433 Teams

MEDICINE

26|Neuro Muscular Junction disorders

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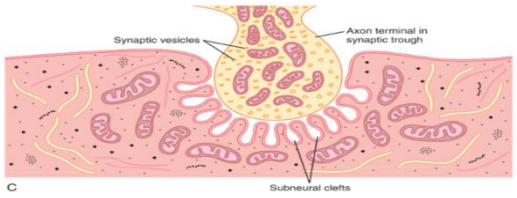
Objectives :

1. Clearly describe the physiology of the neuromuscular junction.
2. Define neuromuscular junction diseases.
3. Differentiate between NMJ diseases and other disorders affecting the peripheral nervous system.
4. Describe the pathogenesis of the most common NMJ disorder (Myasthenia Gravis) and its presentation.
5. Identify the risk factors and the presentation of a myasthenic crisis.
6. Recognize the symptoms and signs of neuromuscular junction disorders (e.g., myasthenia gravis, MG)
7. Understand the pathophysiology of MG.
8. List the appropriate workup for MG
9. List management options for MG.

Physiology: for more understanding

A- Transmission of Impulses from Nerve Endings to Skeletal Muscle Fibers,The Neuromuscular Junction:

The skeletal muscle fibers are innervated by large, myelinated nerve fibers that originate from large motoneurons in the anterior horns of the spinal cord. Each nerve fiber, after entering the muscle belly, normally branches and stimulates from three to several hundred skeletal muscle fibers. Each nerve ending makes a junction, called the ***neuromuscular junction,*** with the muscle fiber near its midpoint. The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends.



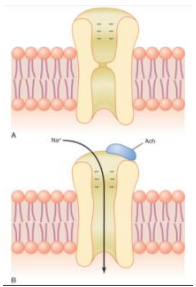
In the axon terminal are many mitochondria that supply adenosine triphosphate (ATP), the energy source that is used for synthesis of an excitatory transmitter, *acetylcholine*. The acetylcholine in turn excites the muscle fiber membrane. Acetylcholine is synthesized in the cytoplasm of the terminal, but it is absorbed rapidly into many small *synaptic vesicles,* about 300,000 of which are normally in the terminals of a single end plate. In the synaptic space are large quantities of the enzyme *acetylcholinesterase,* which destroys acetylcholine a few milliseconds after it has been released from the synaptic vesicles.

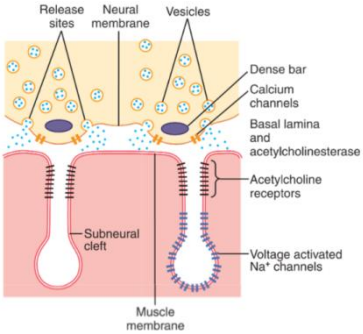
B- Secretion of Acetylcholine by the Nerve Terminals :

When a nerve impulse reaches the neuromuscular junction, about 125 vesicles of acetylcholine are released from the terminals into the synaptic space.

On the inside surface of the neural membrane are linear dense bars. To each side of each dense bar are protein particles that penetrate the neural membrane; these are voltage-gated calcium channels. When an action potential spreads over the terminal, these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal. The calcium ions, in turn, are believed to exert an attractive influence on the acetylcholine vesicles, drawing them to the neural membrane adjacent to the dense bars. The vesicles then fuse with the neural membrane and empty their acetylcholine into the synaptic space by the process of exocytosis.

The principal effect of opening the acetylcholine-gated channels is to allow large numbers of sodium ions to pour to the inside of the fiber, carrying with them large numbers of positive charges. This creates a local positive potential change inside the muscle fiber membrane, called the *end plate potential*. In turn, this end plate potential initiates an action potential that spreads along the muscle membrane and thus causes muscle contraction.





C- Destruction of the Released Acetylcholine by Acetylcholinesterase:

Acetylcholine is removed rapidly by two means:

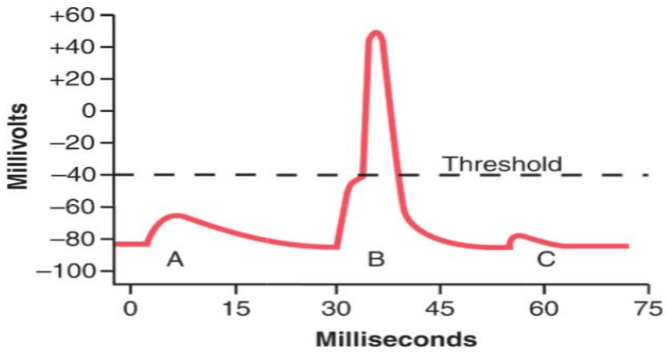
(1) Most of the acetylcholine is destroyed by the enzyme ***acetylcholinesterase***, which is attached mainly to the spongy layer of fine connective tissue that fills the synaptic space between the presynaptic nerve terminal and the postsynaptic muscle membrane.

(2) A small amount of acetylcholine diffuses out of the synaptic space and is then no longer available to act on the muscle fiber membrane.

The short time that the acetylcholine remains in the synaptic space—a few milliseconds at most—normally is sufficient to excite the muscle fiber. Then the rapid removal of the acetylcholine prevents continued muscle re-excitation after the muscle fiber has recovered from its initial action potential

D- Safety Factor for Transmission at the Neuromuscular Junction, Fatigue of the Junction.

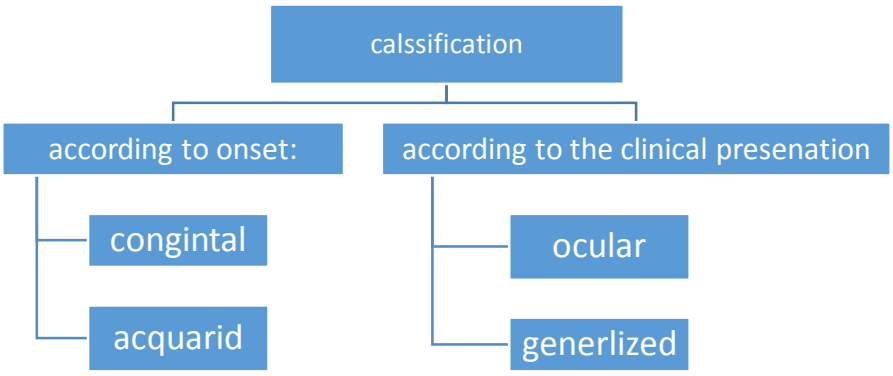
Ordinarily, each impulse that arrives at the neuromuscular junction causes about three times as much end plate potential as that required to stimulate the muscle fiber. Therefore, the normal neuromuscular junction is said to have a high *safety factor*. However, stimulation of the nerve fiber at rates greater than 100 times per second for several minutes often diminishes the number of acetylcholine vesicles so much that impulses fail to pass into the muscle fiber. This is called *fatigue* of the neuromuscular junction, and it is the same effect that causes fatigue of synapses in the central nervous system when the synapses are overexcited. Under normal functioning conditions, measurable fatigue of the neuromuscular junction occurs rarely, and even then only at the most exhausting levels of muscle activity.



(Myasthenia Gravis)

A. General characteristics:

- A post-synaptic NMJ disorder.
- Autoimmune disorder :
  - Caused by an immunoglobulin G(IgG) directed attack on the NMJ nicotinic ACH receptor.
  - Autoantibodies 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.
  - The destruction of the receptors occur via a complement-mediated process.
  - Destruction of the post synaptic folds.
  - Muscles that are stimulated repeatedly (e.g., extraocular muscles) are prone to fatigue.
- MG has 2 peaks :
  1) Early: in 20s and 30s & is more common in female.
  2) Late: in 50s 60s 70s &it's more common in males.
- Prevalence is 200 per million.
- MG doesn't affect sensation and doesn't cause autonomic dysfunction.
- Associated with other autoimmune diseases like, autoimmune thyroid disease, SLE, and rheumatoid arthritis, neuromyelitisoptica.
- Neonatal MG: a transient form, due to trans-placental passage of maternal antibiotic.



B. Clinical features:

1. The hallmark of the disorder is a fluctuating Fatigable weakness.
2. Fluctuating intermittent symptoms sometimes with periods of spontaneous improvement appearing with repetitive activity and worsening as the day progresses.
3. Skeletal muscle weakness—with preservation of sensation and reflexes
   (Weakness is exacerbated by continued use of muscle and improved by rest and symptoms worsen toward the end of the day, due to fatigue).
4. Asymmetric Ptosis, diplopia, and blurred vision—most common initial symptoms.
5. Generalized weakness, dysarthria, and dysphagia.
6. The condition progresses slowly with periodic exacerbations.
7. Diaphragm and intercostal fatigue result in respiratory failure, often requiring mechanical ventilation.
8. Maximum weakness will be reached by 2 years.
9. Ocular presentation 50%:
   Ocular onset most common eventually 90% of patients would have involvement 15% have isolated Ocular symptoms, Ptosis Extra ocular weaknesses frequently begins asymmetrical. Mimics third fourth and sixth rarely INO, Unlike to third nerve palsy, MG never affects pupillary function.
10. Bulbar presentation 15%: (Bulbar palsy refers to impairment of function of the cranial nerves **IX, X, XI and XII**)
    - Bulbar muscular weakness is the best most common.
    - Fatigability and weaknesses of mastication, with the inability to keep the jaw closed after chewing.
    - Dysphagia.
    - Dysarthria: nasal, slurred and hypophonic.
    - Nasal regurgitation.
    - Weight loss and cachexia.
11. 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.
12. Limb weaknesses less than 5%
    - 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 my cement the e bulbar muscle weakness.
13. isolated neck uncommon
14. Isolated respiratory rare:
    - Difficulty breathing.
    - Obstructive sleep apnea.
    - Difficulty sleepy no on flat bed.

-Myasthenic crisis is a medical emergency due to weakness of respiratory muscles or oral pharyngeal muscles.

-MG crisis treatment IV IG or Plasma exchange

INO: intra-nuclear opthalmaplasia:

- Disorder of conjugated lateral gaze with impaired adduction on the side of the lesion nystagmus of the abducting eye
- INO is caused by lesion of medial longitudinal fasciculus (MLF is a fibers meant to coordinate eye movement between nerve 3 and nerve 6) it will cause nystagmus.
- Bilateral INO think of MS unilateral think of stroke.

so this doesn't happen in MG, it's a CNS disorder

C. phases of MG:

Active phase
- frequent episodes of weakness (fluctuation).

More stable phase
- it will have specific things trigger it.

Final phase
- remission may accrue or he may have burn out MG (he will be atrophied, weak, can not be fixed.

Factors exacerbating weakness in myasthenia gravis and potentially triggering myasthenia crisis.
Infections
Stress
Withdrawal of cholinesterase inhibitors (when symptoms not fully controlled)
Rapid introduction or increase or increase of steroids.
Electrolytes imbalance – hypokalemia, hypophosphatemia
Anemia
Medications: most are rarely implicated, except those highlighted
Antibiotics: Aminoglycosides; Gentamicin, Amikacin, telithromycin, etc. Quinolones; ciprofloxacin, norfloxacin, etc. Tetracyclines: doxycycline, minocycline, etc. Antimalrials: Choloroquine
Antirheumatic drugs: Penicillamine
Anesthetic drugs: Succinylcholine
Antiarrhythmic drugs: Quinidine, Procainmide.
Antihypertensive: B-blockers and calcium channel blockers
Neuropsychiatric drugs: lithium, cholorpromazine, phenytoin.
Chemotherapy: cisplatin

Important table !

Fatiguing Maneuvers in Suspected Myasthenia Gravis		
Clinical Fatiguing Maneuver	Manifestation in symptomatic Myasthenia Gravis	Comments
Sustained upgaze (30 to 60 seconds)	Enhance ptosis and elicits medical rectus weakness.	Medical 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 attemps	Early/mild weakness may cause exaggerated lean-forward and "buttocks-first" maneuver.
Counting aloud (1 to 50)	Enhances dysarthria	Nasal, lingual, or labial

In Examination:

- Normal eyelid crease is 6 to 7 mm away from the eyelid margin in adults
- Differentiate between 3rd nerve lesion and MG by pupil it will be spared always in MG because it doesn't affect autonomic nerves system.
- When normal person looks straight forward the distant between upper and lower eyelid should be between 9 – 12 mm.
- Upper eyelid should cover maximum of 2 mm of lumps, if its covering 3 or 4 mm its ptosis
- Distance from a central pupillary light reflex to upper eyelid margin is called the margin reflex distance normally this measures 4 to 5 mm

D. Diagnosis:

- **Best initial test:** acetylcholine receptor antibodies (80%- 90% sensitive). This is a better first answer than edrophonium testing. For patients without those antibodies, get anti-MUSK antibodies (muscle-specific kinase).
- **Edrophonium:** short-acting inhibitor of acetylcholinesterase. The temporary bump up in acetylcholine levels is associated with a clear improvement in motor function that lasts for a few minutes.
- **Most accurate test:** Electromyography shows decreased strength with repeti-tive stimulation.
- **Tensolin test:** not used anymore
- **Ice bag test:** inhibit acetylcholine esterase, by placing an ice pack over the ptotic eyelid for 2 minutes. Positive responses can occur even when edrophonium tests are negative.
- **Serological test:**
- **Anti-acetylcholine receptor antibodies (AChR-Ab):**
  - 80-90% of generalized MG
  - 50% of ocular MG
  - 98 – 90 % will have heavy antibody's if it was generalize the other 10 % will have antiMuSK .If it was ocular it will be 50% of cases, the other 50% will have antiMuSK.
- **Anti Muscle-specific kinase antibodies (MuSK-Ab):**
  - 38-50% of generalized MG who are AChR-Ab-ve
  - Much lower frequency of thymic pathology
  - More common in females
  - Usually present with sever oculo-bulbar weakness or neck,shoulder, and respiratory weakness
  - Patient with antiMuSK will have fisher of tong
  - We must do CT scan of the chest we should do it for every patient with MG because they tend to have thymoma.
- **Electrophysiological studies:**
  - Repetitive nerve stimulation studies :The sensitivity of RNS for diagnosing MG reportedly ranges from 53% to 100% in GMG and 10% to 48% in OMG.
  - Single-fiber EMG the most sensitive test.
- **CT scan of the chest:** We must do CT scan of the chest, for every patient with MG because they tend to have thymoma.

E. Treatment:

Treatment Best initial treatment: Neostigmine or pyridostigmine. These are longer acting versions of edrophonium.

If these medications do not control the disease, the "most appropriate next step in management" is a thymectomy if the patient is under age 60, prednisone is used. Azthioprine, cyclophosphamide, or mycophenolate are used in order to get the patient off of steroids before serious adverse effects occur.

Symptomatic treatment with acetylcholine esterase.

❖ Management of Acute Myasthenic Crisis:

- Myasthenic crisis is a medical emergency due to weakness of respiratory muscles or oral pharyngeal muscles.
- MG crisis treatment IV IG or Plasma exchange (plasmapheresis)
- Thymoctomy is indicated in all patients except 90 years old with mimic hyperplasia with low ptosis.
- Chemotherapy & Steroids (Steroids start with very low doses unless if the patient is MG crisis and already doing plasma exchange then it's safe to give high dose of steroids)
- MG with infection don't give him antibiotics without checking list of medication to avoid (list In the lecture). Over the counter medication can be a cause of MG crisis.

- **Lambert-Eaton Myasthenic Syndrome:** (presynaptic) is autoimmune mediate disorder (antibody against calcium channels) affect middle to old people and 50% associate with cancer. It causes autonomic dysfunction.
  - Presynaptic NMJ disorde.
  - Middle age to old people.
  - Half of cases are associated with malignancy (especially lung cancer).
  - Fluctuating proximal weakness, ocular and oropharyngeal muscles are occasionally affected.
  - Autonomic dysfunction (dry mouth, postural, hypotension..)
  - Associated with P/Q type voltage gated Ca channels antibodies.

F. 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 t seven years. Most myasthenia crises occur in this early period.
- More stable second phase, symptoms are stable but persist. They may want worsen in the setting of infection, medication taper, or other perturbations.
- Followed by 3rd phase, in which remission may occur.

G. Botulism :

- ✓ Presynaptic NMJ disorder.
- ✓ Caused by toxin produced by Clostridium Botulinum.
- ✓ Inhibits the release of Ach from the NMJ, sympathetic and parasympathetic ganglia.
- ✓ Food borne, infantile (ingestion of spores from honey with growth in the immature GI tract) or wound related.
- ✓ Ophthalmoparesis, bulbar weakness, limbs weakness.
- ✓ Loss of pupil reflexes, constipation, respiratory compromise.

H. Differential diagnosis for MG :

- Muscle disease
  - Thyroid ophthalmopathy
- Ocular pharyngeal muscular dystrophy (OPMD)
- Myotonic dystrophy
- Progressive external ophthalmoplegia
- NMJ disorder
- LEMS
- Botulism
- Congenital MG
- Penicillamine-Induced myasthenia
- Ti paralysis

Peripheral nerve

- Oculomotor cranial nerve pathology
- GBS, and CIDP
- Cavernous sinus pathology

Motor neuron disease

- ALS, PMA

NMJ disorder

- Stroke
- MS
- Tumors
- Infections

Other:

- Isolated ptosis
- Isolated dysconjugate gaze (decompensated strabismus)

Summery:

- The hallmark of NMJ disorders is fluctuating Fatigable weakness.
- MG is a post-synaptic disorder that affects all age group.
- MG crisis is a life threatening condition used by weakness that interferes with breathing.
- Certain over the counter medications can interfere with the NMJ function and induce a crisis spy was being careful when prescribing medications for MG patients.
- 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 generalized and 50% of ocular MG patientsm, MuSK antibodies in 5-8% of generalized MG.
- Decremental response to RNS and prolonged jitter or blocking on SFEMG are the neurophysiological hallmarks of MG.
- Monitoring of FVS is vital in patients with severe bulbar weakness.
- Myasthenia weakness is often exacerbated by infections and can lead to myasthenia crisis.
- Pyridostigmine, steroids and immunosuppressants are the mainstay of treatment.
- All patients with MG should be screened for thymoma.
- Thympectomy is often advised in mild to moderate AChR antibody positive

MCQs

1. A 50-year-old male has complained of slowly progressive weakness over several months. Walking has become more difficult, as has using his hands. There are no sensory, bowel, or bladder complaints. There are no problems in thinking, speech, or vision. Examination shows distal muscle weakness with muscle wasting and fasciculations.
There are also upper motor neuron signs, including extensor plantar reflexes and hyperreflexia in wasted-muscle groups. The most likely diagnosis is:

a. Polymyositis
b. Duchenne muscular dystrophy
c. Amyotrophic lateral sclerosis
d. Myasthenia gravis

2. The laboratory test most likely to be abnormal in this patient is:

a. Cerebrospinal fluid white blood cell count
b. Sensory conduction studies
c. CT scan brain
d. Electromyography

3. A 48-year-old auto mechanic presents to the clinic with complaints of many years of "pins and needles" in his left hand that initially occurred only while working but have worsened substantially. He claims the pain wakes him almost every night. Physical examination reveals marked weakness and wasting of the left hand muscles. Which of the following is the most likely diagnosis?

a. Amyotrophic lateral sclerosis
b. Angina
c. Carpal tunnel syndrome
d. Multiple sclerosis
e. Myasthenia gravis

answer : 1-C 2-D 3-C

1. The answer is c. The disease described involves motor neurons exclusively. Amyotrophic lateral sclerosis affects both upper and motor neurons. In this patient, there is upper and lower motor neuron involvement without sensory deficit. Peripheral neuropathy and dementia do not occur. Duchenne muscular dystrophy occurs at a younger age and involves proximal muscle weakness and not motor neurons. Polymyositis is also primarily a muscle disease. Myasthenia gravis would not cause hyperreflexia or Babinski reflex. It is a disease of muscle weakness characterized by fatigability.

2. The answer is d. EMG would show widespread denervation potentials. The other tests would be normal.

3. The answer is C. The mechanic has signs and symptoms of carpal tunnel syndrome, which is entrapment of the median nerve characterized by pain and paresthesia in the medial portion of the palm that may radiate proximally down the forearm. Carpal tunnel syndrome often presents as a work-related illness in persons whose jobs require prolonged use of the hand and wrist. If left uncorrected, carpal tunnel syndrome can lead to severe neuropathy and muscle wasting distal to the point of median nerve entrapment. Myasthenia gravis is an autoimmune disease caused by antibodies against the acetylcholine receptors of the postsynaptic cleft. It is most common in young women, although elderly men can be affected. It typically presents with double vision that is worse as the day progresses and/or difficulty swallowing and proximal muscle weakness. Unilateral muscle wasting is not characteristic of myasthenia gravis.

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