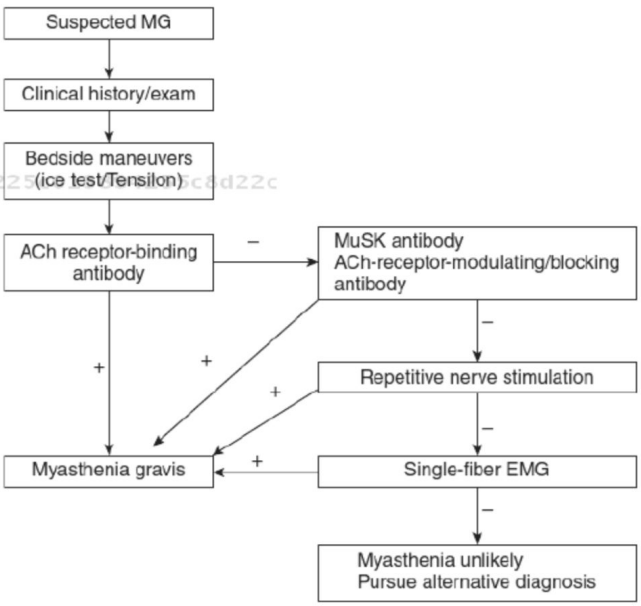


Single Fiber Electromyography (SFEMG)

- Sensitivity up to 95%.
- C. has more jitter (MG pt.)
- Sometime the opposite happens where AP is blocked which also indicated NMJ disorders
- Most Accurate Test.



GURE 2-4 *A*, In single fiber EMG (SFEMG) testing, the recording electrode is positioned to record from two or more time-locked potentials. Jitter is measured as the variation in the time interval between the two action potentials in the pair. *B*, An example of normal jitter; 40 consecutive discharges are superimposed. *C*, Abnormal jitter; 50 consecutive discharges are superimposed.



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**

*Poor adherence

Differential Diagnosis

Muscle Disease

- When symptoms are only ptosis.
- Thyroid ophthalmopathy
- Ocular pharyngeal muscular dystrophy (OPMD)
- Myotonic dystrophy
- Progressive external ophthalmoplegia

NMJ Disorder

- LEMS If limbs are weak
- Botulism
- Congenital MG
- Penicillamine-induced myasthenia
- Tick paralysis

Motor Neuron Disease

- ALS Amyotrophic Lateral Sclerosis
- PMA Progressive Muscular Atrophy

Peripheral Nerve

- Oculomotor cranial nerve pathology when only ocular muscle involved
- GBS Guillain Barre Syndrome
- CIDP Chronic Inflammatory Demyelinating Polyneuropathy
- Cavernous sinus pathology

Brainstem Pathology

- Stroke
- MS
- Tumors
- Infections

Other

- Isolated ptosis (? Weak tissues)
- Isolated dysconjugate gaze (decompensated strabismus)

Treatment

Symptomatic treatment

- Cholinesterase Inhibitors: Pyridostigmine (Mestinon).
- Doesn't affect pathogenesis, only relieves weakness.

Immunosuppressive therapy (Chronic)

- Prednisone most common, Azathioprine (Imuran), Methotrexate
- Cyclosporine, Mycophenolate (CellCept), Cyclophosphamide

MG crisis (Rapid)

- Intravenous Immune Globulin (IVIG)
- Plasmapheresis

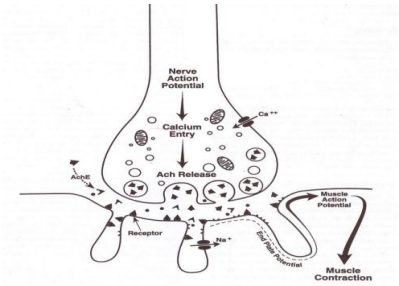
(Used in significant proximal weakness or respiratory/bulbar symptoms)

Surgery

- Thymectomy
- Done to all pts. with thymoma and for anyone with +ve Ach receptor antibodies with GMG except for those who are above 65.
- If they are above 65 and have thymoma then thymectomy is performed. Benefits: lower doses of steroids needed and lower MG crisis

Lambert-Eaton Myasthenic Syndrome (LEMS)

- Paraneoplastic (SCLC) and autoimmune.
- Voltage-Gated Ca++ Channel (VGCC) Ab's present in 90% of cases. Slowing Ca+ entrance.

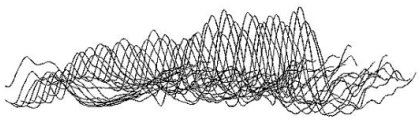


Clinical features

- Weakness/Fatigue in Limb-Girdle Distribution. Lower limbs are more affected
- Mild Ptosis, Diplopia, Dysphagia, Dysarthria may occur.
- Autonomic involvement: dry mouth, postural lightheadedness, sphincter disturbance or impotence. erectile dysfunction is common in men.
- Occasionally Paresthesias, Myalgias. Because it affects other nerves and autonomic ganglia.
- 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)

On Exam

- Proximal arm/leg weakness
- Improvement after few secs of voluntary Contraction with sustained contractions > increase Ca+ > AP is triggered
- Poorly reactive pupils
- Hypo or areflexia
- May have mild distal sensory loss in feet
- ***What is the most important single test in LEMS?*** CT chest to rule out SCC.



Incremental Response at High Rates RNS (20- 50 Hz)

Treatment

- 1st Rx Underlying Malignancy
- 2nd
  - 3,4 DAP diaminopyridine (amifampridine)
  - Guanidine hydrochloride
  - Similar to MG treatment

BOTULISM

- Botulism is caused by a toxin produced by the anaerobic bacterium Clostridium botulinum.
- Eight types of botulinum toxins (A, B, Ca , Cb , D, E, F, and G).
  - Types A and B are the cause of most cases of botulism in the United States
  - Transmission of type E is in seafood
- All forms of the toxin block ACh release from the presynaptic motor nerve terminal and the parasympathetic and sympathetic nerve ganglia.
- The intracellular target is the SNARE proteins of the presynaptic membrane.
- Neuromuscular symptoms usually begin 12 to 36 hours after ingestion of contaminated food and are preceded by nausea and vomiting.

Clinical features

- Cranio-ocular symptoms begin at same time or soon after initial GI Sx with ingested toxin.
- Pupils dilated and fixed in 50-75%.
- Blurred vision.
- Ptosis, EOM weakness nearly universal, symmetrical (may improve a bit with Tensilon).
- Bulbar weakness: dysarthria, dysphagia, facial.
- Limb weakness proximal > distal, symmetrical.
- Respiratory weakness.

Five Forms

- Classic or food-borne
- Infantile
- Wound & IV drug abuse: most common
- Hidden
- Iatrogenic

Treatment

- Treatment consists of administration of bivalent (type A and B) or trivalent (A, B, and E) antitoxin.
- Supportive.
- Infantile botulism: IV human botulism immune globulin (BIG-IV).

Summary	Pathophysiology	Clinical features	Diagnosis	Treatment
Myasthenia Gravis	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	Anticholinesteras: pyridostigmine. · Immunosuppressive therapy: Prednisone · Thymectomy, We do thymectomy for any patient with thymoma.
Lambert Eaton Syndrome	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	-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!

Conclusions

- **MG causes fatigable muscle weakness and often presents with ptosis and ophthalmoplegia.**
- **Early onset (<40 years) MG more commonly affects women, late onset is more common in men.**
- **AChR antibodies are found in 80–85% of generalised and 50% of ocular MG patients, MuSK antibodies in 5–8% of generalised MG.**
- **Decremental response to RNS and prolonged jitter or blocking on SFEMG are the neurophysiological hallmarks of MG.**
- **Monitoring of FVC is vital in patients with severe bulbar weakness.**
- **Myasthenic weakness is often exacerbated by infections and can lead to myasthenic crisis.**
- **Pyridostigmine, steroids and immunosuppressants are the mainstay of treatment.**
- **All patients with MG should be screened for thymoma.**
- **Thymectomy is often advised in mild to moderate AChR antibody positive generalised MG with onset less than 65 years of age.**

Questions

1-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

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. Stroke
E. Lung cancer

1-C

2-E From 435

Questions

3- A 56-year-old military commander has been attacked with nerve gas. He presents with salivation,lacrimation,urination, defecation,and shortness of breath. His pupils are constricted.
What is the first step in the management of this patient?

a. Atropine.
b. Decontaminate (wash)the patient.
c. Remove his clothing.
d. Pralidoxime.
e.No therapy is effective.

Answer: *A.* Atropine blocks the effects of acetylcholine that is already increased in the body. Atropine dries up respiratory secretion. Although removing clothes and washing the patient to prevent further absorption is good, this will do nothing for symptoms that are already occurring. Pralidoxime is the specific antidote for organophosphates.
Pralidoxime reactivates acetylcholinesterase. It does not work as instantaneously as atropine.