NEUROMUSCULAR JUNCTION

Myasthenia gravis

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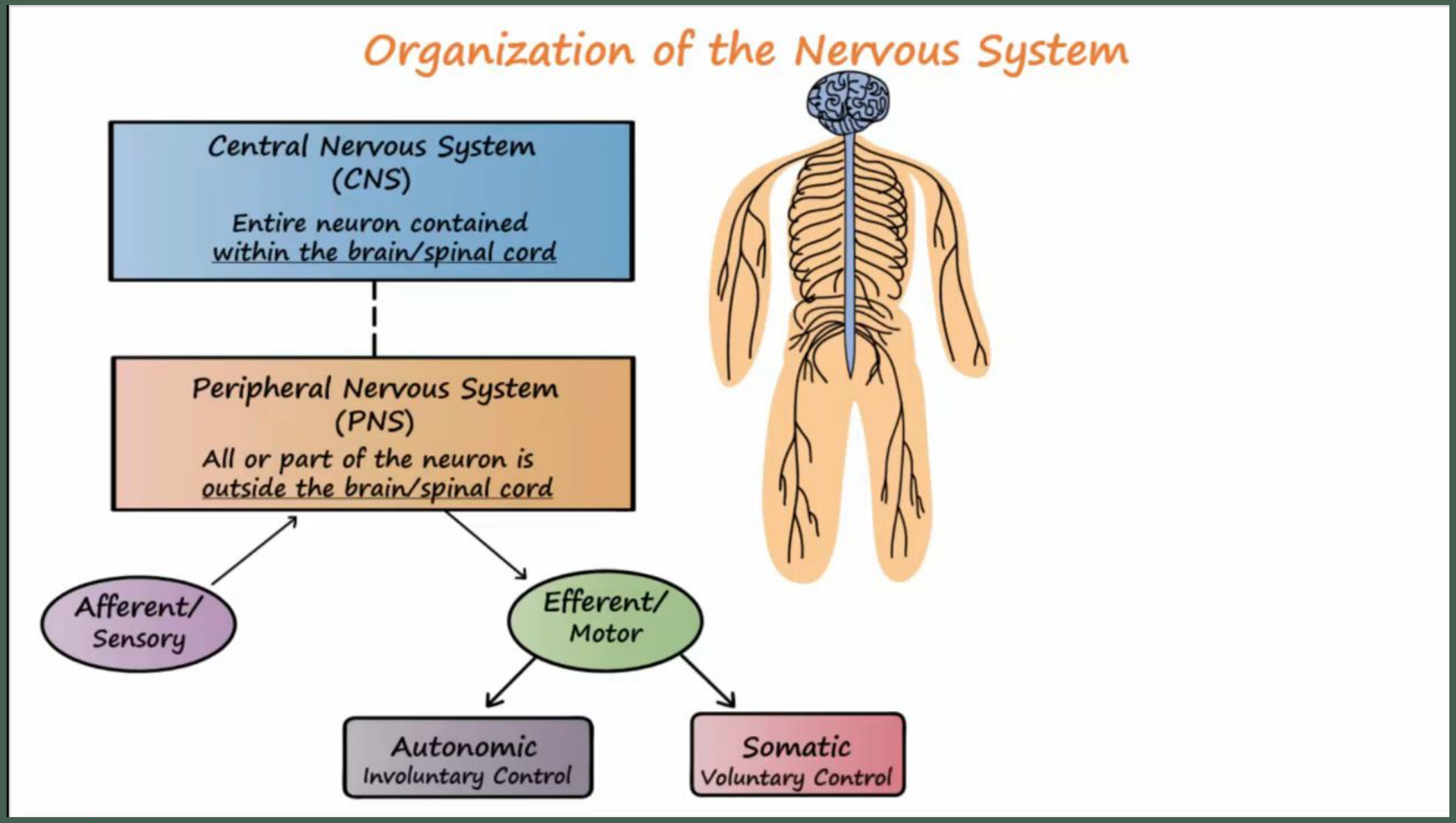
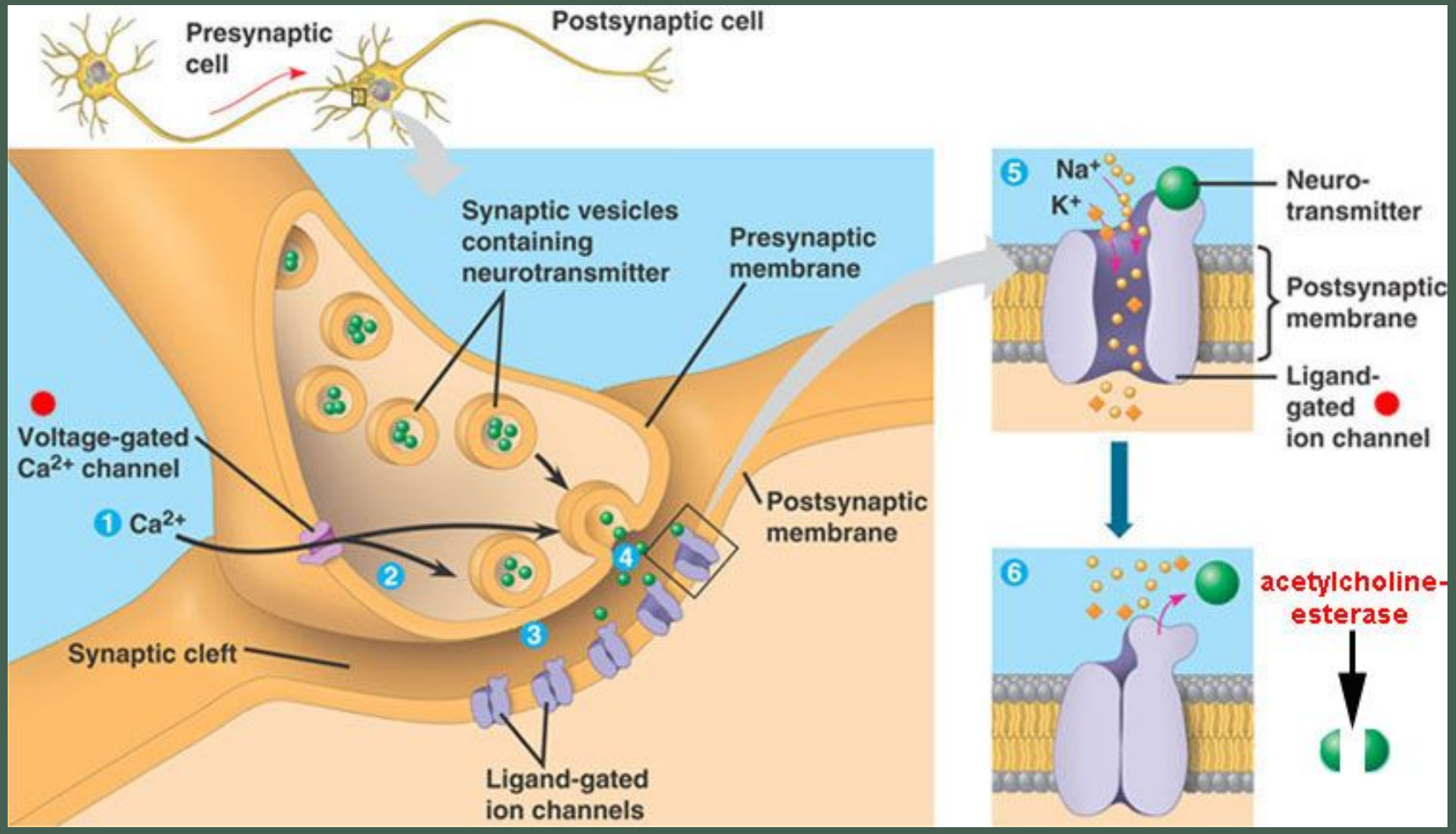


ACETYLCHOLINE (ACH)

NEUROMUSCULAR JUNCTION



MYASTHENIA GRAVIS

- Is an chronic autoimmune disorder which results from antibodies that block or destroy acetylcholine receptors (AChR) at neuromuscular junction and characterized by voluntary muscle weakness which worsen on activity (fatigability).

- Fatigability is progressive inability to sustain a maintained or repeated contraction of voluntary muscle.

EPIDEMIOLOGY

- Myasthenia gravis is uncommon. Estimated annual incidence is 2 per 1,000,000.
- It affect people of any age
- Female incidence peaks in the third decade of life, whereas male incidence peaks in the sixth or seventh decade.
- Mean age of onset is 28 years in females and 42 years in males
- The female-to-male ratio is said classically to be 3:2

PATHOPHYSIOLOGY

The decrease in the number of postsynaptic AChRs is believed to be due to an autoimmune process whereby anti-AChR antibodies are produced and block the AChR. It causes an increase in the turnover of the AChR, and damage of the postsynaptic membrane in a complement-mediated manner.

The exact mechanism of loss of immunologic tolerance to AChR, a self-antigen, is not understood.

MG can be considered a B cell–mediated disease. However, the importance of T cells in the pathogenesis of MG is becoming increasingly apparent. The role of the thymus in the pathogenesis of MG is not entirely clear, but 75% of patients with MG have thymus abnormality (hyperplasia or thymoma).

PATHOPHYSIOLOGY

- Anti-AChR antibody is found in approximately 80-90% of patients with myasthenia gravis.
- Patients without anti-AChR antibodies are recognized as seronegative myasthenia gravis (SNMG). Many patients with SNMG have antibodies against muscle-specific kinase (MuSK).
- The patients with anti-MuSK antibodies are predominantly female at third or fourth decades Where respiratory and bulbar muscles are frequently involved.

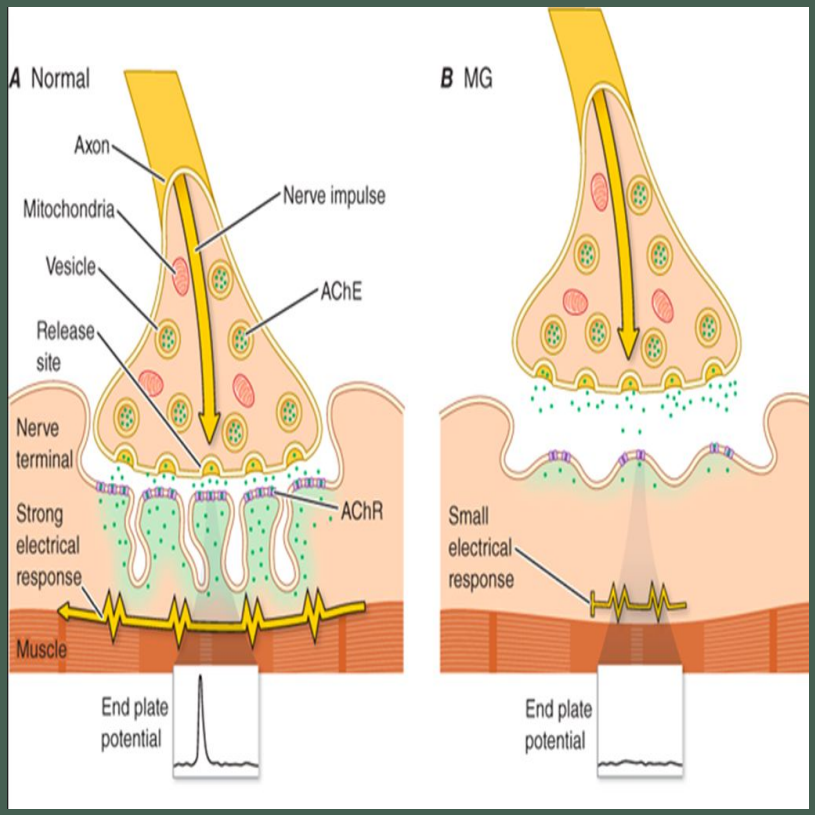
PATHOPHYSIOLOGY

Binding of AChR antibodies to AChR results in impairment of neuromuscular transmission in several ways

- accelerating degradation of AChR molecules decreasing the number of AChRs at the NMJ
- blocking the binding of ACh to AChR
- In MG, the post-synaptic folds is become flattened or simplified by the complement-mediated destruction of junctional folds of the postsynaptic membrane, with resultant decrease in available surface area for insertion of newly synthesized AChRs.

PATHOPHYSIOLOGY

- The endplate potentials will fall below the threshold value for generation of an action potential result of inefficient neuromuscular transmission. When this failure occurs at enough muscle fibers, it can manifest clinically and electrophysiologically
- Patients become symptomatic once the number of AChRs is reduced to approximately 30% of normal.



PATHOPHYSIOLOGY

- The thymus is the central organ in T cell–mediated immunity, and thymic abnormalities such as thymic hyperplasia or thymoma are well recognized in myasthenic patients.
- About 65% of people who have myasthenia gravis have an enlarged thymus gland, and about 15% have thymoma. About half of thymomas are malignant.

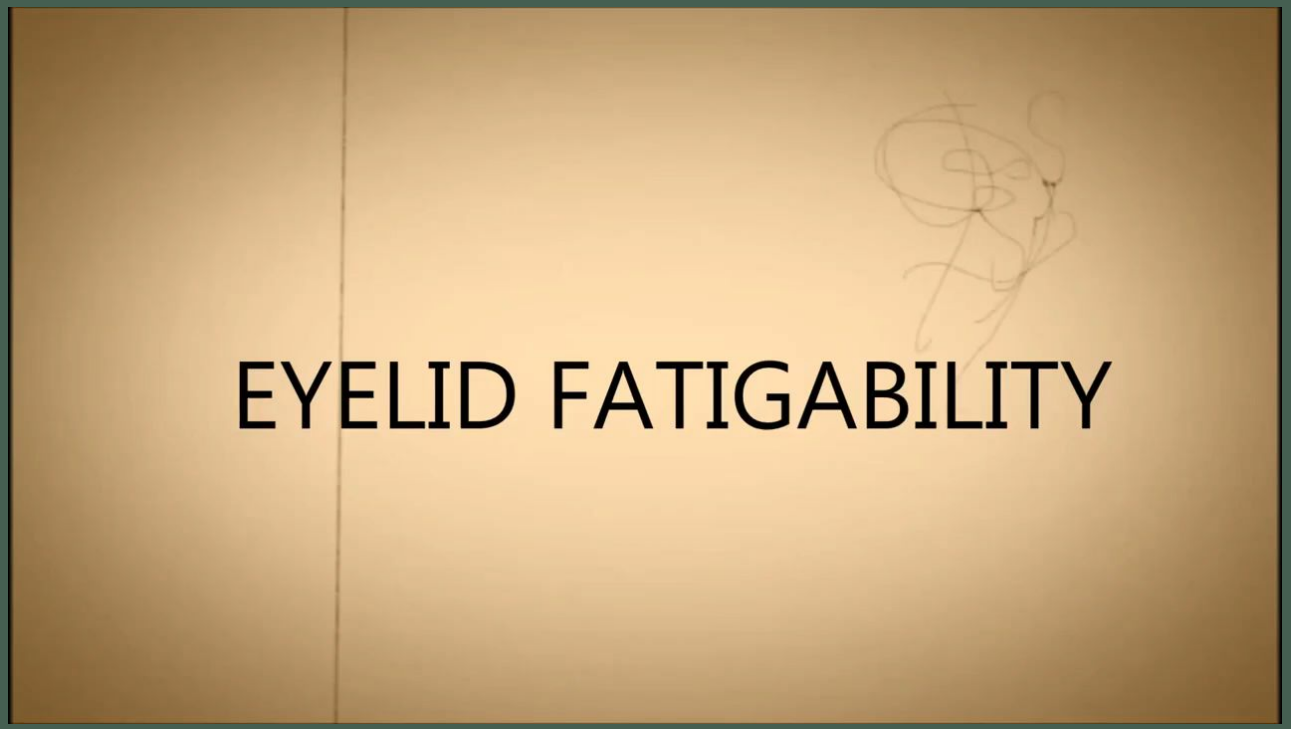
PATHOPHYSIOLOGY

Immunogenic mechanisms play important roles

- presence of associated autoimmune disorders (autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis).
- Infants born to myasthenic mothers can develop a transient myasthenia-like syndrome.
- Patients with myasthenia gravis will have a therapeutic response to various immunomodulating therapies, immunosuppressants and thymectomy.

SIGNS AND SYMPTOMS

CLINICAL FEATURES



Myasthenia gravis is characterized by fluctuating weakness increased by exertion

Weakness increases during the day and improves by rest.

WEAKNESS

Extraocular muscle

- Diplopia or ptosis is present initially in 50% of patients and occurs during the course of illness in 90%. Typically
  - asymmetric
  - is not limited to muscles innervated by a single cranial nerve
- Rarely, patients with severe, generalized weakness may not have associated ocular muscle weakness.
- The disease remains ocular in only 16% of patients..

WEAKNESS

- Limb musculature weakness is usually proximal and symmetric.
- About 87% of patients generalize within 13 months after onset
- Bulbar muscle weakness is also common, along with weakness of head extension and flexion.
- Facial weakness of the muscles is almost always present. Bilateral facial muscle weakness produces a mask-like face with ptosis and a horizontal smile.

WEAKNESS

Respiratory muscle weakness

- Such weakness may produce acute respiratory failure. This is a true neuromuscular emergency, and immediate intubation may be necessary.
- Weak pharyngeal muscles may collapse the upper airway. Careful monitoring of respiratory status is necessary in the acute phase of myasthenia gravis.
- MG weakness progress from mild to more severe disease over weeks to months. Weakness tends to spread from the ocular to facial to bulbar muscles and then to trunk and limb muscles.
- Intercurrent illness or medication can exacerbate weakness, quickly precipitating a myasthenic crisis (respiratory failure).
- Sensory examination and deep tendon reflexes are normal.

DRUGS EXACERBATE MG

- Antibiotics (eg, aminoglycosides, ciprofloxacin, erythromycin, ampicillin(
- Beta-adrenergic receptor blocking agents (eg, propranolol, oxprenolol)
- Lithium , Magnesium , Procainamide , Verapamil , Quinidine
- Chloroquine
- Prednisone
- Anticholinergics (eg, trihexyphenidyl)
- Timolol (ie, a topical beta-blocking agent used for glaucoma)

INVESTIGATIONS

- Anti-acetylcholine receptor antibody

  This test is reliable for diagnosing autoimmune MG. The result of the test for the anti-AChR antibody (Ab) is positive in 74% of patients.

- Anti-MuSK antibody

positive in half of the patients who are seronegative MG

- Antistriated muscle (anti-SM) Ab

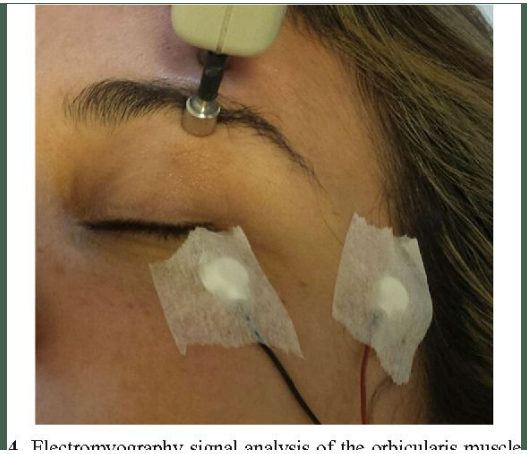
It is present in about 84% of patients with thymoma who are younger than 40 years

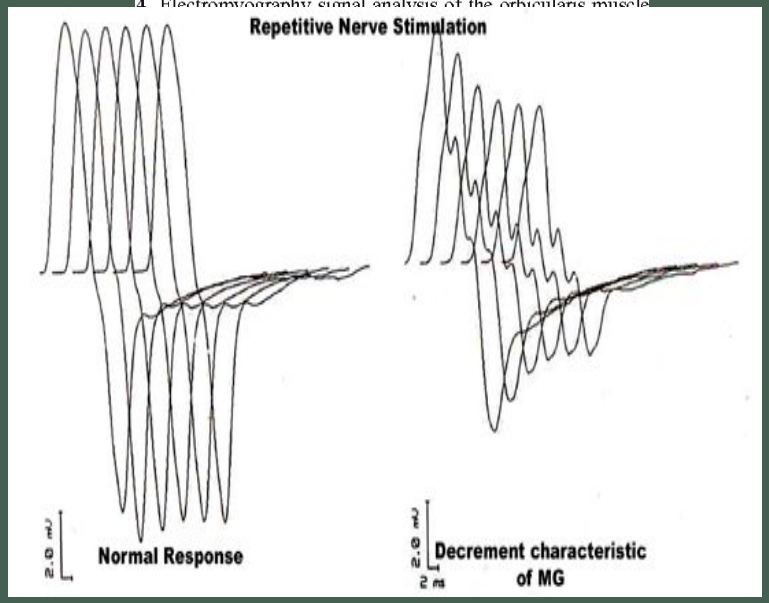
ELECTRODIAGNOSTIC STUDIES

- Single-fiber electromyography

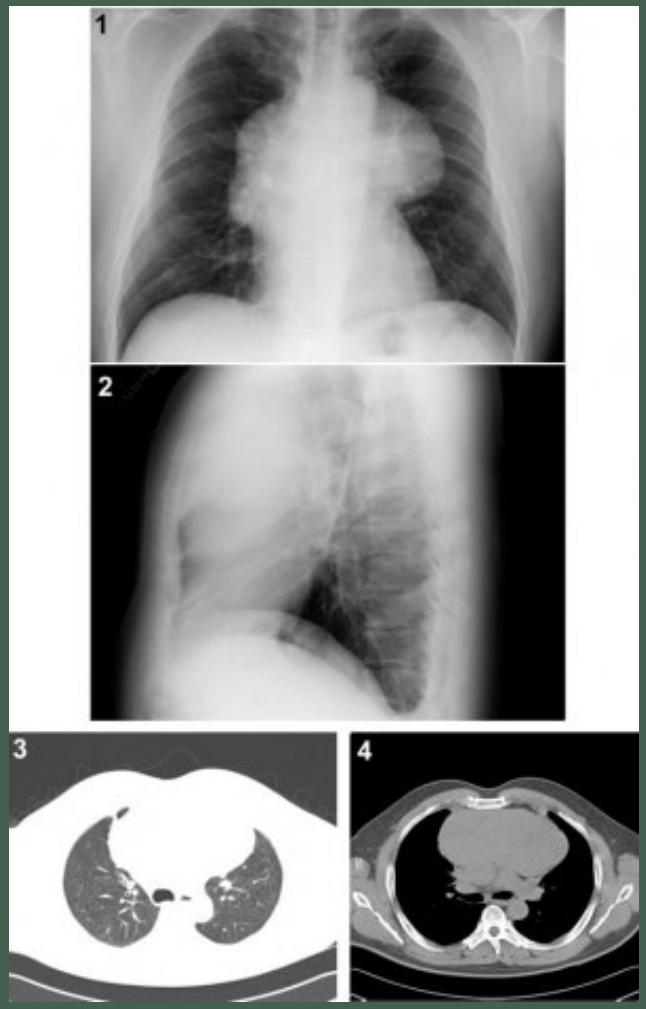
In generalized MG, the extensor digiti communis (EDC) are abnormal in 87% of patients

- Repetitive nerve stimulation (decrement over 10% is considered abnormal) abnormal in only 44-65%.





IMAGING STUDIES



Lymphofollicular hyperplasia of thymic medulla occurs in 65% of MG patients; thymoma, in 15%.

INVESTIGATIONS

edrophonium or

Tensilon test

TREATMENT

AChE inhibitors

The duration of action of acetylcholine is prolonged by inhibiting acetylcholinesterase will maximise the activity of acetylcholine at remaining receptors in the neuromuscular junctions.

- Pyridostigmine bromide (Mestinon)
- Neostigmine (Prostigmin)

Cholinergic crisis may caused by Over dose (muscle fasciculation, paralysis, pallor, sweating, excessive salivation and small pupils).

TREATMENT

Immunomodulating therapies

Medical

Long-term treatments (necessary to continue treatment for months or years)

- Prednisone
- Azathioprine 2.5 mg/kg daily reduces the necessary dosage of glucocorticoids and may allow their withdrawal. Effect on clinical features may be delayed for months •,
- Cyclosporine , Cyclophosphamide, Mycophenolate mofetil: less commonly used

short-term management of an exacerbation and in preparation for surgery

- *Intravenous Immune globulin*
- *Plasmapheresis*

Thymectomy

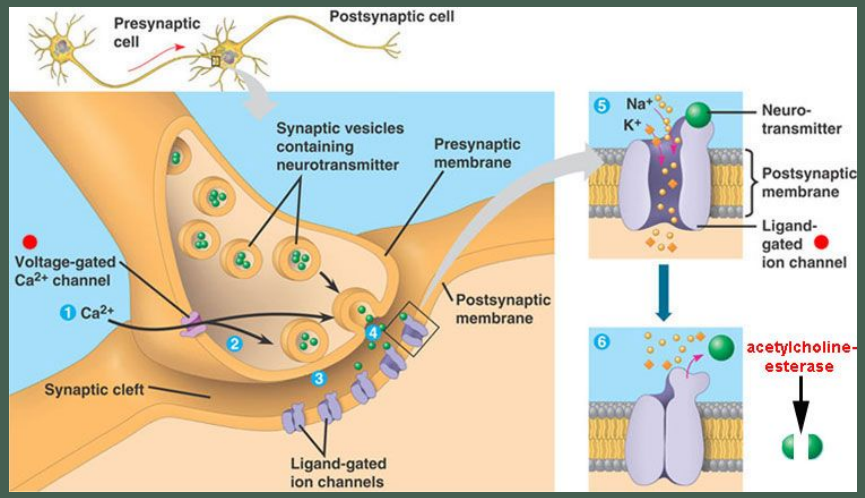
is the first-line therapy in most patients with generalized myasthenia under 45 years & thymoma

PROGNOSIS

- Untreated MG carries a mortality rate of 25-31%. With current treatment the mortality rate has declined to approximately 4%.
- In patients with only ocular involvement at onset, only 16% remain ocular exclusively at the end of 2 years.

LAMBERT-EATON MYASTHENIC SYNDROME

The syndrome is due to an abnormality of the release of acetycholine often in association with antibodies to pre-junctional voltage – gated calcium channels.



LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome is a neuromuscular disorder which causes

- progressive proximal and symmetric weakness of the upper & lower limbs which can return immediately after sustained contraction of same muscle
- absence of deep tendon reflexes
- Dry mouth, eyes, or skin (Autonomic dysfunction)
- Eyelid drooping or double vision (25%)
- Individuals who develop the syndrome at an older age have a greater risk of cancer especially small cell lung cancer.
- A tumor may cause fatigue and weight loss.

DIAGNOSIS & TREATMENT

- Repetitive nerve stimulation show post-tetanic potentiation of motor response at frequency of 20 – 50.
- All individuals with Lambert-Eaton should be screened for cancer, particularly those people who are long-term smokers.
- If tumor is present, treatment should focus on cancer therapy.
- In individuals with the syndrome but without cancer, immunosuppressive drugs such as prednisone and azathioprine can be used to reduce the autoimmune response and lessen symptoms.