Lecture 62

Editing file

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Neuromuscular junction disorders

Objectives:

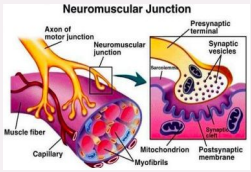
- ★ Recognize the symptoms and signs of neuromuscular junction disorders (e.g., myasthenia gravis, MG)
- ★ Understand the pathophysiology of MG.
- ★ List the appropriate workup for MG.
- ★ List management options for MG.

Color index:

Original text Females slides Males slides
Doctor's notes Textbook Important Golden notes Extra

Introduction

◀ Anatomical description of a NMJ



- **Neuromuscular junction consists of :**
  a. The **Axon terminal of a motor neuron**
  b. **motor end plate** of a **muscle fiber.**
  c. the synaptic cleft between these 2 parts.

1. **The Motor Neuron Part:**
   a. The axon of a motor neuron enters the structure of skeletal muscle and forms many branches called **axon terminals.**
   b. There is a swelling called a **synaptic end bulb** at the end of each axon terminal.
   c. Each synaptic end bulb contains **many synaptic vesicles** each of which contains an important neurotransmitter called **acetylcholine**.
2. **The Muscle Fiber Part:**
   a. 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.**
3. **The Synapse or Neuromuscular Junction (NMJ):**
   a. The area between the axon terminal and the sarcolemma is called the **'synaptic cleft'**

◀ Neuromuscular junction physiology

Release of ACH → that activates the muscle

- When a nerve pulse reaches a **synaptic end bulb** (nerve terminal), 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:

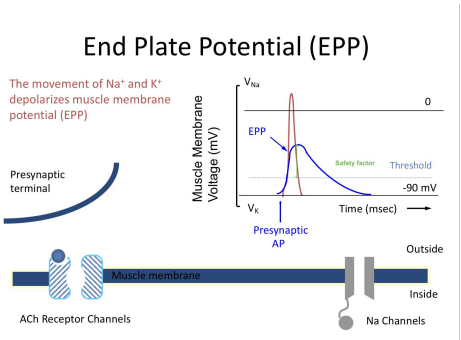
- The motor end plate contains receptors onto which the free ACh binds after diffusing across the synaptic cleft.
- This **binding of ACh to ACh receptors** in the motor end plate causes ion **channels to open & so allow the sodium (Na+) ions to flow across (influx) the membrane into the muscle cell.**

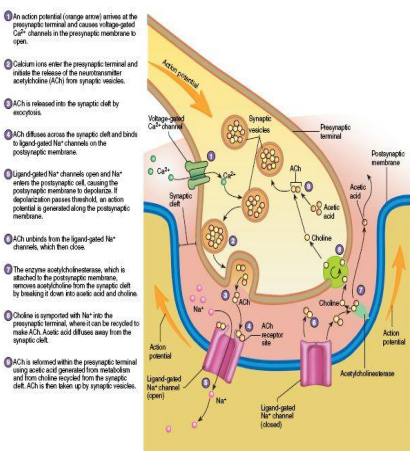
Generation of muscle action potential:

- 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. Generating muscle contraction.

Breakdown of Ach:

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





Classification of NMJ disorders

◀ According to the mechanism of action or etiology

Immune mediated

- **Myasthenia gravis**
- **Lambert Eaton Syndrome**

most common examples

Toxic / Metabolic

- Snake venom poisoning
- Botulism
- Arthropod poisoning
- Organophosphates
- Hypermagnesemia

Congenital

- Congenital myasthenic syndrome

◀ According to the location of the disruption

- Some can affect the Ca++ channels of the pre-synaptic membrane and some the Na+ channels or ACh receptors of the post-synaptic membrane.

Presynaptic

- Different mechanisms.
- Most often this causes a <u>decrease in the release of acetylcholine.</u>
- Mechanism of action can also **impair the calcium channels** that induce exocytosis of the vesicles.
- Other ion channels can also be disrupted, such as the potassium channels causing inefficient repolarization at the presynaptic membrane as in neuromyotonia.
- Examples include:
  - **Lambert Eaton Syndrome** The most common
  - **Botulism**
  - **Congenital myasthenic syndrome**
  - Hypermagnesemia
  - Envenomation
  - Aminoglycosides
  - Autoimmune neuromyotonia

Synaptic

- Congenital myasthenic syndromes
- Cholinesterase inhibitors
- Organophosphate

Postsynaptic

- The **highest number of diseases** affect the neuromuscular junction postsynaptically. either affects the Na+ channels or the ACh receptors.
- **Immune mediated myasthenia gravis (most common)**
- All the diseases that affect the postsynaptic membrane are forms of myasthenia gravis. **Examples includes:**
- Neonatal Myasthenia Gravis
- Drug Induced Myasthenia Gravis: Penicillamine

- Congenital myasthenic syndromes can either affect the pre-synaptic or mostly the post-synaptic membrane

Myasthenia gravis

Definition

- Myasthenia gravis is the **most common** disorder of neuromuscular transmission.
- The **hallmark** of the disorder is a **fluctuating degree** and variable combination of **weakness in ocular either alone or in combination with , bulbar, limb, and respiratory muscles.**

Epidemiology

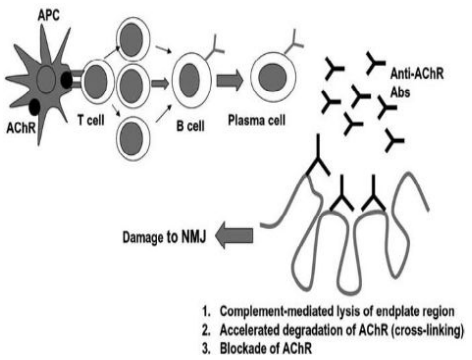
- Myasthenia gravis is a relatively uncommon disorder with an annual incidence of approximately 7 to 23 new cases per million, 10 – 20 per 1,000,000/year and Prevalence of 20 per 100,000
- Gender and age influence the incidence of MG
- Myasthenia gravis occurs at any age, but there is a **bimodal distribution** to the age of onset:
  - **Early peak** in the second and third decades (**female predominance**) in younger age groups
  - Women are affected nearly three times more often than men before age 40.
  - **Late peak** in the sixth to eighth decade (**male predominance**). in older age groups, however, it can occur to male patients at any age
  - The incidence is higher in males after age 50 and roughly equal during & before puberty.

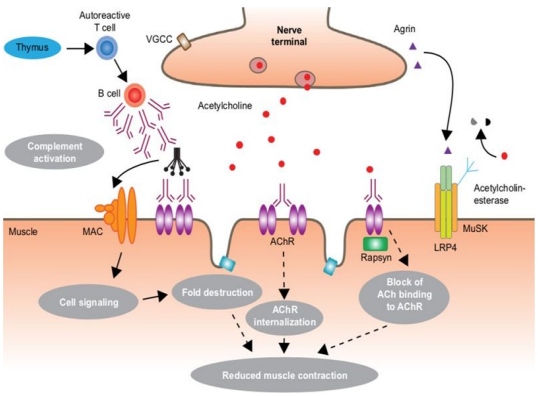
◄ Pathogenesis

- 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
- **Mechanisms underlying the pathology of MG:**
  - Anti-bodies activate the the complement cascade which will lead to the activation of membrane attack complex (MAC), which is C5,6,7,8 and 9. The MAC will destroy the membrane (Most important mechanism)
  - Anti-bodies will bind to the binding site of ACh on the ACh receptor
  - Anti-bodies cross link 2 receptors together → Internalize the receptor and degraded



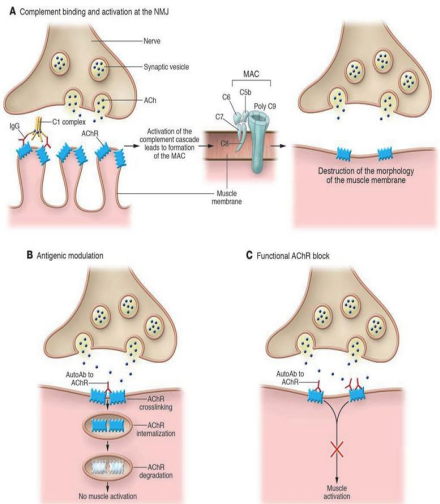


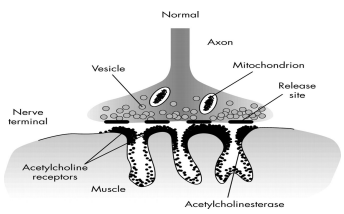
Myasthenia gravis

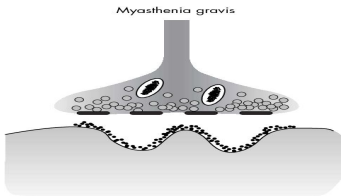
◀ Pathophysiology of MG

1. Simplified postsynaptic membrane.
2. Decreased of AchR's.
3. Remaining AchR's not localized to peaks of the membrane.
4. **Lower safety factor**

- It is an autoimmune response that affects the post-synaptic membrane
- The **amount of ACh released by the presynaptic motor neuron** normally **decreases** with every nerve impulse because of a temporary depletion of the presynaptic ACh stores (a phenomenon referred to as **presynaptic rundown) which is a normal physiological phenomena.**
    - There are primary (closest to the synaptic cleft), secondary, and tertiary storage vesicles → whenever the primary vesicles are used, it takes time for the secondary and tertiary vesicles to get closer to the cleft.
- In **MG**, there is **reduction of postsynaptic AChRs** due to production of **anti-AChR antibodies** that block receptors from binding to Ach and causes damage the postsynaptic membrane.
- Reduction in the number of AChRs available at the muscle endplate and **flattening of the postsynaptic folds.**
- Even if a normal amount of ACh is released, fewer endplate potentials will be produced, and they may fall below the threshold value for generation of an action potential. The end result of this process is **inefficient neuromuscular transmission.** → no muscle contraction because there in no muscle AP
- **Inefficient neuromuscular transmission** together with the normally present **presynaptic rundown** phenomenon results in a **progressive decrease in the amount of muscle fibers** being activated by successive nerve fiber impulses. This explains the **fatigability** seen in MG patients
- Patients become **symptomatic** once the number of **AChRs is reduced to approximately 30%** of normal.
- The **cholinergic receptors** of **smooth and cardiac muscle** have a different antigenicity than **skeletal muscle** and usually are not affected by the disease. **MG only affects nicotinic receptors of skeletal muscles.**







Myasthenia gravis

◀ Clinical features

- **>50%** of patients present with **ocular symptoms of ptosis** (drooping of eyelids) **and/or diplopia** (double vision). **most common manifestations.**
  - Of those who present with ocular manifestations, about **half** (80%) **will develop generalized disease** within two years.
- After 2 years with no limb Sx, disease usually remains purely ocular.
- **15%** of patients present with **bulbar symptoms**.
  - These include dysarthria, dysphagia, and fatigable chewing
- <5% present with proximal limb weakness alone.
- Usually progresses for weeks-months, and maximum severity is usually in first year of disease
- There are no sensory signs or signs of involvement of the CNS, although **weakness of the oculomotor muscles** may mimic a central eye movement disorder.
- It tends to run a **relapsing** and **remitting** course
- The distinguishing clinical feature in MG is **fatigable weakness.**
- Weakness: **better in the morning and after rest, and worse with use**

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.**

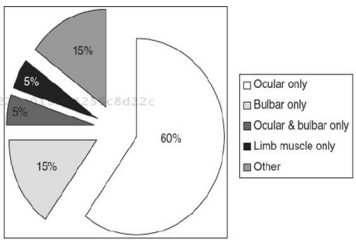


Figure 15.1. Initial symptoms in 919 patients with myasthenia gravis seen at the Duke University myasthenia gravis clinic (Sanders DB and Massey JM, unpublished data). Seventy percent had ocular symptoms (ptosis, diplopia, or blurred vision) at onset, and these were the only initial symptoms in 60%.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

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.

ABLE 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

The vast majority of MG pts present with ocular manifestation at onset, and as the disease progress in the first 2 yrs they will develop limb and bulbar weakness. After 2yrs, only a minority will be having ocular manifestations only.

Myasthenia gravis

◄ Clinical features

Ocular muscles:

- Weakness of the eyelid muscles can lead to **Asymmetric ptosis** (**fluctuating**).
- The **ptosis** may start bilaterally and improve in one eye, resulting in unilateral ptosis or alternate.
- **Variable** severity from one patient to another.
- **Extraocular muscles** involvement -**weakness-**(**binocular diplopia**) double vision that is apparent when both eyes are open and typically disappears when one eye is closed. It may be **horizontal or vertical.** depending on the extra-ocular muscles involved.
- **Pupils spared**

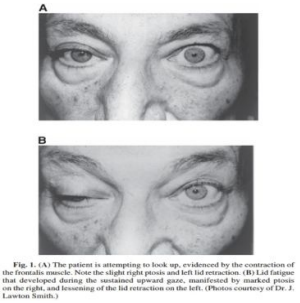


Fig. 1. (A) The patient is attempting to look up, evidenced by the contraction of the frontalis muscle. Note the slight right ptosis and left lid retraction. (B) Lid fatigue that developed during the sustained upward gaze, manifested by marked ptosis on the right, and lessening of the lid retraction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

Bulbar muscles

- Muscles of jaw closure **(fatigable- prolonged chewing)**. Sometimes this can be severe to the extent that it will lead to **jaw drop**.
- **Oropharyngeal muscle weakness** produces **dysarthria** , **dysphagia** and **difficulty clearing secretions.**
- Palatal muscles weakness causing breathy **nasal speech and nasal regurgitation** patient complains that liquids swallowed regurge through the nose

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> **Weak eye closure.**

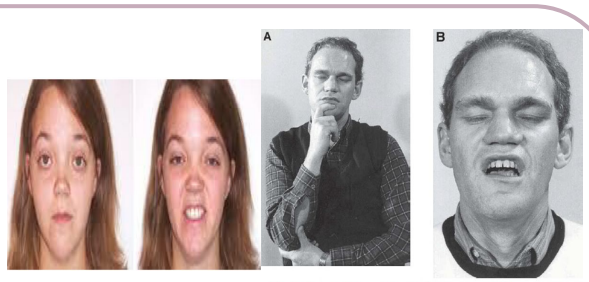


Fig. 1. A 36-year-old man with typical facial weakness. (A) He needs to support his jaw by holding his mouth closed. (B) When he attempts to close his eyelids firmly, his eyelashes remain visible, and the orbicularis oris weakness is evidenced by the straight smile.

Neck and limb muscles :

- **Neck extensor and flexor** muscles are commonly affected.
  - Neck Flexors> Neck Extensors (Musk : NE>NF) Musk anti-bodies is a subtype of MG, they tend to involve neck extensors more than neck flexors
- **Dropped head syndrome.** if significantly weak
- **Limb weakness:** Proximal > distal, usually **symmetric (unlike ocular)**, (the arms > the legs).
  - UL: Deltoid, triceps, wrist extensors (WE), finger extensors (FE) and finger flexors.
  - LL: Hip flexors (HF) , and Ank. DF (dorsiflexion)
- Wrist and finger extensors and foot dorsiflexors. if the distal limbs were involved

Respiratory muscles :

- SOB that's worse in supine position due to diaphragm weakness (**orthopnea**)
- Respiratory muscle weakness can leads to **respiratory insufficiency** and pending respiratory failure "**myasthenic crisis.“** serious consequence
- It may occur spontaneously during an active phase of the disease or may be precipitated by a variety of factors (any stressors) including surgery, infections, certain medications (a list of medications is given to any patient with MG to avoid myasthenic crisis, eg. Abx or some cardiac medications), or tapering of immunotherapy.

Myasthenia gravis

◀ Differential Diagnosis

Muscle Disease[1]	NMJ Disorders	Motor neuron disease
• Thyroid ophthalmopathy • Ocular pharyngeal muscular dystrophy (OPMD) • Myotonic dystrophy • Progressive external ophthalmoplegia	• LEMS • Botulism • Congenital MG • Penicillamine-induced myasthenia • Tick paralysis	• ALS Amyotrophic Lateral Sclerosis • PMA Progressive Muscular Atrophy

Peripheral nerve	Brain stem pathology	Other
• Oculomotor cranial nerve pathology • GBS Guillain Barre Syndrome • CIDP Chronic Inflammatory Demyelinating Polyneuropathy • Cavernous sinus pathology	• Stroke • MS • Tumors • Infections	• Isolated ptosis (? Weak tissues) • Isolated dysconjugate gaze (decompensated strabismus)

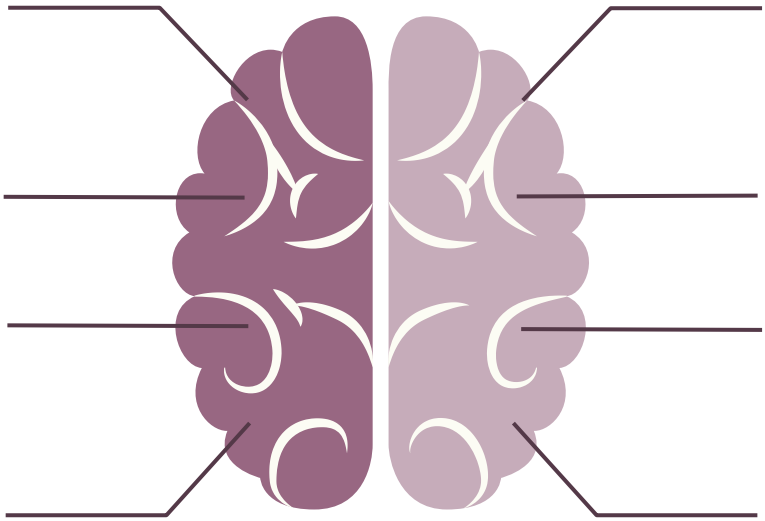
◀ Investigations

CBC, LFT, RFT, CK (To exclude myopathies)**, TSH, ESR, ANA.**

Ocular Cooling /"ice-pack" test.

Acetylcholine Receptor (AChR) Antibodies. (Best initial)

Edrophonium Chloride (Tensilon) Test.



Anti-MUSK Antibodies.

Repetitive nerve stimulation (RNS).

SFEMG. (MOST SENSITIVE TEST)

CT chest (To exclude thymoma)

1- Fatigability isn't a feature of muscle diseases

Myasthenia gravis

Ocular Cooling/“ice-pack” Test

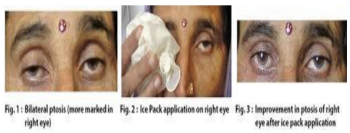


Fig. 1 : Bilateral ptosis (more marked in right eye) Fig. 2 : Ice Pack application on right eye Fig. 3 : Improvement in ptosis of right eye after ice pack application

- A bag (or surgical glove) is filled with ice and placed on the closed lid that has ptosis for 2 minutes. The ice is then removed and the extent of ptosis is immediately assessed.
  prolongation of the opening of Na+ channels that are responsible for the binding of ACh with AChR → transient ptosis improvement
- A meta-analysis showed this test to have high sensitivity (appears to be about 80%) and specificity in MG ,suggesting that it may be useful in patients with lid ptosis, particularly if the edrophonium test is negative or contraindicated.
- It can be used in patients with ptosis.

Edrophonium Chloride (Tensilon) Test

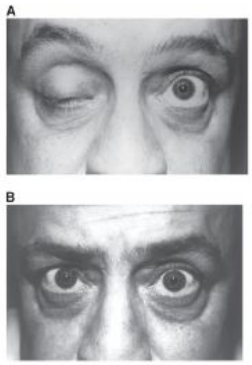
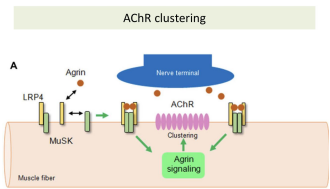


Fig. 2. (A) An almost complete right ptosis in a patient with ocular myasthenia. The frontalis muscle contraction, elevating the eyebrows, reflects the patient's effort to keep the lids open. (B) After administration of intravenous edrophonium chloride (Tensilon), the right ptosis is resolved. (Photos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

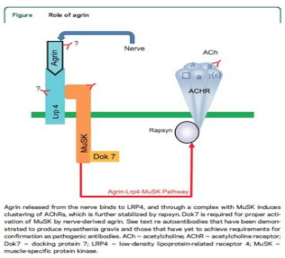
- Rarely used now because it causes bradycardia.
- The test is most reliable when the patient has ptosis or diplopia, and is positive in more than 90% of patients with MG.
- Is an **acetylcholinesterase inhibitor** injection with rapid onset (30 to 45 seconds) and short duration of action (5 to 10 minutes).
- 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.
- Used in patients with obvious ptosis or ophthalmoparesis, in whom improvement after infusion of the drug can easily be observed
- Cover with intravenous **atropine** is necessary to **avoid bradycardia**
- When the **test is positive**, there is substantial **improvement** in weakness within seconds and this lasts **for up to 5 minutes.**

Acetylcholine Receptor binding Antibodies

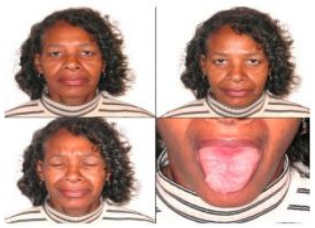


- Typically mostly used, measured from the serum.
- Not all patients have +ve antibodies, it’s found in 80-90% with generalized disease (15% are seronegative, out of these, 7% are Anti-Musk abs positive and 7% are double seronegative) and 40-55% with ocular myasthenia
- highly specific for MG and confirm the diagnosis.

Anti- MuSK antibodies



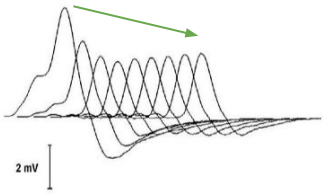
Agrin released from the nerve binds to LRP4, and through a complex with MuSK induces clustering of AChRs, which is further stabilized by rapsyn. Dok7 is required for proper activation of MuSK by nerve-derived agrin. See text re autoantibodies that have been demonstrated to produce myasthenia gravis and 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.



- If they were seronegative to antiAchR do anti Musk. What is the chance of it to be positive ? 38-50%
- MuSK antibodies are present in 38-50% of those with generalized myasthenia gravis who are AChR-Ab negative
- Present in up to 40 % of GMG patients who are seronegative for AChR antibodies and in some patients with OMG.
- Anti-MuSK antibodies define a sub- group of MG patients characterized by weakness predominantly in bulbar, facial and neck muscles.
  - Typically seen in young female

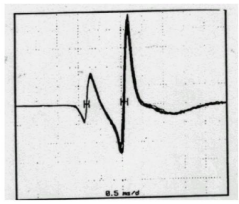
Myasthenia gravis

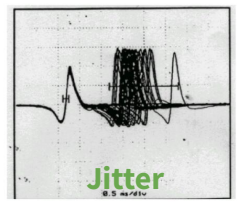
Repetitive Nerve stimulation (RNS)



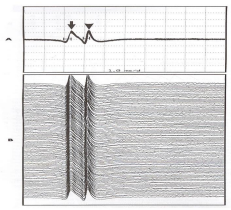
- The sensitivity of RNS for diagnosing MG reportedly ranges from 53% to 100% in GMG and 10% to 48% in OMG
- The nerve is electrically stimulated repetitively 6 to 10 times at low rates (2 or 3 Hertz).
- In normal muscles, there is no change in CMAP (compound muscle action potential)amplitude with repetitive nerve stimulation from the 1st to the 10th stimuli.
- In myasthenia there may be a progressive **decline in the CMAP amplitude with the first four to five stimuli**
- Repetitive stimulation during nerve conduction studies may show a **characteristic decremental response**

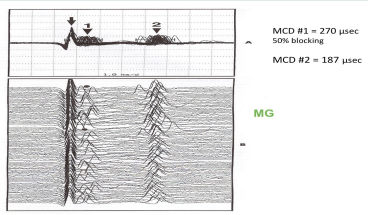
Single Fiber Electromyography (SFEMG) (Most sensitive)





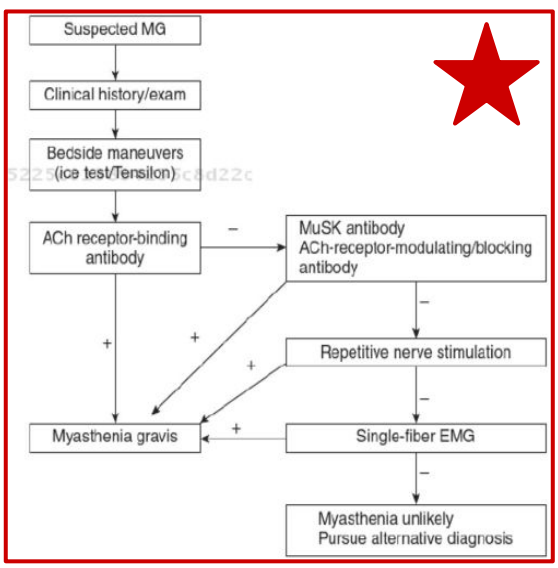
- Decreased # of interactions between Ach and receptors > takes longer to reach threshold
- Single-fibre EMG of orbicularis oculi is more sensitive than repetitive stimulation and shows block and jitter.
- Time required for EPP to reach threshold varies – **JITTER**
- Sometimes EPP fails to reach threshold – **BLOCKING**
- It is positive in greater than 90% of those with generalized myasthenia





CT mediastinum

- To detect common conditions associated with MG.
- In AChR antibody positive myasthenia gravis,>75% of patients have thymic abnormalities.
- **Thymic hyperplasia is most common 85%.**
- Thymic tumors (primarily thymoma) in up to 15%. usually in elderly groups although can be seen in young age group.
- **All patients should have a thoracic CT** to exclude thymoma
  - especially those **without** anti-acetylcholine receptor antibodies.



Autoimmune disorders

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

Myasthenia gravis

- A combination of symptomatic treatment and long term immunomodulating therapy.
- The goals of treatment are to **maximise the activity of acetylcholine at remaining receptors** in the neuromuscular junctions and to **limit or abolish the immunological attack on motor end plates.**

Symptomatic treatment (anticholinesterase agents)

- **Cholinesterase Inhibitors: Pyridostigmine (Mestinon).**
  - symptomatic relief , taken multiple times per day. consider it as panadol for headache.
  - Overdosage may cause a '**cholinergic crisis**' due to depolarisation block of motor end plate with muscle fasciculation, paralysis, pallor, sweating, excessive salivation and small pupils.

chronic Immunotherapy

- **(glucocorticoids/immunosuppressive drugs).**
  - **Prednisone (Main one),** Azathioprine (Imuran), Methotrexate
  - Cyclosporine, Mycophenolate (CellCept), Cyclophosphamide, Tacrolims,.
- We **start with steroids** and combine it with cellcept or imuran as it takes time to act (6-8 months). The advantage of prednisolone over other immunomodulators that it has a fast onset 7-10 days. Usually we use imuran or cellcept to avoid steroids side effects .

MG crisis (Rapid therapy)

- **Plasma exchange and intravenous immune globulin [IVIG]**

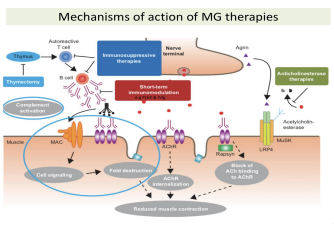
1. Intravenous Immune Globulin (IVIG)
   a. Lowers production of antibodies and rapidly reduces weakness
2. Plasmapheresis
   a. Removing antibody from the blood may produce marked improvement; this is usually brief, so is normally reserved for myasthenic crisis or for pre-operative preparation.

Refractory MG

– Eculizumab (Works on C5 of the MAC), rituximab (Works on B-cells), maintenance IVIG or PLEX, steroids +/-

Surgery

- **Thymectomy**
  - Thymectomy is performed only in **2 scenarios:**
    Patient has thymoma **Or** Positive ACh receptor antibodies + Generalised MG + Young patient
  - Studies showed benefit from thymectomy in those patients and they might reach complete remission. The onset of improvement is variable and doesn't always mean complete remission, it means reducing the number of relapses , admission and the ability to reduce steroid dose.
  - Should be considered in any antibody-positive patient under 45 years with symptoms not confined to extraocular muscles, unless the disease has been established for more than 7 years



TREATMENT OF MYASTHENIA GRAVIS
TYPICAL TIME TO CLINICAL EFFECT AFTER INITIATING THERAPY

THERAPY	TIME
Edrophonium (not used as therapy)	1-2 minutes
Pyridostigmine	10-15 minutes
Plasmapheresis	1-14 days
IVIG	1-4 weeks
Prednisone	2-8 weeks
Mycophenolate	2-6 months
Cyclosporine	2-6 months
Azathioprine	3-18 months
Thymectomy	Several months to several years

Myasthenia gravis

◀ Prognosis

- Prognosis is variable and remissions may occur spontaneously.
- When myasthenia is entirely ocular, prognosis is excellent and disability slight.
- Rapid progression of the disease more than 5 years after onset is uncommon.

◀ 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 65 years of age.

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**

Lambert-Eaton Myasthenic Syndrome (LEMS)

- It is a **rare** presynaptic disorder of neuromuscular transmission in which quantal **release of acetylcholine (ACh) is impaired.** Rather than post-synaptic like in MG, so there is no problem with ACh binding, but a problem on ACh release.

◀ Epidemiology

- The true incidence of LEMS is **unknown**, but the condition is **uncommon** and occurs much less frequently than myasthenia gravis
- Approximately 1/2 of LEMS cases are associated with a **malignancy**, mainly **small cell lung cancer** (SCLC)
- The incidence and prevalence of LEMS in patients with SCLC are estimated to be approximately 3%
- The other tumors associated with LEMS are lymphoproliferative disorders **(Hodgkin lymphoma)**.

◀ Pathophysiology

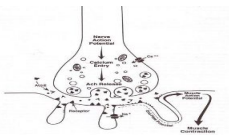
1. Caused by an autoimmune attack directed against the **voltage-gated calcium channels (VGCCs)** on the presynaptic motor nerve terminal results in a loss of functional VGCCs at the motor nerve terminals. no influx of Ca++ ⟶ no exocytosis of ACh

2. The number of quanta (vesicle that contains 5000-10000 molecules of ACh) released by a nerve impulse is diminished.

3. Because presynaptic stores of ACh and the postsynaptic response to ACh remain intact, rapid repetitive stimulation or voluntary activation that aids in the release of quanta will raise the endplate potential above threshold and permit generation of muscle action potential. Increased nerve AP ⟶ temporarily increase in ACh release ⟶ generation of muscle AP ⟶ temporary facilitation of movement and muscle strength.

4. Clinically, this phenomenon is noted by the appearance of previously absent tendon reflexes following a short period of strong muscle contraction by the patient. Temporary improvement.

5. Parasympathetic, sympathetic, and enteric neurons are all affected Ca++ channels. Another difference from MG.



◀ Etiology

Autoimmune

- Antibodies directed against the **voltage-gated calcium channel (VGCC).**
- These antibodies interfere with the normal calcium flux required for the release of acetylcholine.
- Typically in younger age groups.

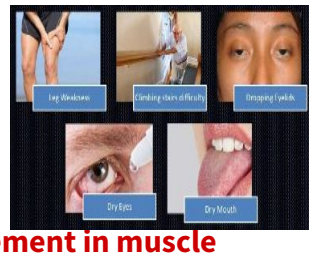
Paraneoplastic

- 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 LEMS.
- The manifestation of an underlying malignancy.
- Usually in elderly age groups.

Lambert-Eaton Myasthenic Syndrome (LEMS)

◀ Clinical features

- Weakness/Fatigue (LL>UL) in Limb-Girdle Distribution (Unlike MG, weakness improves with use in LEMS bc the more you use the muscle the more Ca enters → More ACh release)
- Most patients with LEMS present with slowly progressive **proximal muscle weakness**, **particularly involving the legs.** More than the arms.
- Deep tendon reflexes are typically depressed or absent only at the beginning, after repetitive muscle stimulation they appear.
- Autonomic symptoms including **dry mouth** (most common among autonomic symptoms) and erectile dysfunction ,postural lightheadedness, sphincter disturbance, dilated pupils
- Occas Paresthesias, Myalgias
- Dysphagia, Dysarthria may occur
- Ocular symptoms, especially ptosis and diplopia, may occur with LEMS but are **rarely the presenting or dominant feature of the illness. (Unlike MG)**
- Most patients do not have significant respiratory muscle weakness
- **Post-tetanic potentiation: Recovery of lost deep tendon reflexes or improvement in muscle strength with vigorous, brief muscle activation is a unique aspect of LEMS**
- Hypo or areflexia
- Poorly reactive pupils
- May have mild distal sensory loss in feet

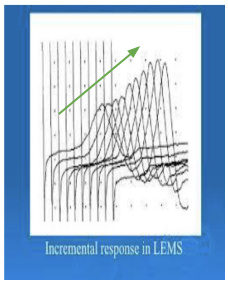


◀ Diagnosis

1. The diagnosis of LEMS is usually clinical and **confirmed by the presence of antibodies to voltage-gated calcium channel (VGCC)** and by electrodiagnostic studies

2. Antibodies against the **P/Q-type** VGCC are present in approximately 85-95% of patients with LEMS

3. **High frequency (10, 20 to 50 Hz)** repetitive nerve stimulation (RNS) or brief (10 seconds) maximal isometric muscle activation result in significant increment (>60%, unlike MG in which there's decrement) with a marked increase in the CMAP amplitude



temporary 100-200% improvement

◀ Treatment

- **1st Rx**
  - Search for and **treat a primary underlying malignancy** in patients with any risk factors for small cell lung cancer.
- **2nd**
  - Symptomatic therapies for LEMS include medications that increase the amount of acetylcholine available at the postsynaptic membrane.
  - These are **guanidine hydrochloride**, **aminopyridines such as 3,4-diaminopyridine (3,4-DAP, aka Amifampridine),** and acetylcholinesterase inhibitors such as **pyridostigmine**
- Immunologic therapies include intravenous immune globulin (IVIG) or oral immunosuppressive agents.

Botulism

◀ Definition

- It is an uncommon and life-threatening disease caused by bacteria in the **Clostridium** family including C. **botulinum, C barati and C butyricum** That affects the pre-synaptic membrane.
  - They are all gram-positive, anaerobic, spore-forming rods, which have evolved to produce a potent neurotoxin.
  - 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.

◀ it occurs in 4 forms, differentiated by the mode of acquisition:

Food borne botulism

- occurs after ingestion of **food contaminated** by preformed botulinum toxin

Infant botulism

- occurs after the ingestion of clostridial spores (Typically in honey) that then colonize the host's gastrointestinal (GI) tract and releases toxin

Wound botulism

- occurs after infection of a wound by Clostridium botulinum with subsequent production of neurotoxin

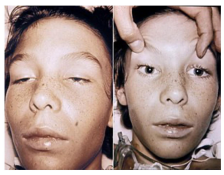
Adult enteric infectious botulism

- or adult infectious botulism of unknown source is similar to infant botulism in that toxin is produced in the GI tract of an infected adult host

Epidemiology

- An average of 110 cases of botulism is reported each year in the United States.
- Approximately 72% of these cases are infant botulism, 25% are food borne botulism (typically from homemade foods like jam), and 3% are wound botulism.

Botulism



Clinical features

- Acute onset (Unlike MG) of bilateral cranial neuropathies associated with symmetric descending weakness.
- Cranio-ocular symptoms begin at same time or soon after initial GI symptoms **(nausea & vomiting)** with ingested toxin.
- Pupils **dilated** and fixed in 50-75% of the patients.
- **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.

Symptoms usually start from the eyes and descend down

Key features of botulism syndrome

- **Absence of fever**
- Symmetric neurologic deficits
- **The patient remains responsive** doesn't affect level of consciousness.
- Normal or slow heart rate and normal blood pressure
- No sensory deficits

Diagnosis

- The diagnosis is usually clinical as routine lab tests are nonspecific and specific laboratory confirmation may take up to days.
- Electrodiagnostic studies are helpful in diagnosis of botulism.
- Repetitive nerve stimulation (RNS) at **low frequencies** of 2 to 5 Hz causes **decremental** response.
- RNS at **high frequencies** stimulation or exercise causes **incremental response**, or postactivation facilitation (in 60% of adult botulis).
- The amount of facilitation seen with botulism **(40-100%) is usually less than that seen in Lambert-Eaton myasthenic syndrome (200%).**

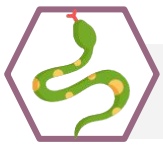
Treatment

- 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)
- Suspected cases should be hospitalized immediately and monitored for signs of respiratory failure.
- There are two botulism antitoxin therapies available.
- **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

Other NMJ disorders

Tick paralysis

- Several tick species produce a **toxin** that inhibits transmission at the neuromuscular junction by **blocking influx of sodium ions** In the postsynaptic membrane.
- This prevents presynaptic terminal axon depolarization and inhibits release of acetylcholine at the nerve terminal.
- The ticks primarily responsible include the Rocky Mountain wood tick (Dermacentor andersoni), the American dog tick (Dermacentor variabilis), the Lone Star tick (Amblyomma americanum), the black-legged tick (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.
- The **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 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**).

Clinical features

- Cranial nerves neuropathy resulting in **ptosis, ophthalmoplegia, dysarthria, dysphagia, and drooling.**
- Weakness of limb muscles.
- impaired coagulation profile.
- 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

Management

- **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.** Only supportive therapy.

Other NMJ disorders

Organophosphate and carbamates toxicity

- Commonly seen.
- Organophosphates and carbamates are **potent inhibitors of acetylcholinesterase**, causing excess acetylcholine concentrations in the synapse.
- Commonly used as pesticides.
- Exposure routes include oral ingestion, inhalation, or dermal contact.

Clinical features

- Both sympathetic and parasympathetic systems are involved.
- Symptoms include 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.
- Central nervous system symptoms may be present including anxiety, confusion, seizures, and coma

Management & diagnosis

- The diagnosis is made clinically by the presence of clinical features of cholinergic excess and history of exposure.
- Emergency management (ABC management) **often requires endotracheal intubation** and volume resuscitation.
- 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.

Hypermagnesemia / hypocalcemia

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

STEP UP

Summary

	Myasthenia Gravis
General characteristics	1. Autoimmune disorder—Auto antibodies are directed against the nicotinic acetylcholine receptors of the neuromuscular junction, which leads to a reduced postsynaptic response to acetylcholine and results in significant muscle fatigue. 2. Muscles that are stimulated repeatedly (e.g., extraocular muscles) are prone to fatigue 3. The peak incidence in women is age 20 to 30; in men, 50 to 70. It is more common in women.
Clinical features	1. Skeletal muscle weakness with preservation of sensation and reflexes. a. Weakness is exacerbated by continued use of muscleand improved by rest Symptoms worsen toward the end of the day (due to fatigue). b. Involved muscles vary and may include the following: Cranialmuscles: extraocular muscles, eyelids (ptosis), facial muscles (facial weakness, difficulty in chewing, slurred speech). Limb muscles (proximal and asymmetric). 2. Ptosis, diplopia, and blurred vision most common initial symptoms. 3. Generalized weakness, dysarthria, and dysphagia. 4. The condition progresses slowly with periodic exacerbations. Myasthenic crisis is a **medical emergency** that occurs in 15% of patients. Diaphragm and intercostal fatigue result in respiratory failure, often requiring mechanical ventilation
Diagnosis	1. Acetylcholine receptor antibody test is the test of choice (most specific). Nevertheless, 20% of patient with clinical manifestations of myasthenia gravis may be "antibody negative." 2. EMG shows a decremental response to repetitive stimulation of motor nerves. 3. A CT scan of the thorax can rule out thymoma. 4. Edrophonium (Tensilon) test—anticholinesterase (AChE) medications cause marked improvement of symptoms, but a high false-positive rate limits utility
Treatment	**1. AChE inhibitors— pyridostigmine.** a. Inhibiting AChE increases concentration of acetylcholine at the synapse by decreasing the breakdown of acetylcholine. b. This is a symptomatic benefit only. 2. **Thymectomy.** a. This provides a symptomatic benefit and complete remission in manypatients, even in the absence of a thymoma. b. Although usually benign, thymoma is an absolute indication for thymectomy. 3. **Immunosuppressive drugs.** a. Use corticosteroids for patient with a poor response to AChE inhibitors. b. Azathioprine and cyclosporine are alternative third-line agents.

Lecture Quiz

Q1: A 70-year-old woman presents with asymmetrical ptosis, which is more pronounced on her right eye, and intermittent diplopia. Her symptoms fluctuate daily, and they improve with rest but worsen in the evening. Her symptoms have been present for more than 1 year, with periods of spontaneous remission. On the whole, the symptoms do not interfere with her daily activities. On clinical examination, mild fatigability of neck extensors and arm proximal muscles is also evident. Myasthenia gravis is diagnosed by detecting anti-AChR antibodies, increased jitter on SF-EMG, and a positive response to neostigmine. Thoracic computed tomography scan is negative. The patient also has diabetes controlled by diet. Which of the following is the correct recommendation as first treatment in this patient?

A. Pyridostigmine
B. Prednisone and azathioprine
C. Thymectomy
D. Plasmapheresis

Q2: A 55-year-old woman complains of double vision. She finds that she is more tired than usual and has difficulty climbing stairs, especially when they are very long. She has difficulty getting items off high shelves at work and lately even brushing her hair is a problem. During the consultation, her voice fades away during conversations. Reflexes are present and equal throughout. Which sign or symptom is most indicative of myasthenia gravis?

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

Q3: 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

Q4: A 54-year-old man has been recently diagnosed with anti-AChR-positive myasthenia gravis. The disease has had an acute onset and rapid progression, leading in few weeks to severe generalized weakness with marked bulbar symptoms, including dysphagia, dysarthria, neck weakness, and impaired respiratory function. A thymoma is detected on thoracic computed tomography scan. Symptoms are not satisfactorily relieved by fulldose pyridostigmine treatment. Which of the following should be considered as first therapeutic option in this case?

A- . Immediate thymectomy
B. Plasmapheresis (or immunoglobulin infusion) and prednisone
C. Plasmapheresis
D. Azathioprine
E. Rituximab

Answers: Q1:A | Q2:D | Q3:E | Q4:B

Answers Explanation File!

THANKS!!

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Send us your feedback:
We are all ears!