Myasthenia Gravis

dr. Ken Wirastuti,MKes,Sp.S, KIC
Bagian Ilmu Penyakit Saraf
FK. UNISSULA

DEFINISI

- MG is a chronic, neuromuscular junction disorder, autoimmune disease that involves a decrease in the number and effectiveness of acetylcholine (Ach) receptors at the neuromuscular junction.
- Affects the voluntary muscles of the body, especially the eyes, mouth, throat, and limbs
- Characterized by remissions & relapse/ exacerbation's.

PREVALENCE OF MYASTHENIA GRAVIS

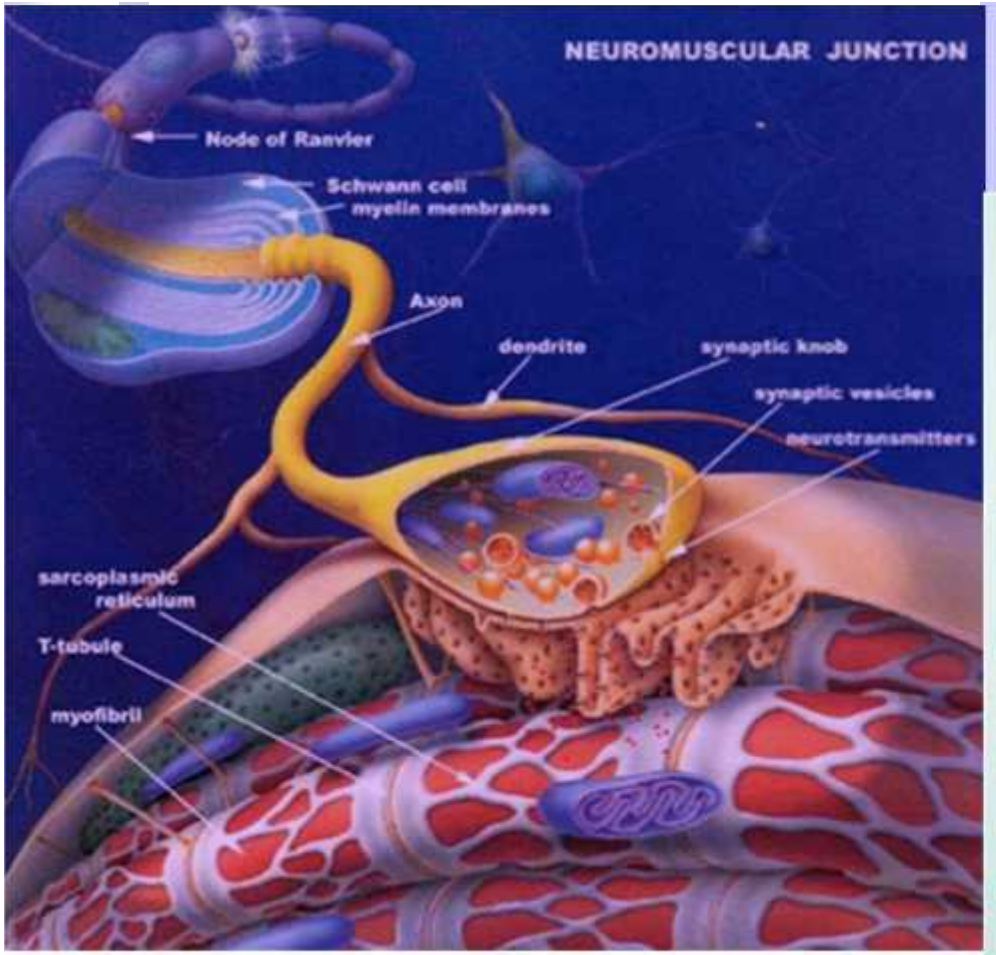
- It affects individuals in all age groups from neonatal to above 60 and more common in women younger than 40 and in men older than 60
- Peaks of incidence occur in women in their twenties and thirties and in men in their fifties and sixties.
- Women are affected more frequently than men, in ratio of approximately 3:2

Pathogenesis

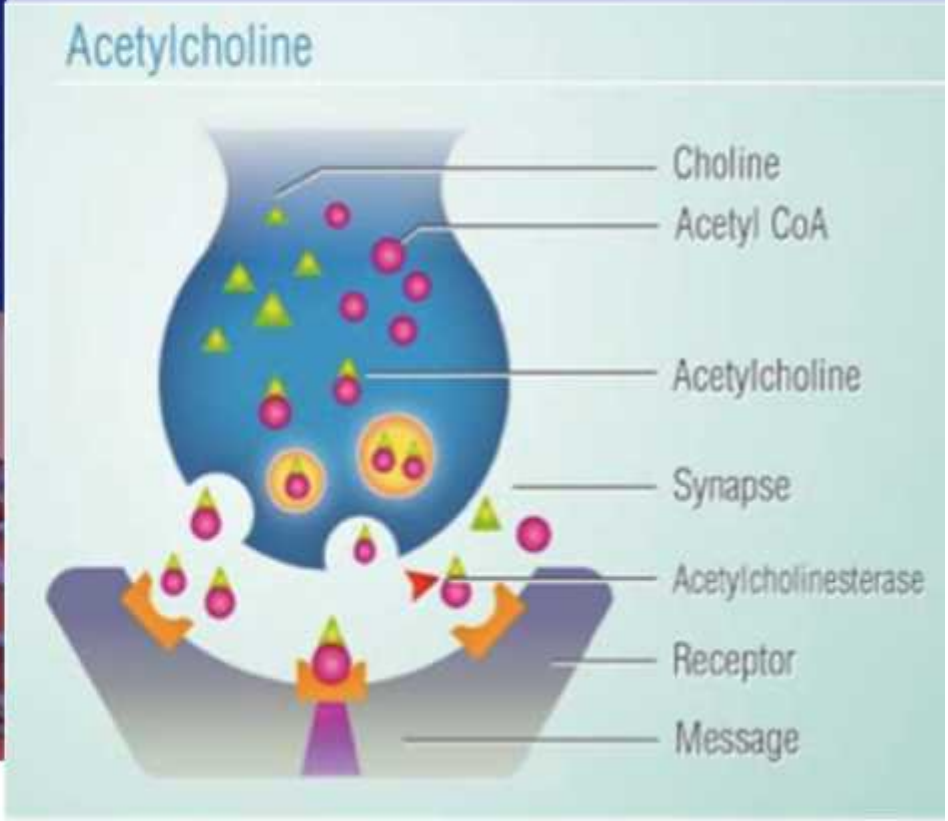
- It is due to an autoimmune process in which antibodies against acetylcholine receptors cause a disordered conduction in myoneural junction.

Pathology

- Characteristic clusters of lymphocytes in between the muscle fibres.
- Thymus gland : may show hyperplasia or a thymic tumor (thymoma) .



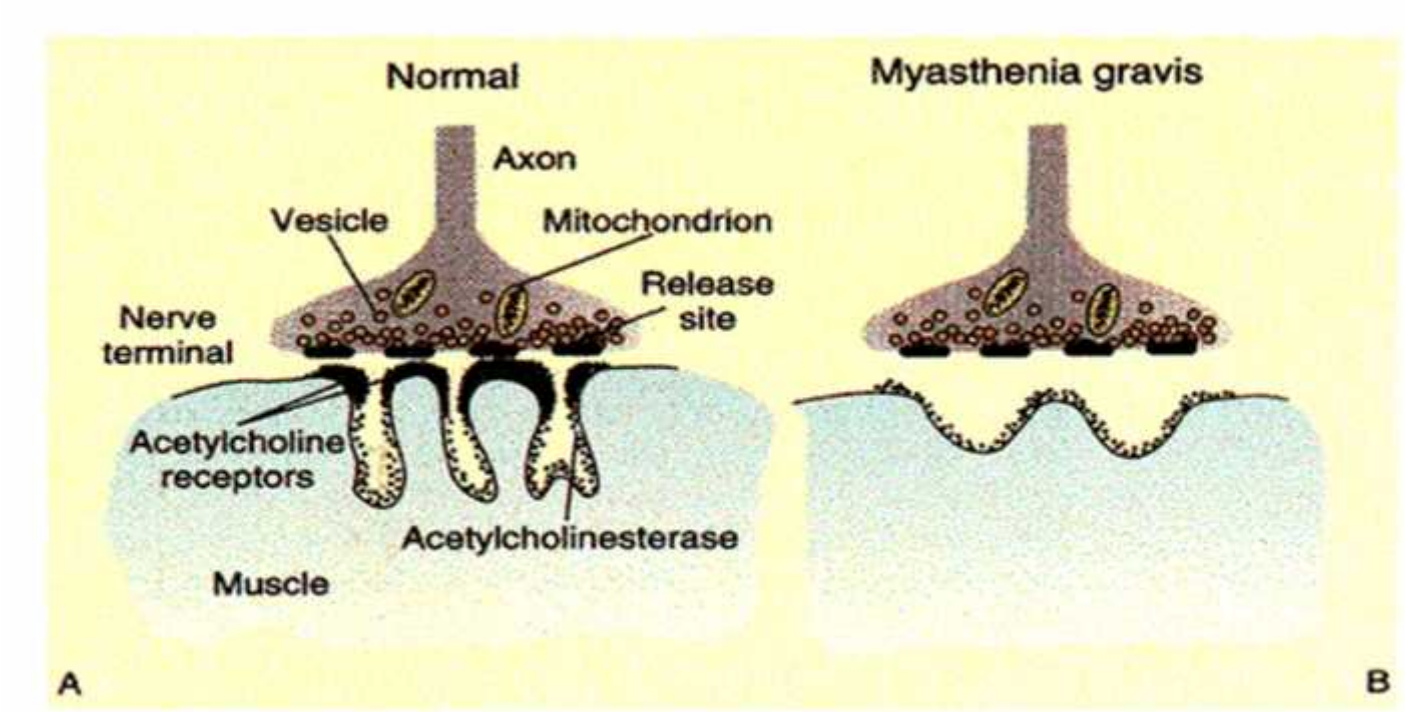
Neuromuscular junction



Acetyl-CoA + choline —(acetylcholine transferase)→ acetylcholine (ACh)

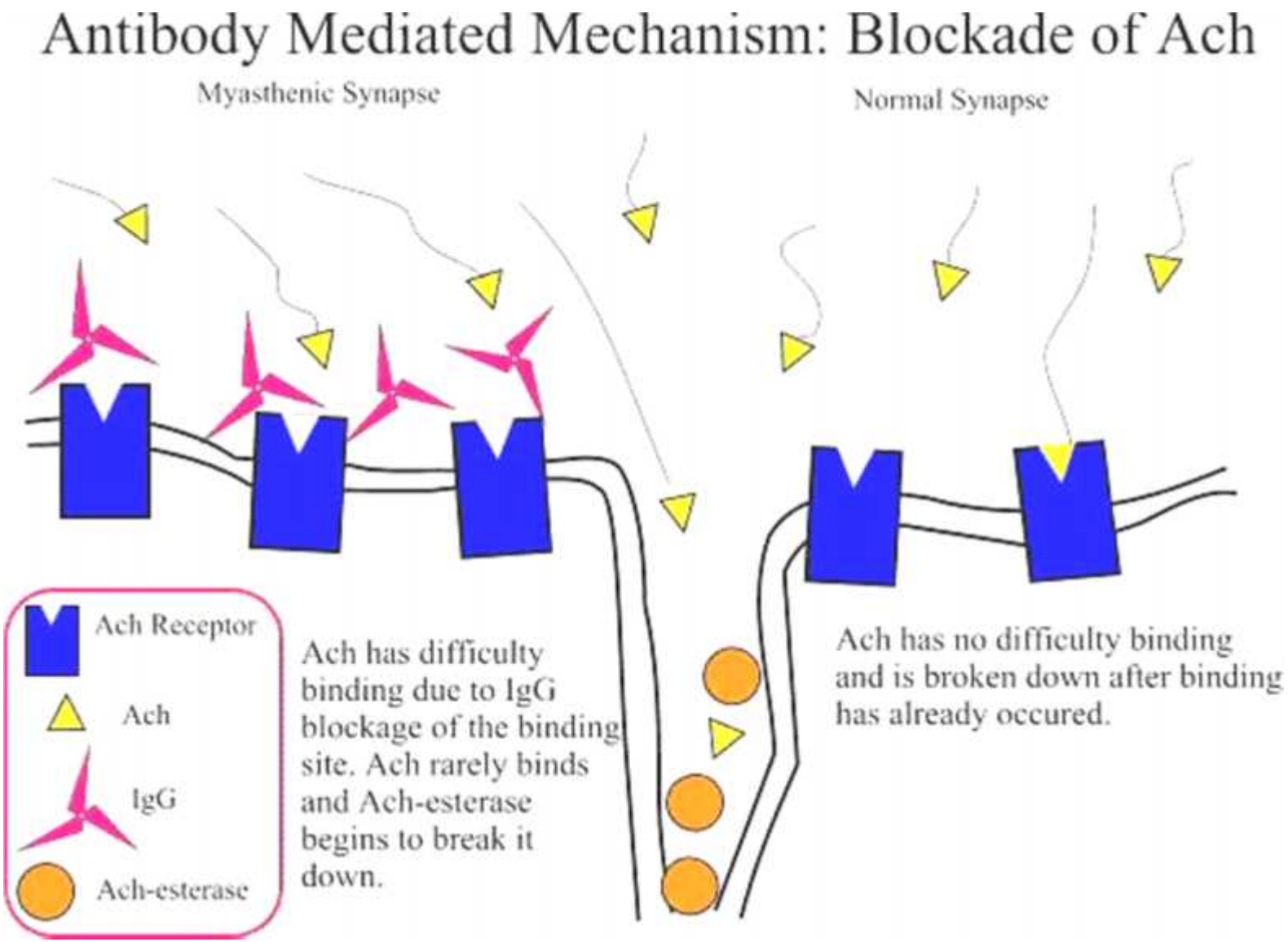
acetylcholine (ACh) —(acetylcholine esterase)→ acetate and choline

PATHOGENESIS



In MG, antibodies are directed toward the acetylcholine receptor at the neuromuscular junction of skeletal muscles

- Results in:
  - Decreased number of nicotinic acetylcholine receptors at the motor end-plate
  - Reduced postsynaptic membrane folds
  - Widened synaptic cleft



Blockade of Ach binding site (Cornelio, 2002)

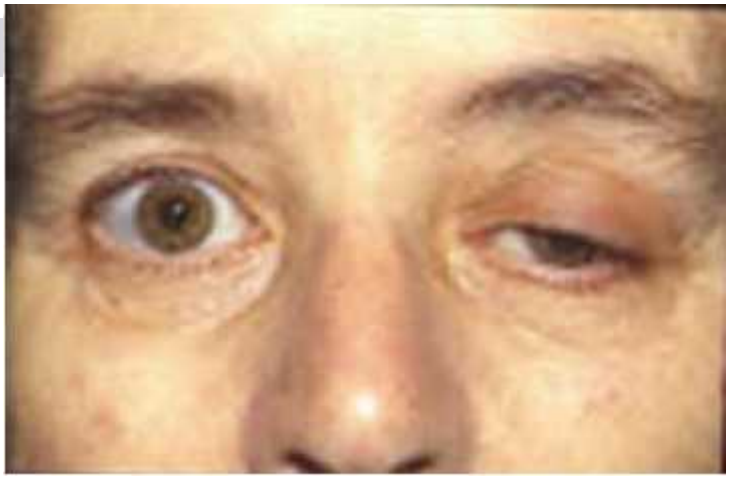
Clinical features

It has a characteristic descending march course,

- Ocular (ptosis, diplopia) *45-50%*
- Bulbar (dysarthria, dysphagia) *20%*
- Extremity weakness (usually proximal) *30-35%*
- Distal extremity *rare*
- Respiratory *rare*

- Insidious onset
- Often fluctuation
- Progression
  - Craniocaudal direction

Eye muscles



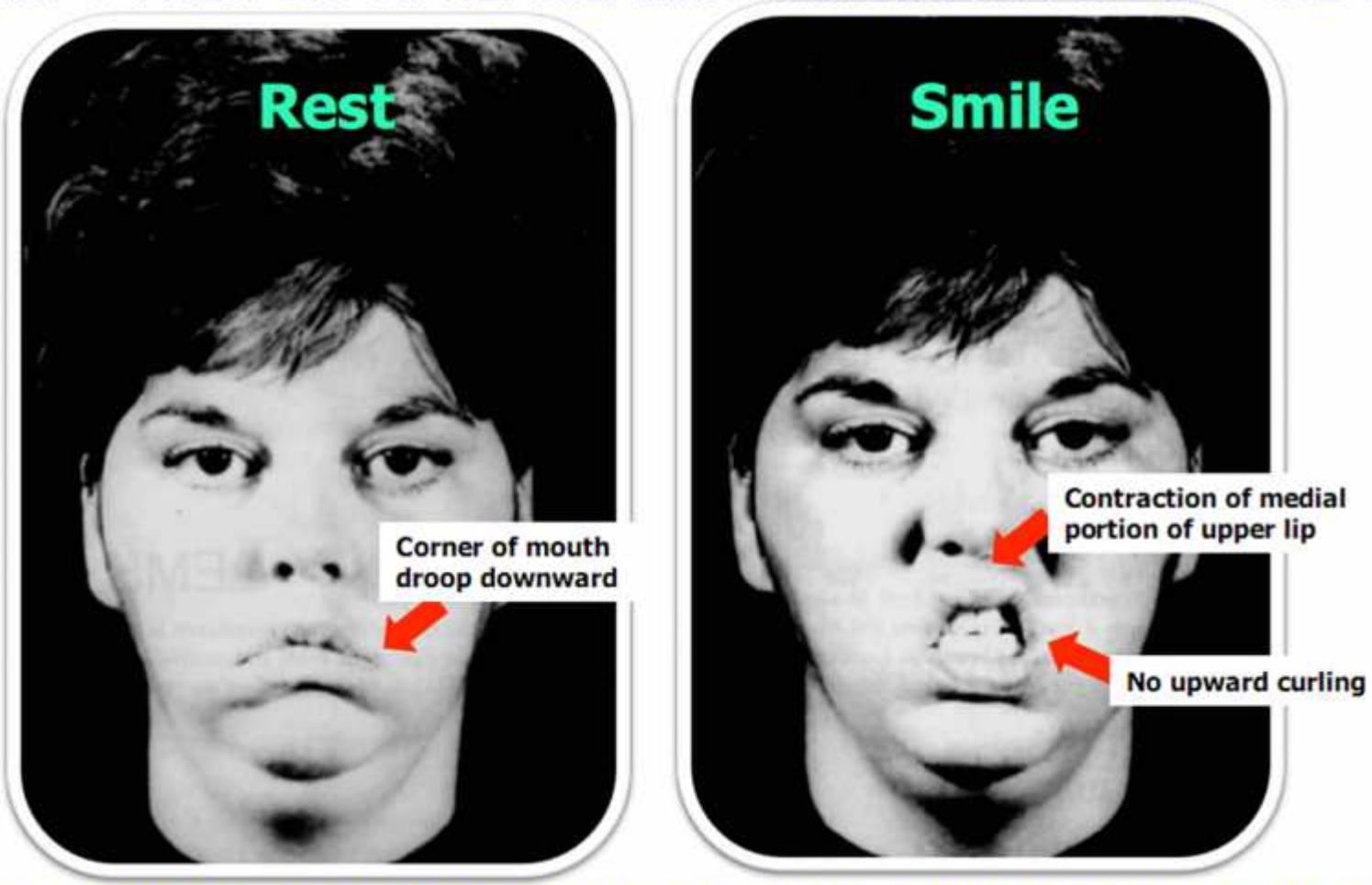
In more than half the people who develop MG, their first signs and symptoms involve eye problems

- most commonly affecting muscles
  - Levator palpebrae.
    Drooping of one or both eyelids **(ptosis**)
  - Extraocular muscles (**diplopia**)

Face and throat muscles

In about 15 percent of people with myasthenia gravis, the first sy se diff

- **Sp** al, de
- **Sw** ult to ne out
- **Ch** ut hal rd to
- **Fa**



Family members may note "lost smile" if the muscles that control facial expressions are affected.

Arm and leg muscles

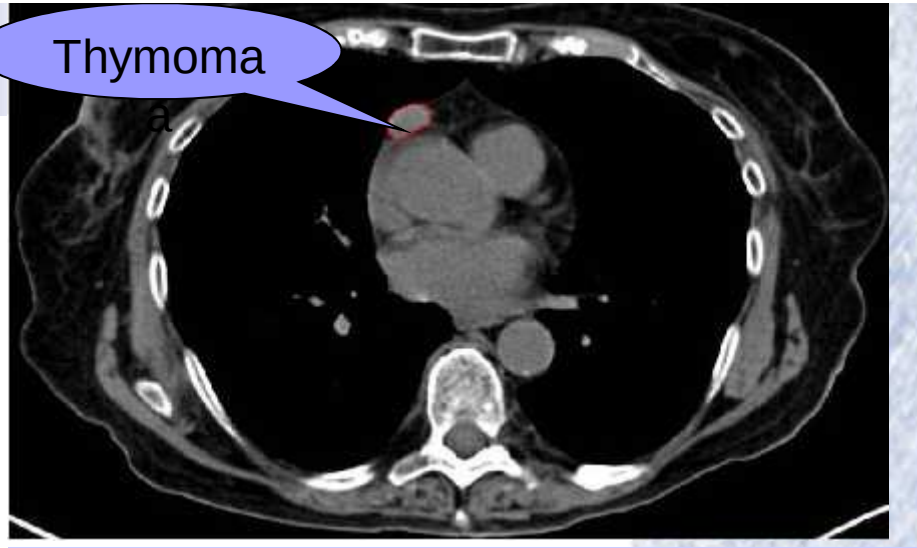
- Myasthenia gravis can cause weakness in arms and legs, but this usually happens in conjunction with muscle weakness in other parts of the body – such as eyes, face or throat.
- The disorder usually affects arms more often than legs.
- If it affects legs, may waddle when walking.

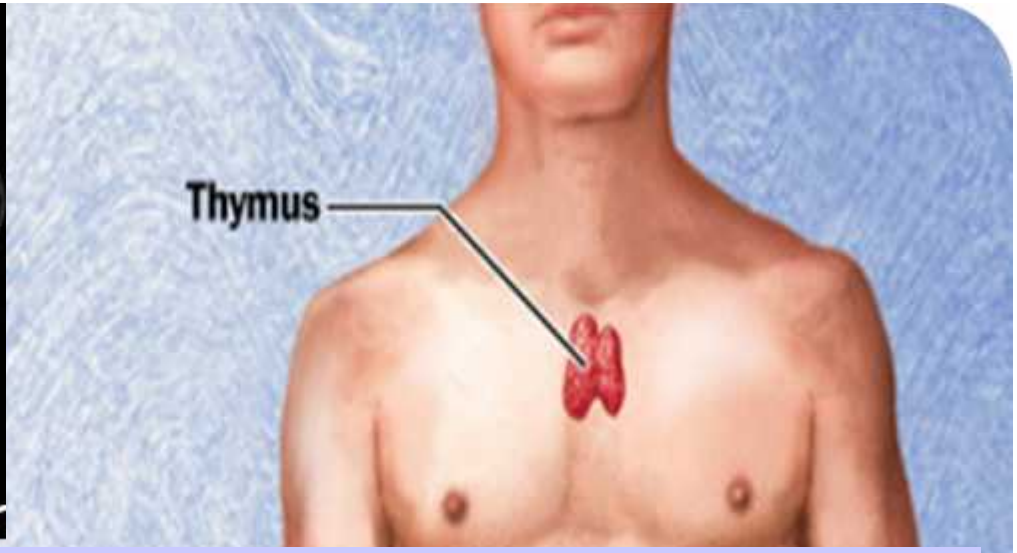
Normal dumbbell

Weakness dumbbell

CAUSES

- Myasthenia gravis may be inherited as a rare, genetic disease, acquired by babies born to mothers with MG, or the disorder may develop spontaneously later in childhood.
- In myasthenia gravis, immune system produces antibodies that block or destroy many of the muscles' receptor sites for a neurotransmitter called acetylcholine.
- With fewer receptor sites available, muscles receive fewer nerve signals, resulting in weakness.





- It's believed that the thymus gland, a part of the immune system located in the upper chest beneath the breastbone, may trigger or maintain the production of these antibodies.
- Large in infancy, the thymus is small in healthy adults. But, in some adults with myasthenia gravis, the thymus is abnormally large.
- Some people also have tumors of the thymus.
- Usually, thymus gland tumors are noncancerous.

Precipitating factors

- Physical exertion
- Hot temperature
- Emotional upsets
- Infections
- Hyperthyroidism
- Surgery
- Menstruations
- Pregnancy (1st trimester)
- Postpartum
- Hypokalemia

- Drugs induced MG
  - Aminoglycoside
  - Fluoroquinolones
  - B-blockers
  - Ca Channel blocker
  - High dose steroid
  - D-penicillamine
  - Chloroquine
  - Quinine
  - Quinidine
  - Lithium
  - Clopromazine
  - Procainnamide

Modified Osserman Classification

- Class I: Ocular weakness
- Class II: Mild weakness
  - IIa : limb and/or axial involvement
  - IIb : oropharyngeal and/or respiratory involvement
- Class III: Moderate weakness
  - IIIa : limb and/or axial involvement
  - IIIb : oropharyngeal and/or respiratory involvement
- Class IV: Severe weakness
  - IVa : limb and/or axial involvement
  - IVb : oropharyngeal and/or respiratory involvement
- Class V: Defined by intubation c/s mechanical ventilator

Diagnosis of MG

Neurology Examination

- Reflexes
- Muscle strength
- Muscle tone
- Senses of touch and sight
- Coordination
- Balance

Confirmation of Clinical Diagnosis of MG

- ***Pharmacologic tests***
  - Edrophonium
  - Neostigmine
  - Pyrodostigmine
- ***Serologic tests***
  - AChR antibodies
  - (sensitivity 80%, high specificity)
  - Muscle antibodies
  - MuSK antibodies (Muscle Spesific Kinase)
- ***Electrophysiologic tests***
  - Repetitive nerve stimulation
  - Single fiber EMG
- ***Miscellaneous tests***
  - Ice pack test
  - Muscle biopsy

Diagnosis of MG

- Serology:
  - Anti-AchR (sensitivity 80%, high specificity)
- EMG: Repetitive nerve stimulation
  - CMAP decremental >10% at 3 Hz (sensitivity 75%)
- Edrophonium/ Tensilon test
  - (sensitivity 80%, not specificity)
- Ice test
  - (80% sensitivity, high specificity)

Pemeriksaan Laboratorium

- Human Anti Reseptor IgC di dalam serum dengan metode Radioimmunoassay

Imaging scans: CT scan or an MRI to confirm a tumor or other abnormality in thymus.

1.Tensilon(Edrophonimum)/Prostigmine Test

(sensitivity 80%, not specificity)

- Inhibits acetylcholinesterase
- Prolongs presence ACh in the NMJ
- Results in enhanced muscle strength

Initially

Dosing: 2 mg of edrophonium iv as a test dose

Monitoring HR: Bradycardia , ventrical fibrillation, cardiac arrest may develop

Prepare the antidotum (sulphate atrophine)

Follow-up

Observing for about 2 minutes,

Up to 8 additional mg of edrophonium is injected

2. Test Neostigmin

- 1.5 mg Neostigmin metilsulphate im
- Perbaikan timbul dlm wkt 10 – 15 mnt, mencapai puncak pada 30 mnt, berakhir stlh 2 – 3 jam
- Efek samping : efek muskarinik (nausea, vomiting, pallor, sweating, salivation, colic, diarrhea, miosis, bradycardia)

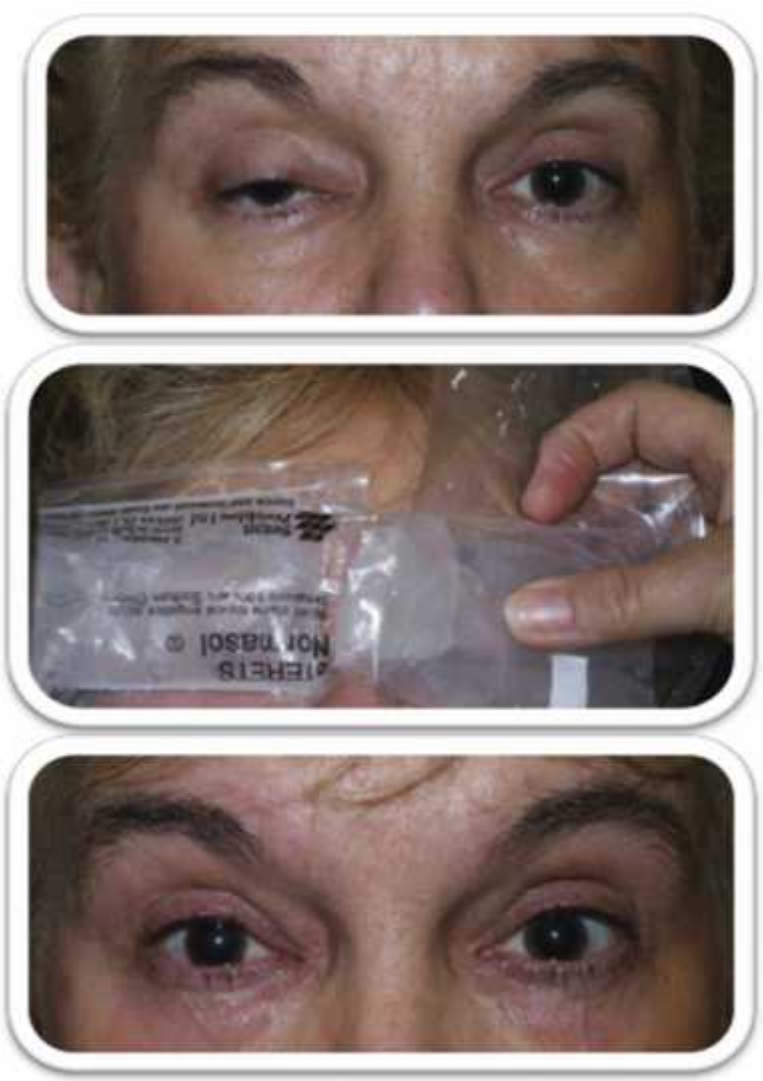
  Antidotum : sulphate atrophine

3. Tes Kurare

- Bila hasil test edrophonium dan tes neostigmin meragukan
- Dosis normal 3 mg d-tubocurarin per 18 kgBB
- Penderita: 2 % dosis normal diberikan iv, bila dlm 5 mnt tdk terjadi kesulitan pernafasan ditambah lagi 5 % dosis normal.
- Terjadinya kelemahan yg makin memberat menunjukkan MG atau sindrome miastenia eaton lambert

ICE TEST

(80% sensitivity, high specificity)



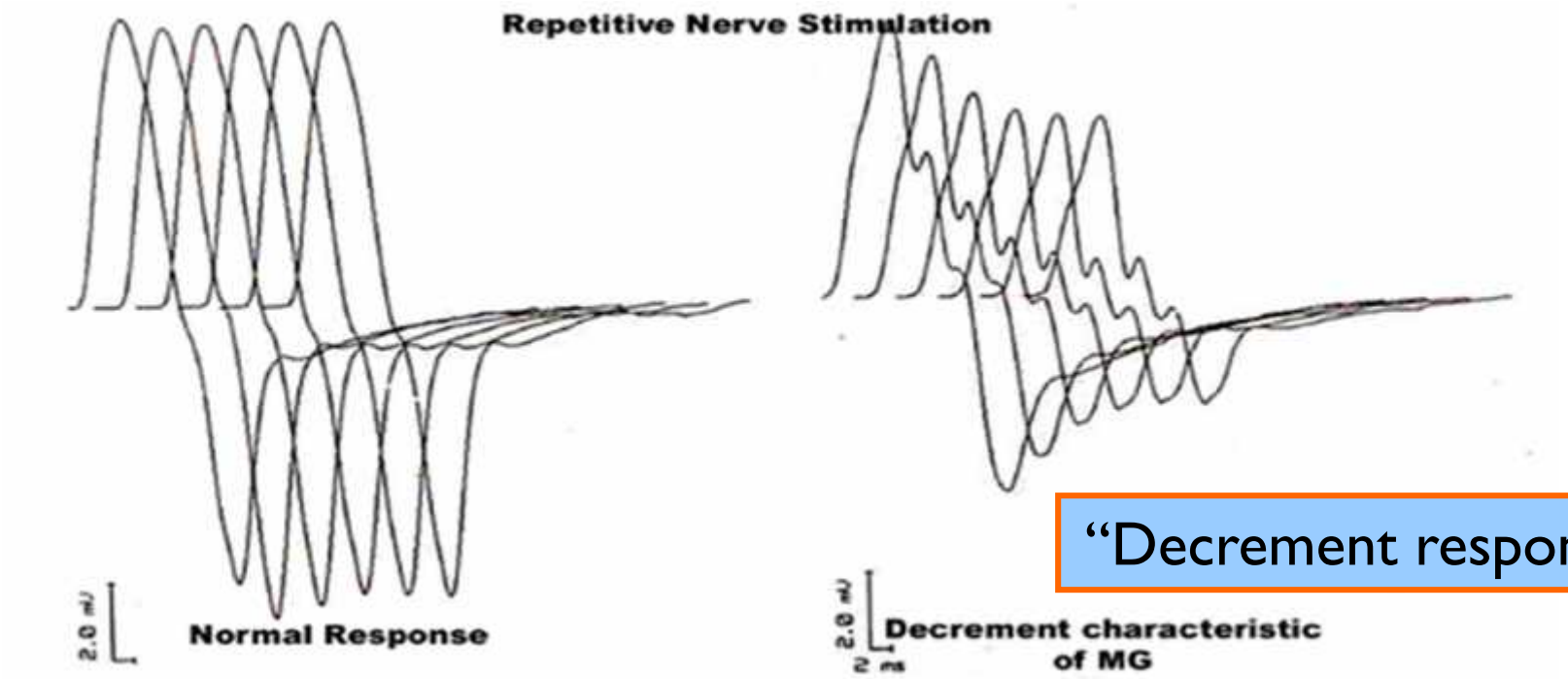
Preceding the test

An ice pack is applied to the closed left eye for 2 minutes

Right upper eyelid ptosis is significantly improved

Elektromiografi (EMG)

Repetitive Nerve Stimulation
CMAP decremental >10% at 3 Hz (sensitivity 75%)

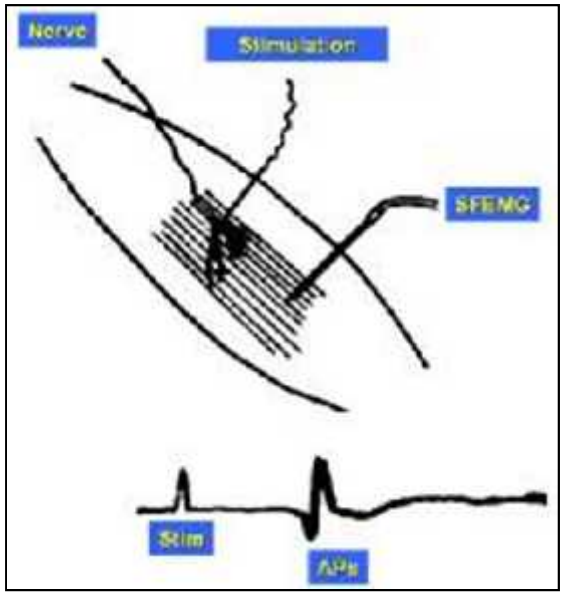


"Decrement response"

Diagnosis: Electrophysiologic Testing

Single Fiber EMG (SFEMG):

- Most sensitive test for detection of abnormality at the NMJ.
- Abnormalities are seen even in clinically unaffected muscles.



Diagnostic Test Sensitivities

Test	Ocular MG	Generalized MG
AChR Ab	50%	90%
edrophonium	60-95%	70-95%
Repetitive nerve stim.	10-17%	53-100%
Single fiber EMG	82-99%	82-99%
Ice Test	89%	

TREATMENTS & DRUGS

- No cure for MG, but the symptoms can be controlled.
- MG is a life-long medical condition and the key to medically managing MG is early detection.
- The goal of treatment is to prevent respiratory problems and provide adequate nutritional care to the child since the swallowing and breathing muscles are affected by this condition.

Medications

- **Cholinesterase inhibitors**
  - Improve neuromuscular transmission
  - pyridostigmine (Mestinon), prostigmin. These drugs don't cure, but improves muscle contraction and strength.
- **Corticosteroids**. These types of drugs inhibit the immune system, limiting antibody production.
- **Immunosuppressant drugs**. Can alter immune system, like

1. Azathioprine (Imuran)
2. Cyclosporine
3. Cisplatin
4. Doxorubicin
5. Cyclophosphamide

- **Plasmapheresis**. a procedure that removes abnormal antibodies from the blood and replaces the patient's blood with normal antibodies through donated blood. This procedure uses a filtering process similar to dialysis. Blood is routed through a machine that removes the antibodies that are blocking transmission of signals from nerve endings to muscles' receptor sites. However, the beneficial effects usually last only a few weeks.
- **Intravenous immune globulin**. This therapy provides body with normal antibodies, which alters immune system response. It has a lower risk of side effects than do plasmapheresis and immune-suppressing therapy, but it can take a week or two to start working and the benefits usually last less than a month or two.
- **Surgery (Thymectomy)**– removal of thymus gland

Acethycholineaterase inhibitors

Increase the response of muscles to nerve impulses -> muscle strength improved.

- Pyridostigmine bromide (Mestinon ®)
  - Start low, titrate up
  - 60 mg - 180 mg BID-QID
  - Side effects : Muscarinic effects
    - Abdominal pain
    - Diarrhea
    - Salivation, lacrimation
- Neostigmine 7.5 mg- 45 mg q 2-6 h PO
  - Only partial remission
  - Reduce/ discontinue when possible
  - S/E - cholinergic crisis, TX with **atropine**

KORTIKOSTEROID

- Derajat sedang sampai berat yg tdk menunjukkan perbaikan stlh timektomi atau tdk berrespons thd obat anticholinesterase

- Prednison 45 mg/hari atau 90 mg/2 hari

- Penderita dg eksaserbasi akut : metilprednisolon 2 gr dilarutkan dlm 250 cc NaCl fisiologis selama 12 jam tiap 5 hari

Complication

- **Myasthenia crisis** - an exacerbation of the myasthenic symptoms caused by undermedication with anticholinesterase drugs.
- **Cholinergic crisis** - an acute exacerbation of muscle weakness caused by overmedication with cholinergic drugs.
- Can be mixed also.

Myasthenia crisis vs Cholinergic crisis

- Myasthenic crisis
  - Respiratory distress
  - Increased pulse and blood pressure
  - absence of cough & swallow reflex
  - Dysphagia
  - Cyanosis
  - Bowel & bladder incontinence
  - Improve with edrophonium
- Cholinergic crisis
  - Abdominal cramps
  - Diarrhea
  - Nausea and vomiting
  - Excessive secretions
  - Miosis
  - Fasciculations/facial muscle twitching
  - Hypotension
  - pallor
  - Worse with edrophonium

Prognosis

- Ocular MG 10% → 90% turn to Generalized (usually in 2 years)
- Untreated weakness → fixed and atrophic
- Spontaneous remission rate 20%
- 20-30% will die within 10 years without treatment

Thank you