MEDICINE

432 Team

53 Neuromuscular Junction Disorders

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

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.

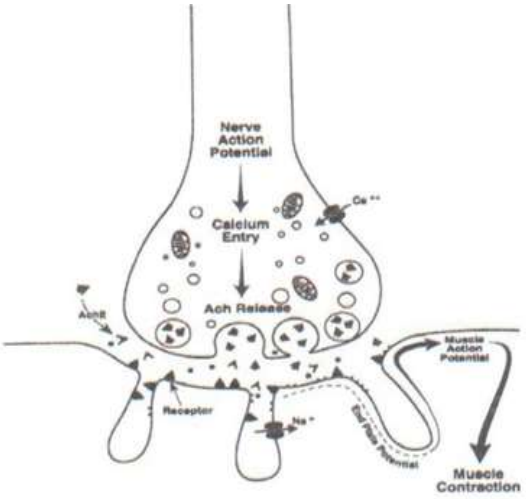
Quick review: ANATOMY & PHYSIOLOGY

- **Neuromuscular Junction (NMJ)**
  - Components:
    - Presynaptic membrane
    - Postsynaptic membrane
    - Synaptic cleft

1. Presynaptic membrane contains vesicles with Acetylcholine (ACh) which are released into synaptic cleft in a calcium dependent manner
2. ACh attaches to ACh receptors (AChR) on postsynaptic membrane
3. The Acetylcholine receptor (AChR) is a sodium channel that opens when bound by ACh
4. There is a partial depolarization of the postsynaptic membrane and this causes an excitatory postsynaptic potential (EPSP)
5. If enough sodium channels open and a threshold potential is reached, a muscle action potential is generated in the postsynaptic membrane
6. In the synaptic cleft, ACH is broken down by the enzyme acetylcholinesterase

MG:

- ***Acquired autoimmune disorder***
- ***Clinically characterized by:***
  - Weakness of skeletal muscles
  - Fatigability on exertion



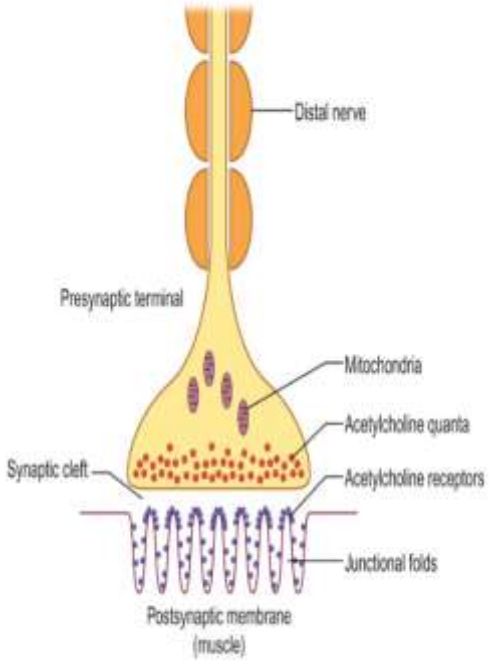
http://www.youtube.com/watch?v=y7X7IZ_ubg4

Definition of NMJ Disorders:

1. Disorders affecting the junction between the presynaptic nerve terminal and the postsynaptic muscle membrane
2. Pure motor syndromes
3. Preferentially affect proximal, bulbar, or extraocular muscles

- **NMJ Disorders:**
  1- Immune-mediated:
  - Myasthenia Gravis
  - Lambert–Eaton myasthenic syndrome

  2- Toxic/Metabolic Disorders
  - Botulism
  - Hypermagnesemia



The junctional folds increase the space, thus increase in Ach receptors → in NMJ disorders, the folds get damaged → decrease in the receptors.

Myasthenia Gravis

- **The most common disorder of neuromuscular transmission**
- **Myasthenia: Means Muscles without strength (My: muscles, a: without thenia: strength)**
- **Caused by an immunoglobulin G (IgG)-directed attack on the NMJ nicotinic ACh receptor**
- **A post-synaptic NMJ disorder.**
- **Hallmark of the disorder is a *fluctuating fatigable weakness***

❖ Classification

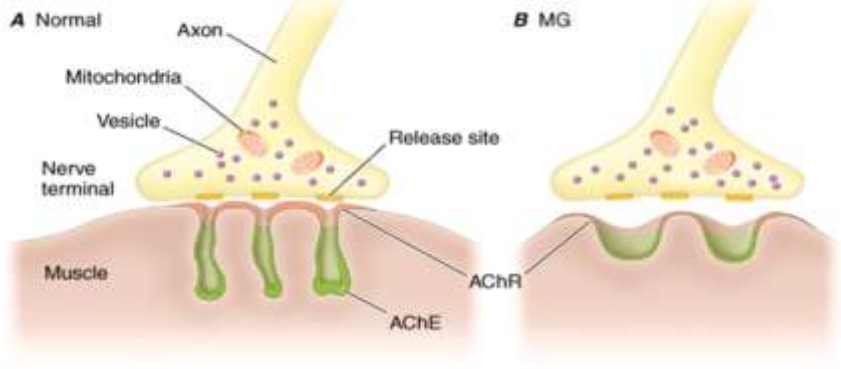
- According to onset
  A. Congenital (The affected person will have the disease for life)
  B. Acquired
- According to clinical presentation:
  A. Ocular (most common presentation)
  B. Generalized

❖ 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 does not last for life) due to trans-placental passage of maternal antibodies (the mother has MG) (Neonatal ≠ Congenital)
- **Association with other autoimmune diseases as, autoimmune thyroid disease, SLE, and rheumatoid arthritis, neuromyelitis optica**

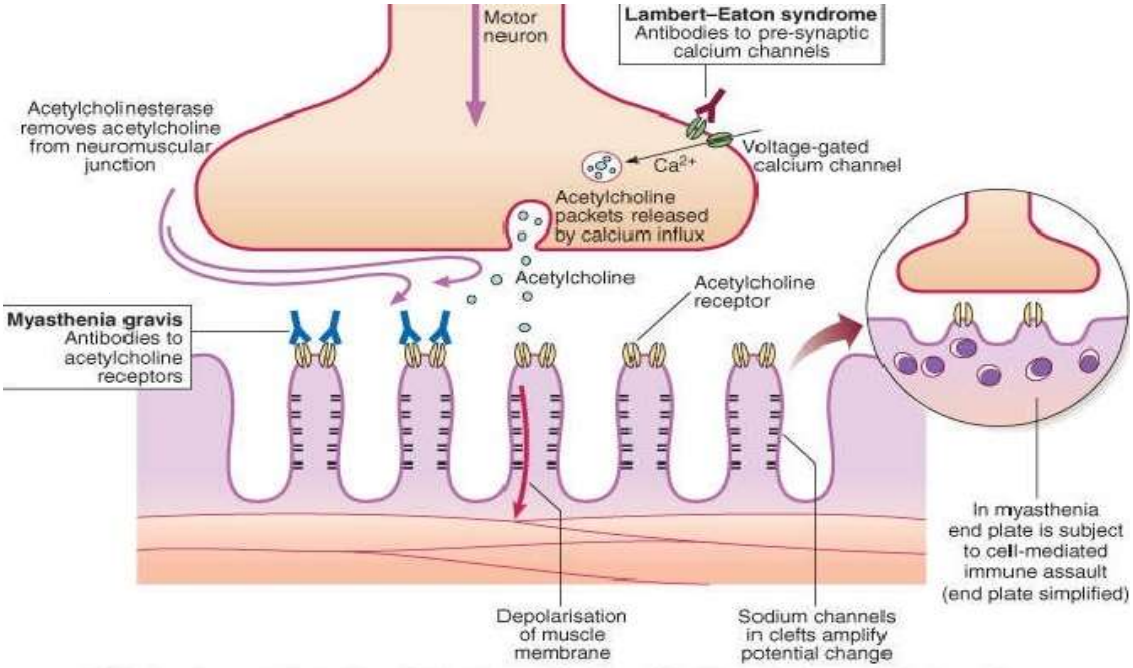
❖ Pathogenesis of MG

1. **Autoantibodies against the nicotinic AChR at the post synaptic membrane of NMJ**
2. Decrease in the number of active acetylcholine as a consequence of AChR antibody binding
3. Destruction of receptors occurs via a complement-mediated process
4. Destruction of the post-synaptic junctional folds
5. **Associated with thymus pathology.**
   - **60-70% of AChR ab positive patients have thymic hyperplasia and 10-12% have thymoma**
   - **Produces AChR subunits that triggers the immune response**



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

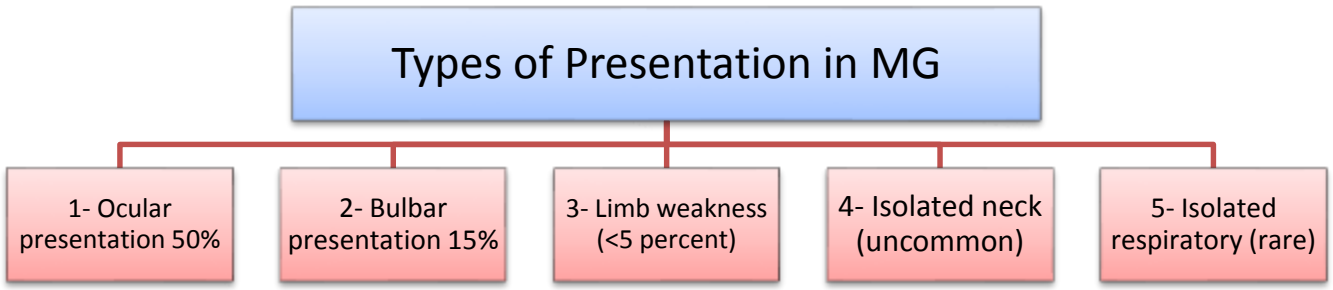
Destruction of the junctional folds (simplification of the folds) → decrease in the AChR



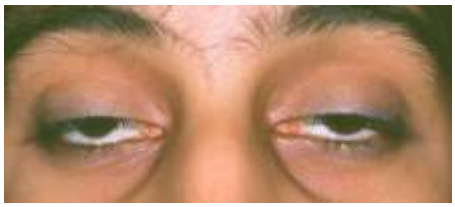
- **In myasthenia there are antibodies to the acetylcholine receptors on the post-synaptic membrane which block conduction across the neuromuscular junction (NMJ). Myasthenic symptoms can be transiently improved by inhibition of acetylcholinesterase**
- **Some drugs (aminoglycosides) my exacerbate NM blockade and should be avoided in MG patients *(Davidson's)***

❖ Clinical features of MG

- **Fluctuating weakness**, intermittent symptoms sometimes with periods of spontaneous improvement. And it tends to run a relapsing and remitting course in early years.
- **Ocular: *Ptosis, diplopia (double vision) and blurred vision* (most common initial symptoms)**
- Appearing with repetitive activity and worsening as day progresses
- Muscle fatigue and weakness (worsening contractile force, not tiredness) **no muscle pain.**
- No abnormality of mental state, sensory or autonomic function
- Characteristically affects the **extra-ocular, bulbar or proximal limb muscles**
- MG might be limited to extraocular muscles (only eye symptoms), especially in elderly patients.



1- Ocular-onset MG



- The most common
- Eventually 90% of MG patients will have ocular involvement
- %15continue to have isolated ocular symptoms
- Ptosis (droopy eyelids)
- Extraocular weakness (squint or double vision) frequently begins asymmetrically
- **Mimics** 3rd , 4th , and 6th nerve palsies and, rarely INO [Internuclear Ophthalmoplegia]
- Unlike true 3rd nerve palsies **MG never affects pupillary function**

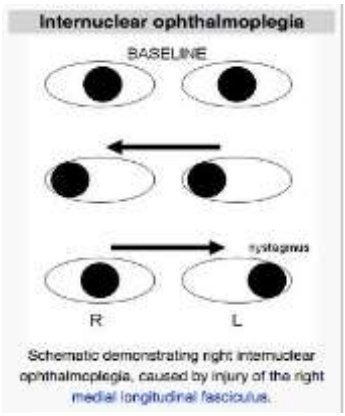
Inter-nuclear ophthalmoplegia (INO) (CNS disorder)

• Disorder of conjugate lateral gaze with impaired adduction of the eye on the side of the lesion and nystagmus of the abducting eye

• Lesion in the medial longitudinal fasiculus (MLF) that connects the ipsilateral 3rd nerve nucleus to the contralateral 6th nerve nucleus-PPRF complex

• Bilateral INO in young patient always R/O MS (because MLF is heavily demyelinated fiber)

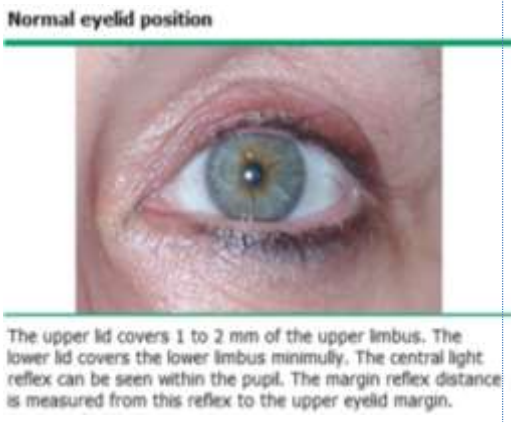
• Unilateral INO in an elderly R/O stroke



Right INO (right eye fails to adduct)

➢ **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
- Normal pupillary light reflex.



2- Bulbar-onset MG

- Bulbar muscles weakness is the next most common
- Dysphagia
- Fatigability and weakness of mastication, with the inability to keep the jaw closed after chewing .
- Dysarthria: nasal speech, slurred and hypophonic
- Nasal regurgitation
- Weight loss and cachexia

➢ **Facial muscles involvement**

- Facial muscles are frequently involved
- Patient appear expressionless
- **"myasthenic sneer"** on attempting to smile where the mid-lip rises but the outer corners of the mouth fail to move

Myasthenic sneer

3- Limb involvement in MG

- Limbs weakness, **usually symmetric and proximal**
- Wrist and finger extensors and foot dorsiflexors are often involved
- Rare patients present with an isolated limb weakness and never develop eye movement or bulbar muscle weakness
- Preservation of sensation and deep tendon reflexes.

4- Respiratory Involvement in MG

- Difficulty breathing, **SOB**
- Obstructive sleep apnea
- Difficulty sleeping on flat bed

❖ Diagnosing MG

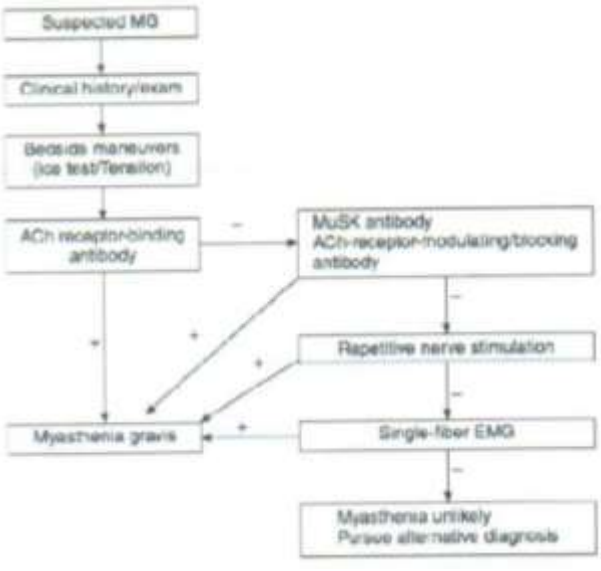
➢ Bed side tests:

- **Edrophonium (Tensilon) test**: injection of edrophonium (acetylcholinesterase inhibitor) in patients with ptosis or ophthalmoparesis looking for improvement, but it has a high false-positive.
- **Ice pack test: placing ice pack over ptotic eyelid for 2 minutes** (cold temperature will affect the enzyme action)

➢ Serologic testing:

- ***Antiacetylcholine receptor antibodies (AChR-Ab):***
  A. 80-90% of generalized MG
  B. 50% of ocular MG
  C. Best initial test.

- ***Anti-Muscle-specific kinase antibodies (MuSK-Ab):***
  A. 38-50% of generalized MG who are AChR-Ab –ve
  B. much lower frequency of thymic pathology
  C. More common in females
  D. Usually present with severe oculobulbar weakness along or neck, shoulder, and respiratory weakness



➢ Electrophysiological studies:

- Repetitive nerve stimulation studies: Decrement occurs in the evoked muscle AP.
- **Single-fiber EMG the most sensitive test.**
- EMG will show a reduced response to repetitive stimulation of motor nerves.

➢ CT scan of the chest

- **To rule out Thymoma or thymic hyperplasia.**

❖ 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, in which remission may occur
-

❖ Treatment of MG:

- **Symptomatic treatment**: ACHE inhibitors (Pyridotgmine, neostigmine). Best initial therapy.
- **Thymectomy:** is an absolute indication in case of thymoma.
- **Immunosuppressive treatment**: steroids, azathioprine ,cylosprine and cyclophosphamide are alternative third line therapy.
- **Crisis and exacerbation**: Plasmapheresis and IV immunoglobulin therapy.

❖ Myasthenic Crisis

- **life-threatening condition.**
- Definition: weakness from acquired MG that is severe enough to necessitate intubation *due to weakness of respiratory muscles .*
- Intubation is indicated in case of FVC > 1L. [force vital capacity]
- Severe oropharyngeal muscle weakness often accompanies the respiratory muscle weakness, or may be the predominant feature
- **Triggered by infections 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.

Treatment: IVIG or Plasma exchange

❖ Drugs that unmask and exacerbate myasthenia gravis:

- ❖ **Antibiotics- aminoglycosides and tetracycline.**
- ❖ B-blockers
- ❖ Antiarrythmtics- quinidine, procainamide and lidocaine.

❖ Lambert Eaton Myasthenic Syndrome

- Associated with Small Cell Lung Cancer. (Paraneoplastic manifestation of SCC).
- Presynaptic NMJ disorder. With Autonomic dysfunction [dry mouth, postural hypotension…]
- Middle age to old people
- 50% of cases are associated with malignancy (especially lung cancer)
- **Fluctuating proximal muscle weakness and hyporeflexia → abscent of tendon reflexes (AN IMPORTANT SIGN and it differentiate it from MG).**
- Ocular & Bulbar involvements is not very common
- Associated with P/Q type voltage gated **Ca channels antibodies (presynaptic)**
- IMPORTANT: Distinguished from MG in which the symptoms here IMPROVES with repeated muscle stimulation! [STEP-UP]. [Unlike MG where muscle weakness with repeated stimulation]

❖ Botulism

- Presynaptic NMJ disorder
- Caused by toxin produced by Clostridium Botulinum [present in certain food e.g. honey] and if this food is given to babies, their low immunity cannot defend their bodies against the released toxins, these toxins lead to weakness.
- Inhibits the release of Ach from the NMJ, sympathetic and parasympathetic ganglia
- Food borne or wound related
- Descending weakness and autonomic disturbance

- Ophthalmoparesis, bulbar weakness, limbs weakness

- Loss of pupil reflexes, constipation, respiratory

SUMMARY

1. **The hallmark in MG disorder is FFW (Fluctuating Fatigable Weakness)**
2. **MG is a post-synaptic NMJ disorder that affect the nicotinic AcH receptors.**
3. **Ptosis, Diplopia & blurred vision are the most initial Sx in MG**
4. **MG crisis is a life-threatening condition caused by weakness to the respiratory muscles usually.**
5. **Crisis and exacerbation: Plasmapheresis and IV immunoglobulin therapy .**
6. **ACHE inhibitors (Pyridotgmine , neostigmine) is the best initial therapy**
7. **Certain drugs could interfere with the functions of NMJ, and could induce the crisis in MG patients**

IMPORTANT NOTES FROM EXTERNAL RESOURCES

	Notes
Davidson's	• MG symptoms are worsening at the end of the day which is a characteristic sign of MG • There are NO signs of sensory or CNS involvement (reflexes)
Step-up	**Diagnostic tests:** AcHR Antibodies: is the most specific test. EMG: showing decrement on RNS (repetitive nerve stimulation) Edrophonium (Tensolin) & Ice pack tests

Approach to Myasthenia Gravis

Myasthenia Gravis

DIFFERENTIAL DIAGNOSIS OF PTOSIS

MECHANICAL aponeurotic ptosis (spontaneous dehiscence of the levator aponeurosis), eyelid infections, eyelid tumors.
NEUROMUSCULAR third nerve palsy (usually unilateral), Horner's syndrome (usually unilateral), myasthenia gravis (bilateral or unilateral), botulism (usually bilateral), myotonic dystrophy (usually bilateral).

CLINICAL FEATURES

HISTORY: ptosis (classically fluctuating and asymmetric in myasthenia gravis), diplopia, bulbar weakness (slurred speech, hoarseness, difficulty chewing and swallowing), limb weakness, shortness of breath, symptoms better with rest and worse with prolonged use, past medical history (malignancy, trauma), medications
PHYSICAL: vitals, pulmonary examination, measure palpebral fissure at rest and after upward gaze for 30 s, extraocular eye movements, and orbicularis oculi weakness (cannot bury eye lashes). Peek sign is positive when palpebral fissure can be seen after patient tries to gently close the eye lids), voice changes, assess for weakness of neck flexor, deltoids, hip flexors, finger/wrist extensors, and foot dorsiflexors with repeated challenges. Sensory examination should be normal and reflexes should demonstrate fatigability
SPECIAL TESTS FOR MYASTHENIA GRAVIS: ice test (improvement of ptosis with palpebral fissure increase of 2 mm after applying ice over eyelid for 2 min), sleep test (improvement of ptosis with palpebral fissure increase of 2 mm after resting in dark room for 30 min), curtain sign, lid twitch sign, cover uncover test (examiner covers one eye as patient fixates on a distant object. Observe for deviation of the uncovered eye during lateral and then upward gazing. With extraocular weakness, the uncovered eye will drift)

INVESTIGATIONS

BASIC:

- **LABS** TSH, ANA, RF
- **IMAGING** CT chest (thymoma, malignancy), CT/MR head (if third nerve palsy)

SPECIAL:

- **EDROPHONIUM/TENSILON** TEST injection of acetylcholinesterase inhibitor, improvement may be detected in 30 s and lasts <5 min
- **ANTIBODIES** anti acetylcholine receptor antibody (sens 80 90%, very high spc), muscle specific receptor tyrosine kinase antibody
- **SINGLE FIBER EMG WITH/WITHOUT REPETITIVE STIMULATION**

MANAGEMENT OF DKA

MYASTHENIA GRAVIS pyridostigmine 30 mg PO q3 6h. Thymectomy (controversial if no thymoma). Other treatments include corticosteroids, azathioprine, cyclosporine, mycophenolate plasmapheresis, IVIG
MYASTHENIC CRISIS **ICU** admission, treat any precipitating infection, discontinue any anticholinesterase agents, correct electrolyte abnormality, monitor respiratory status, and intubate if VC <15 mL/kg, plasmapheresis

Questions

1) A 20-year-old woman complains of weakness that is worse in the afternoon, worse during prolonged activity, and improved by rest. When fatigued, the patient is unable to hold her head up or chew her food. On physical examination, she has no loss of reflexes, sensation, or coordination. Which of the following is the likely pathogenesis of this disease?

a. Antiacetylcholine receptor antibodies causing neuromuscular transmission failure
b. Destruction of anterior horn cells by virus
c. Progressive muscular atrophy caused by spinal degeneration
d. Demyelinating disease
e. Defect in muscle glycogen breakdown

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

a. Weakness worsens as the day progresses
b. Weakness is severe in the morning
c. Limb weakness is more severe distally than proximally
d. Weakness is not affected by the level of activity
e. Weakness progresses in severity very rapidly

3) One of the following is an acetyl cholinesterase used in the treatment of Myasthenia Gravis

a. Azathioprine
b. Pyridostigmine
c. Azathioprine
d. Cyclosporine A
e. Methotrexate

432 Medicine Team Leaders

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For mistakes or feedback: *medicine341@gmail.com*

Answers:

1st Questions: a

2nd Questions: a

3rd Questions: b