

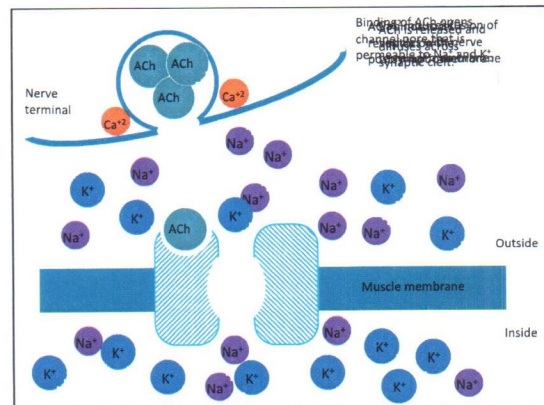
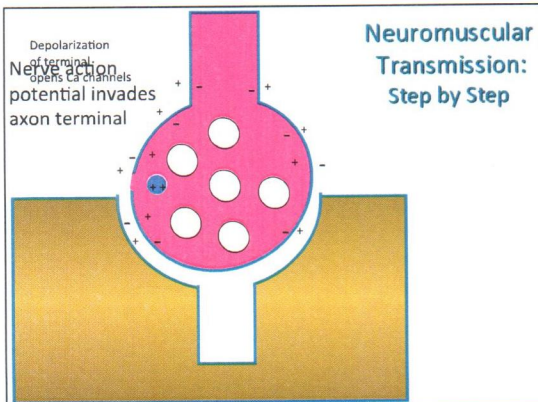
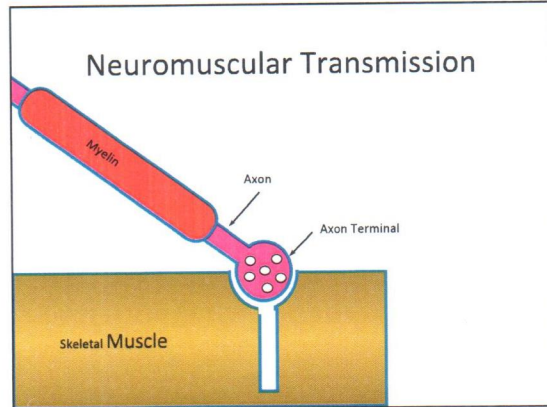
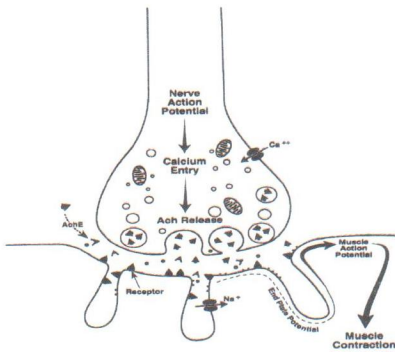
NMJ disorders: Myasthenia Gravis

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Objectives

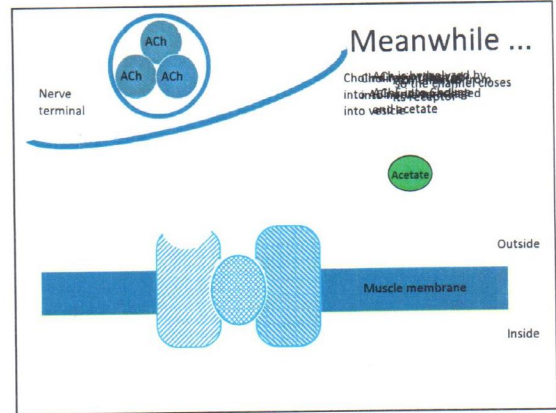
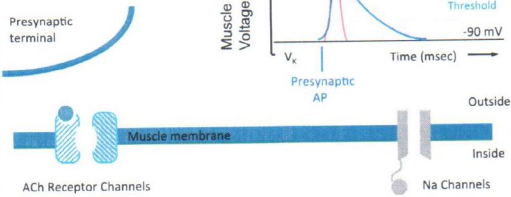
By the end of the lecture the student should be able to:

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.



End Plate Potential (EPP)

The movement of Na^+ and K^+ depolarizes muscle membrane potential (EPP)



Classification

- Presynaptic
 - Lambert Eaton Syndrome
 - Botulism
 - Congenital myasthenic syndrome
 - Hypermagnesemia
 - Envenomation
 - Aminoglycosides
- Synaptic
 - Congenital myasthenic syndromes
 - Cholinesterase inhibitors
 - Organophosphate
- Post-synaptic
 - Myasthenia gravis
 - Congenital myasthenic syndromes
 - Penicillamine

Myasthenia Gravis (MG)

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 and before puberty.

Clinical presentation

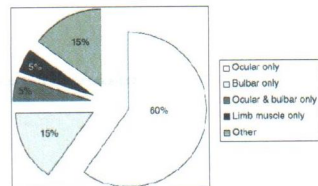


Figure 15.1. Initial symptoms in 919 patients with myasthenia gravis seen at the Duke University myasthenia gravis clinic (Sanders DB and Massey JM, unpublished data). Seventy percent had ocular symptoms (ptosis, diplopia, or blurred vision) at onset, and these were the only initial symptoms in 60%. 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 1%; 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.

- 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.

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.

- Weakness in MG
 - Fatigable and fluctuates
 - Less pronounced in the morning and improves after rest.
 - Asymmetric ptosis and EOM weakness, sparing pupils.
 - Weak eye closure.
 - Breathily nasal speech (palatal weakness)
 - Dysphagia and difficulty clearing secretions.
 - SOB due to diaphragm weakness (orthopnea)
 - NF > NE weakness
 - Proximal > distal limb weakness, usually symmetric.
 - Deltoid, triceps, WE, FE, Ank. DF weaker than other limb muscles.

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 | 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 | 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 |

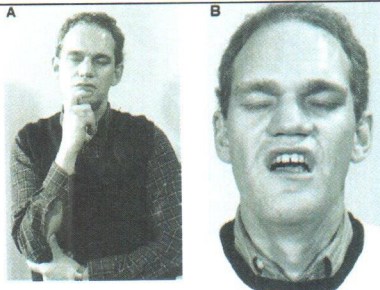


Fig. 1. A 36-year-old man with typical facial weakness. (A) He needs to support his jaw by holding his mouth closed. (B) When he attempts to close his eyelids firmly, his eyelashes remain visible, and the orbicularis oris weakness is evidenced by the straight smile.

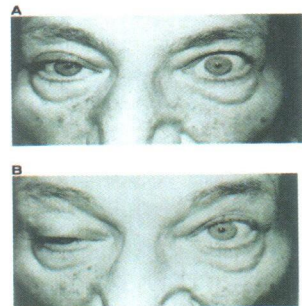
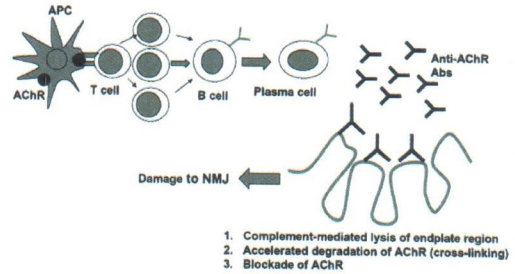


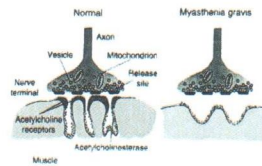
Fig. 1. (A) The patient is attempting to look up, evidenced by the contraction of the frontalis muscle. Note the slight right ptosis and left lid retraction. (B) Lid fatigue thus developed during the sustained upward gaze, manifested by marked ptosis on the right, and lessening of the lid retraction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

Pathogenesis



What Happens in MG

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



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. 5-11. All edrophonium (Tensilon) test in a patient with ocular myasthenia. The ptosis (drooping eyelids) is resolved after the patient is given 2 mg of the drug. (B) After administration of edrophonium chloride, the ptosis is resolved. (Photos courtesy of Dr. S. Lerman, Boston.)

Ocular Cooling/"ice-pack" test

- 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 (AChR) ANTIBODIES

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

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
 - Aminglycosides: 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

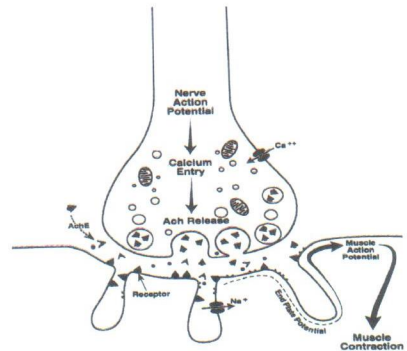
Neurology in practice, 2009;9:364-371

MG 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 60 years of age.

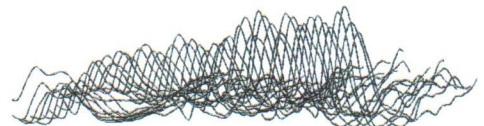
LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)

- Paraneoplastic (SCLC) and autoimmune.
- Voltage-Gated Ca^{++} Channel (VGCC) Ab's present in 90% of cases.
- Clinical features
 - Weakness/Fatigue in Limb-Girdle Distribution
 - Mild Ptosis, Diplopia, Dysphagia, Dysarthria may occur
 - Autonomic involvement: dry mouth, postural lightheadedness, sphincter disturbance or impotence.
 - Occas Paresthesias, Myalgias

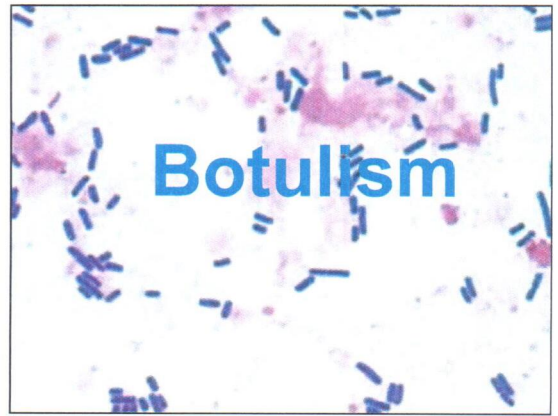


- On Exam:
 - Proximal arm/leg weakness
 - Improvement after few secs of voluntary Contraction
 - Poorly reactive pupils
 - Hypo or areflexia
 - May have mild distal sensory loss in feet

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



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



- Botulism is caused by a toxin produced by the anaerobic bacterium *Clostridium botulinum*
- Eight types of botulinum toxins (A, B, C_a, C_b, 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.

- five forms:
 - classic or food-borne,
 - infantile,
 - wound,
 - hidden, and
 - iatrogenic

- 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

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)