### NEUROMUSCULAR JUNCTION DISORDERS

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# OUTLINE:

>Anatomy and physiology of neuromuscular junction.

Classifications of NMJ disorders

>Myasthenia gravis.

>Lambert Eaton myasthenic syndrome.

>Other neuromuscular junction disorders (toxins).

### ANATOMICAL DESCRIPTION OF A NMJ

Neuromuscular junction consists of the axon terminal of a motor neuron and the motor end plate of a muscle fiber.

The Motor Neuron Part:

- The axon of a motor neuron enters the structure of skeletal muscle and forms many branches called axon terminals.

- There is a swelling called a synaptic end bulb at the end of each axon terminal.

- Each synaptic end bulb contains many synaptic vesicles each of which contains an important neurotransmitter called acetylcholine.

### ANATOMICAL DESCRIPTION OF A NMJ

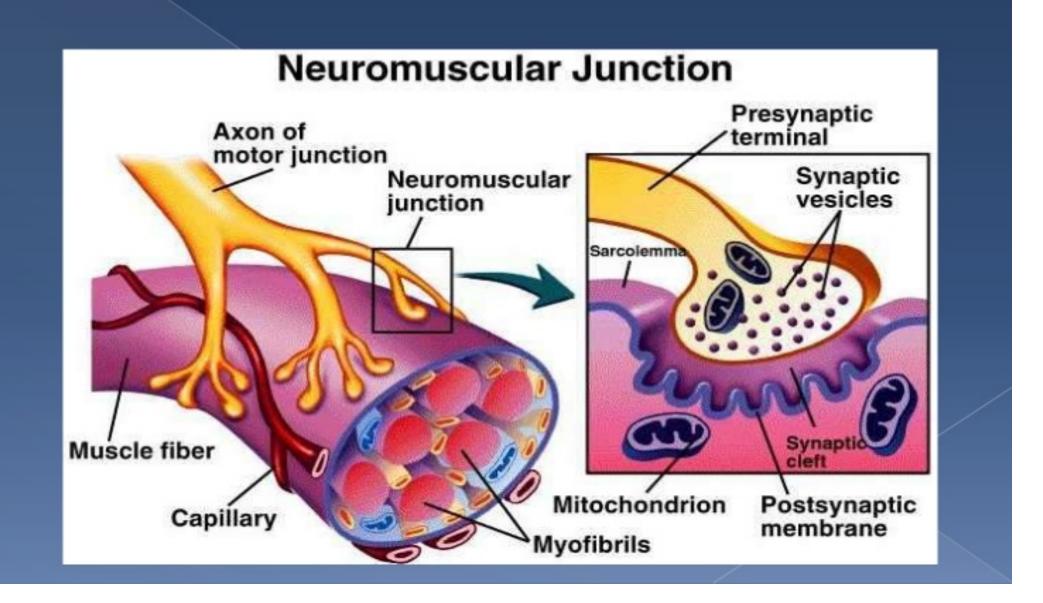
The Muscle Fiber Part:

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.

### ANATOMICAL DESCRIPTION OF A NMJ

<u>The Synapse or Neuromuscular Junction (NMJ)</u>:

The area between the axon terminal and the sarcolemma is called the 'synaptic cleft'.



### NEUROMUSCULAR JUNCTION PHYSIOLOGY

#### **Release of Ach:**

- When a nerve pulse reaches a synaptic end bulb, 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 the membrane into the muscle cell.

## NEUROMUSCULAR JUNCTION PHYSIOLOGY

#### **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.

## NEUROMUSCULAR JUNCTION PHYSIOLOGY

#### Breakdown of Ach:

The ACh that is released is only available to take part for a short time before it is broken down by an enzyeme called acetylcholinesterase (AChE). This breakdown of ACh occurs within the synaptic cleft. An action potential (orange arrow) arrives at the presynaptic terminal and causes voltage-gated Ca<sup>2+</sup> channels in the presynaptic membrane to open.

Calcium ions enter the presynaptic terminal and initiate the release of the neurotransmitter acetylcholine (ACh) from synaptic vesicles.

ACh is released into the synaptic cleft by exocytosis.

CACh diffuses across the synaptic cleft and binds to ligand-gated Na\* channels on the postsynaptic membrane.

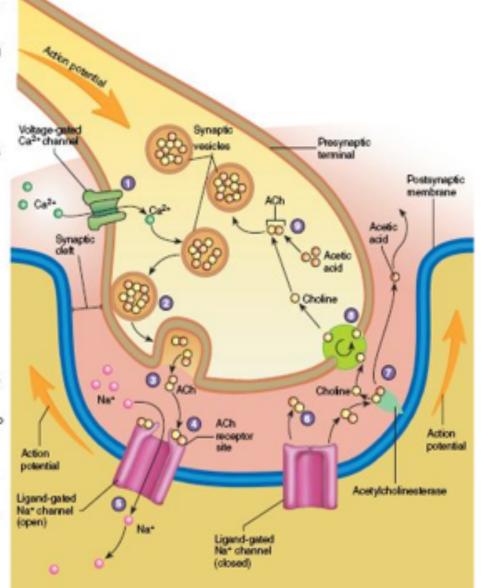
Ligand-gated Na\* channels open and Na\* enters the postsynaptic cell, causing the postsynaptic membrane to depolarize. If depolarization passes threshold, an action potential is generated along the postsynaptic membrane.

ACh unbinds from the ligand-gated Na\* channels, which then close.

The enzyme acetylcholinesterase, which is attached to the postsynaptic membrane, removes acetylcholine from the synaptic cleft by breaking it down into acetic acid and choline.

Choline is symported with Na\* into the presynaptic terminal, where it can be recycled to make ACh. Acetic acid diffuses away from the synaptic cleft.

ACh is reformed within the presynaptic terminal using acetic acid generated from metabolism and from choline recycled from the synaptic cleft. ACh is then taken up by synaptic vesicles.



### CLASSIFICATION OF NMJ DISORDERS

#### According to the mechanism of action or etiology:

> Immune-mediated disease.

> Toxic/metabolic.

> Congenital syndromes.

#### Immune-mediated:

Myasthenia gravis, and Lambert-Eaton syndrome

#### Toxic/metabolic:

Include snake venom poisoning, botulism, arthropod poisoning, organophosphates and hypermagnesemia

#### **Congenital:**

Congenital myasthenic syndromes

#### According to the location of their disruption:

- > ThePresynaptic membrane of the motor neuron.
- > Synapse.
- > Postsynaptic membrane (the muscle fiber).

#### **Presynaptic**

- Different mechanisms.
- Most often this causes a decrease in the release of acetylcholine.
- 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: autoimmune neuromyotonia, Lambert-Eaton syndrome, congenital myasthenia gravis and botulism

#### **Postsynaptic**

- The highest number of diseases affect the neuromuscular junction postsynaptically.
- Immune mediated Myasthenia Gravis is the most common.
- All the diseases that affect the postsynaptic membrane are forms of myasthenia gravis. Examples includes: Neonatal Myasthenia Gravis, Drug Induced Myasthenia Gravis and several types of Congenital myasthenia.

### MYASTHENIA GRAVIS

 $\geq$  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, bulbar, limb, and respiratory muscles.

# **MYASTHENIA GRAVIS**

There are two clinical forms of myasthenia gravis: ocular and generalized.

•Ocular myasthenia: the weakness is limited to the eyelids and extraocular muscles.

•Generalized disease, the weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.

## **MYASTHENIA GRAVIS**

#### **EPIDEMIOLOGY** :

> Myasthenia gravis is a relatively uncommon disorder with an annual incidence of approximately 7 to 23 new cases per million.

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)

-Late peak in the sixth to eighth decade (male predominance).

> 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).

>In MG, there is reduction of postsynaptic AChRs due to production of anti-AChR antibodies that block receptors and causes damage the postsynaptic membrane.

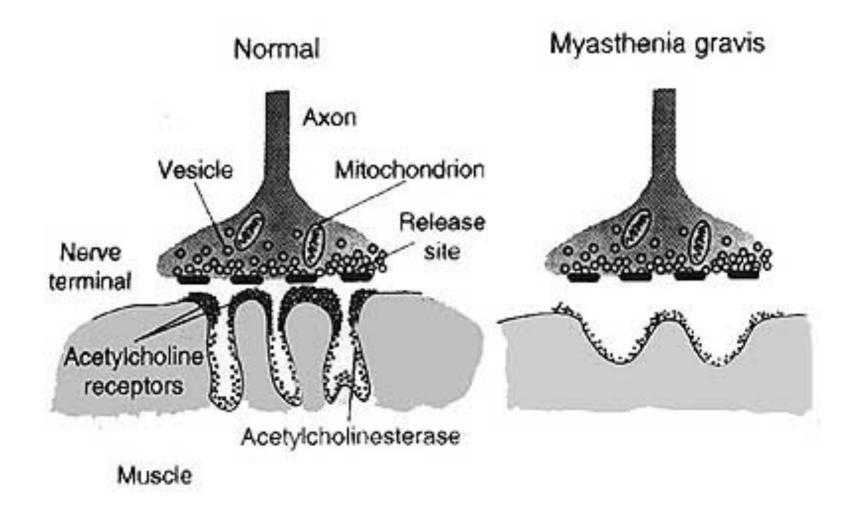
Reduction in the number of AChRs available at the muscle endplate and flattening of the postsynaptic folds.

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.

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



> >50% of patients present with ocular symptoms of ptosis and/or diplopia.

> Of those who present with ocular manifestations, about half will develop generalized disease within two years.

>15% of patients present with bulbar symptoms. These include dysarthria, dysphagia, and fatigable chewing.

> <5% present with proximal limb weakness alone.

#### Ocular muscles:

- Weakness of the eyelid muscles can lead to ptosis (flactuating).
- The ptosis may start bilaterally and improve in one eye, resulting in unilateral ptosis or alternate.
- Variable severity
- Extraocular muscles involvement( binocular diplopia). It may be horizontal or vertical.

#### **Bulbar muscles**

- Muscles of jaw closure (fatigable chewing).
- Oropharyngeal muscle weakness produces dysarthria and dysphagia.
- Palatal muscles weakness causing nasal speech and nasal regurgitation

#### **Facial muscles**

- Frequently involved and causing expressionless face.
- Transverse smile may be evident on examination "myasthenic sneer," where the midlip rises but the outer corners of the mouth fail to move.
- Orbicularis oculi weakness.



#### Neck and limb muscles :

- Neck extensor and flexor muscles are commonly affected.
- Dropped head syndrome.
- Proximal limb weakness (the arms > the legs).
- Wrist and finger extensors and foot dorsiflexors.

#### <u>Respiratory muscles :</u>

Respiratory muscle weakness can leads to respiratory insufficiency and pending respiratory failure "myasthenic crisis."

It may occur spontaneously during an active phase of the disease or may be precipitated by a variety of factors including surgery, infections, certain medications, or tapering of immunotherapy.

#### **BEDSIDE TESTS:**

Ice pack test:

It can be used in patients with ptosis.

A bag (or surgical glove) is filled with ice and placed on the closed lid for two minutes. The ice is then removed and the extent of ptosis is immediately assessed.

The sensitivity appears to be about 80%.



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

eye after ice pack application

#### Edrophonium(Tensilon) test:

 $\geq$  Is is an acetylcholinesterase inhibitor with rapid onset (30 to 45 seconds) and short duration of action (5 to 10 minutes).

 $\geq$  It prolongs the presence of acetylcholine in the neuromuscular junction and results in an immediate increase in muscle strength in many of the affected muscles.

> Used in patients with obvious ptosis or ophthalmoparesis, in whom improvement after infusion of the drug can easily be observed.

#### Serological testing:

Acetylcholine receptor binding antibodies found in 80-90% with generalized disease and in 40-55% with ocular myasthenia

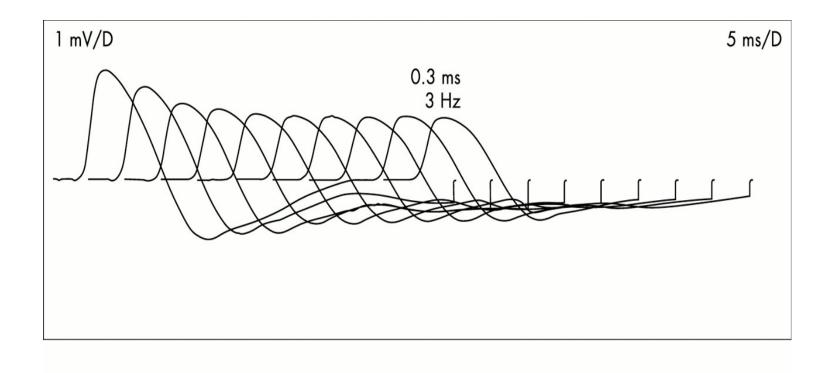
> MuSK antibodies are present in 38-50% of those with generalized myasthenia gravis who are AChR-Ab negative

#### **ELECTROPHYSIOLOGIC CONFIRMATION**

#### Repetitive nerve stimulation:

- The nerve is electrically stimulated 6 to 10 times at low rates (2 or 3 Hertz).
- In normal muscles, there is no change in CMAP amplitude with repetitive nerve stimulation.

In myasthenia there may be a progressive decline in the CMAP amplitude with the first four to five stimuli



#### Single fiber electromyography:

It is positive in greater than 90% of those with generalized myasthenia.

# DIAGNOSIS OF MG

#### CT Mediastinum:

In AChR antibody positive myasthenia gravis,>75% of patients have thymic abnormalities.

- > Thymic hyperplasia is most common 85%.
- $\geq$  Thymic tumors (primarily thymoma) in up to 15%.

### DIAGNOSIS OF MG

#### Autoimmune disorders:

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

#### TREATMENT OF MG

> Symptomatic treatments (anticholinesterase agents)

> Chronic immunotherapies (glucocorticoids/immunosuppressive drugs).

> Rapid immunotherapies (plasma exchange and intravenous immune globulin [IVIG]).



# LAMBERT EATON SYNDROME

> It is a rare presynaptic disorder of neuromuscular transmission in which quantal release of acetylcholine (ACh) is impaired.

# PATHOPHYSIOLOGY OF LEMS

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.

 $\geq$  The number of quanta released by a nerve impulse is diminished.

# PATHOPHYSIOLOGY OF LEMS

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.

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

>Parasympathetic, sympathetic, and enteric neurons are all affected

# ETIOLOGY OF LEMS

#### Autoimmune:

Antibodies directed against the voltage-gated calcium channel (VGCC).

These antibodies interfere with the normal calcium flux required for the release of acetylcholine.

#### 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.

# EPIDEMIOLOGY OF LEMS

> 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).

# CLINICAL MANIFESTATION OF LEMS:

- Most patients with LEMS present with slowly progressive proximal muscle weakness, particularly involving the legs.
- Deep tendon reflexes are typically depressed or absent
- Autonomic symptoms including dry mouth and erectile dysfunction
- Ocular symptoms, especially ptosis and diplopia, may occur with LEMS but are rarely the presenting or dominant feature of the illness.

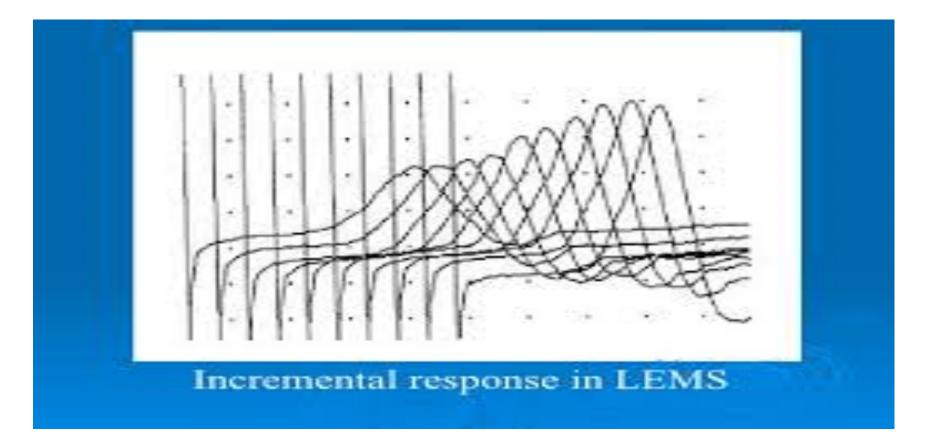
# CLINICAL MANIFESTATION OF LEMS

Most patients do not have significant respiratory muscle weakness

Recovery of lost deep tendon reflexes or improvement in muscle strength with vigorous, brief muscle activation is a unique aspect of LEMS

# **DIAGNOSIS OF LEMS :**

- The diagnosis of LEMS is usually clinical and confirmed by the presence of antibodies to voltage-gated calcium channel (VGCC) and by electrodiagnostic studies
- Antibodies against the P/Q-type VGCC are present in approximately 85-95% of patients with LEMS
- High frequency (10 to 50 Hz) repetitive nerve stimulation (RNS) or brief (10 seconds) maximal isometric muscle activation result in significant increment with a marked increase in the CMAP amplitude



# TREATMENT OF LEMS:

Search for and treat a primary underlying malignancy in patients with any risk factors for small cell lung cancer.

- Symptomatic therapies for LEMS include medications that increase the amount of acetylcholine available at the postsynaptic membrane.
- These are guanidine, aminopyridines such as 3,4-diaminopyridine (3,4-DAP), and acetylcholinesterase inhibitors such as pyridostigmine

# TREATMENT OF LEMS:

Immunologic therapies include intravenous immune globulin (IVIG), oral immunosuppressive agents.

#### **OTHER NEUROMUSCULAR JUNCTION DISORDERS**

# BOTULISM

It is an uncommon and life-threatening disease caused by bacteria in the Clostridium family including C. botulinum, C barati and C butyricum

> They are all gram-positive, anaerobic, spore-forming rods, which have evolved to produce a potent neurotoxin

# BOTULISM

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 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

# BOTULISM

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, and 3% are wound botulism.

# CLINICAL MANIFESTATION OF BOTULISM:

> Acute onset of bilateral cranial neuropathies associated with symmetric descending weakness.

> Key features of the botulism syndrome (US CDC):

•Absence of fever

- •Symmetric neurologic deficits
- •The patient remains responsive
- •Normal or slow heart rate and normal blood pressure
- •No sensory deficits

# **DIAGNOSIS OF BOTULISM:**

- 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 OF BOTULISM:

> Suspected cases should be hospitalized immediately and monitored for signs of respiratory failure.

 $\geq$  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

# TICK PARALYSIS:

> Several tick species produce a toxin that inhibits transmission at the neuromuscular junction by blocking influx of sodium ions.

 $\succ$  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).

# TICK PARALYSIS:

> 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.

 $\geq$  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

# SNAKE VENOM

The postsynaptic-acting toxins bind irreversibly to the acetylcholine receptor site, and prevent the opening of the associated sodium channel (an example is alphabungarotoxin).

# SNAKE VENOM

#### **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

# SNAKE VENOM

#### 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.

### **ORGANOPHOSPHATE AND CARBAMATE TOXICITY**

> 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 MANIFESTATION:**

> 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

# **DIAGNOSIS AND MANAGEMENT**

> The diagnosis is made clinically by the presence of clinical features of cholinergic excess.

> Emergency 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.

 $\succ$  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

# Thank you