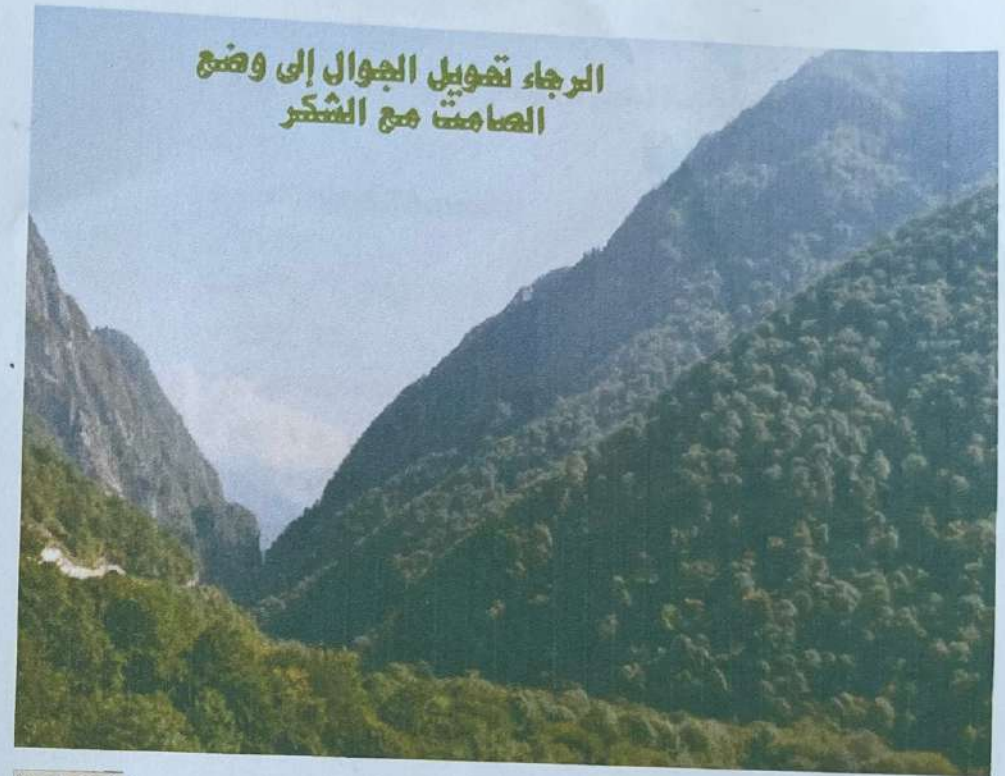


Lecture: 17

Myasthenia Gravis and Myotonia

Dr. Eyad M. Hussein

MD, Ph.D of Neurology
Consultant in Neurology Department,
Nasser Hospital,
Assistant Professor,
Faculty of Medicine, Islamic University
Faculty of Dentistry, University of Palestine



Case – Girl S.

... Case - Girl S.

A 5-year old Palestinian female, previously healthy, presented with gradually progressive bilateral eyelid dropping and squint since February 2007.

She was seen by Ophthalmologist and Pediatric specialists in Gaza.

After investigations (CBC, Full chemistry, TFTs, Opht. exam., EEG and Brain CT) she was diagnosed as:

Bilateral Oculomotor Nerve Palsy

Case- S. in Tel-Hashomer Hospital

She was transferred to Tel-Hashomer hospital and admitted from 30.04.2007 to 7.05.2007 for investigation and management and was seen by Ophthalmologists, Neuroophthalmologist, and Pediatric specialists.

Initial diagnosis:

Bilateral Oculomotor Nerve Palsy



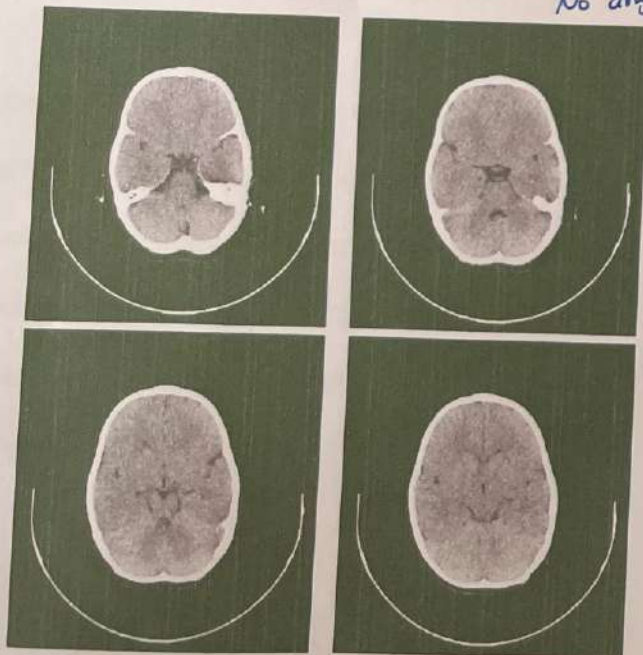
Case- S. Investigation in Tel-Hashomer Hospital

- CBC,
- Full Blood Chemistry,
- TFTs,
- PTT, PT, INR,
- CRP, RF,
- Complement C3 and C4,
- ANA
- DNA (ds) antibodies,
- HBsAg, HCV, HIV
- Blood culture

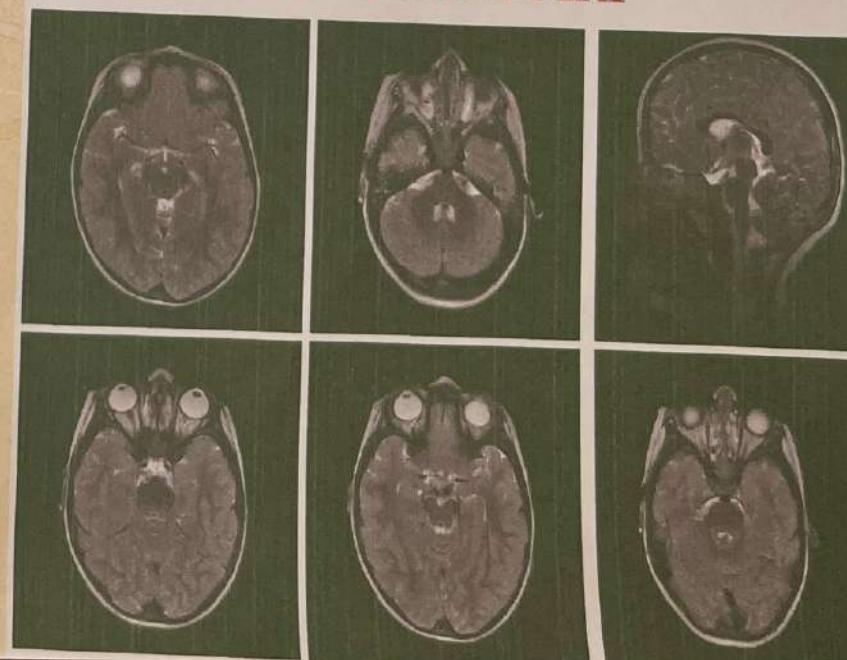
All of the above investigation were normal

Case- S. Brain CT

No any lesion



Case- S. Brain MRI



Case- S. Cervical Spine MRI

Normal



Case- S in St. John Eye Hospital in Jerusalem

The course of her condition during 2007–2008 was a gradually progressive deterioration of her condition.

She was transferred to St. John eye hospital in Jerusalem and discharged with the same diagnosis:

Bilateral Idiopathic Oculomotor Nerve Palsy

Case- S. Final Diagnosis in Tel-Hashomer Hospital

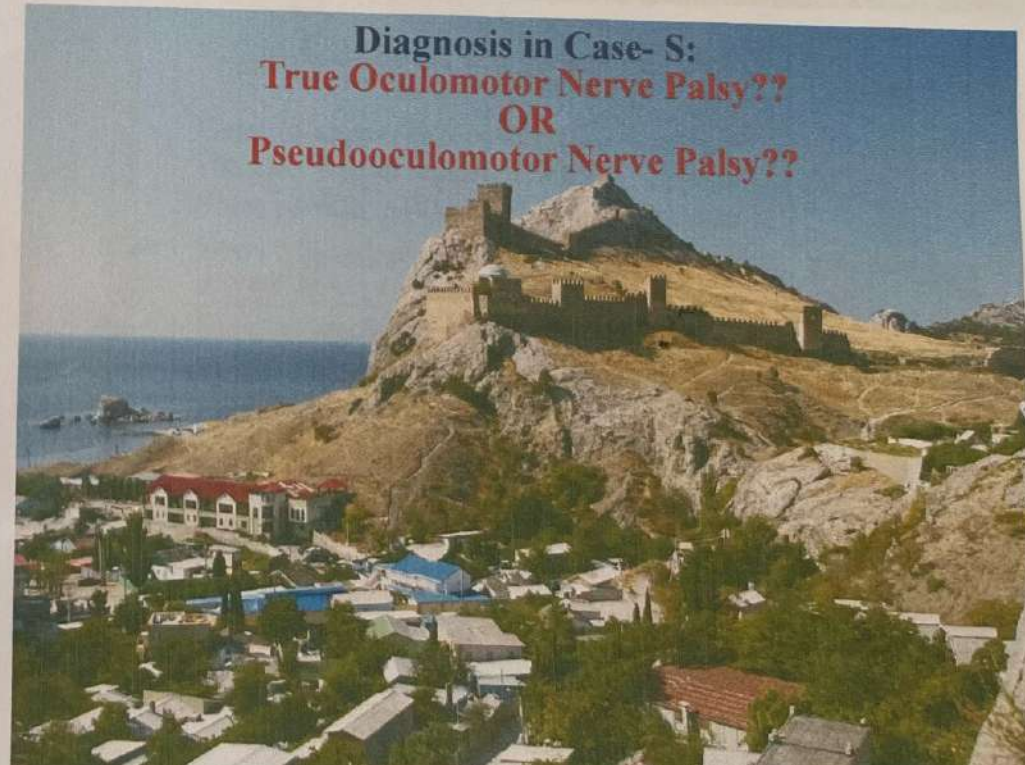
After all of investigations no medications were prescribe and discharged with the final diagnosis:

Bilateral Idiopathic Oculomotor Nerve Palsy

Recommendation:

1. Coverage the left eye 3-4 hours a day.
2. Follow up by ophthalmologist after two months.

**Diagnosis in Case- S:
True Oculomotor Nerve Palsy??
OR
Pseudooculomotor Nerve Palsy??**



Case- S. In Nasser Hospital

- I had the pleasure to see the patient on May 2008, she presented with gradually progressive both eyelid drooping, and limitation eyes movement medially more on the left side.
- This condition was started on February 2007.
- Her father noted mild improvement in the morning without any treatment.

Case- S. Past Medical and Family History

Past Medical & Surgical History: recurrent tonsillitis and upper respiratory tract infection.

Family History: no neurological diseases run in the family similar to the patient's presentation.



Case- S. Physical Examination

- **General appearance:** conscious, cooperative, BP- 100/60 mm Hg, HR- 92/min regular, Temp. 36.5, Weight- 15 Kg.
- **Skin:** no rash, no change in color or growth.
- ✓ **Eyes:** bilateral ptosis, pupils RRR and limitation eyes elevation and adduction Lt. > Rt. *→ regular, round, reactive* *4.5x 3.5x 3.5x* *.. oculomotor*
- **Ears:** no discharge, no redness.
- **Mouth:** no growth on tongue, no pus on tonsils.
- **Lymph Nodes:** normal size lymph nodes palpated on the neck.
- **Chest:** symmetrical chest expansion, adequate air entry in both sides, no added sounds.
- **Heart:** normal placed apex, no murmur.
- **Breast:** no discharge from nipple.
- **Abdomen:** soft, non-tender, no organomegaly, no peritoneal irritation.
- **Extremities:** normal size, no edema, no ulcers.

Case- S. Neurological Status

- **Mental status:** conscious, oriented and cooperative.
- **Speech:** intact.
- **Meningeal signs:** negative.
- **Cranial Nerves:** bilateral ptosis Lt. > Rt. (with increasing after repetitive opening and closing the eyes), pupils RRR, limitation of elevation and adduction both eye Lt. > Rt. Others cranial nerves were intact.
- **Sensory system:** she had normal sensory (both superficial and deep).
- **Motor system:** normal gait, with normal muscle tone and power and deep tendon reflexes with no pathological reflexes.
- **Coordination:** her balance and coordination were normal.

لا كانت تفتحها غرضي
رغمي عينيه
لما من
زاد ال
ptosis

Ophthalmological examination

Bilateral ptosis Lt > Rt.

Pupils RRR

Limitation elevation and adduction both eye Lt. > Rt.

Both corneas clear.

Both lens clear

Both fundus normal

Case- S. Others Investigation & Laboratory Tests

* نتي المكو د MG

- **Chest X-Ray & CT:** no signs of thymoma or thymic hyperplasia
- **Repetitive nerve stimulation:** progressive decrement in the amplitude of muscle action potentials after repetitive nerve stimulation.
↓ A. Potential : m. contraction
- **The ice pack test** (placing ice over the lid): positive →
- **Pharmacological test (Anti cholinesterase test):**
① Neostigmine bromide test 0.6 mg i.m (0.04 mg/kg)
② and atropin 0.15 mg (0.01 mg/Kg): dramatic improvement was recorded at 20 min.

Decrement
Test

لا كانت تفتح
حينها عيها
improving eye
opening
5 د
بعد
eyelid
elevation

Case- S. Positive the ice pack test



good improvement
is elevation eyelid
bilaterally.

Case- S. Positive anti cholinesterase test (after 20 min)



Case- S. Long Term Medication

Acetylcholinesterase inhibitors (anticholinesterase or cholenergic) medications: **Pyridostigmine bromide**

(Mestinon): $15\text{kg} \times 3\text{mg} = 45\text{ mg}$ ($15\text{mg} \times 3$) $\rightarrow$ 8 h كل 15mg

Oral children dose: 7 mg/kg/24 hours divided into 3-5 doses

ب ٨ كل ١٥
ب ٣ / ٧

The Final Diagnosis in Case- S.

الشيفه بالاحر :

Juvenile Ocular Myasthenia Gravis

“Juvenile Pseudooculomotor Nerve Palsy”

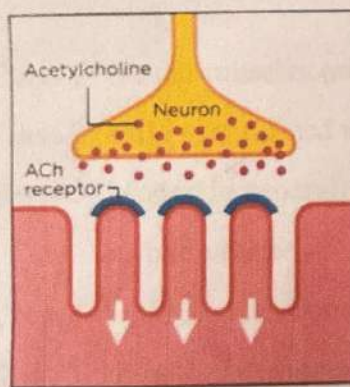


Myasthenia Gravis (MG)

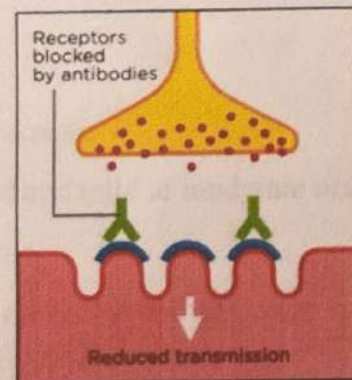
ما يجيب ال smooth m. والدليل : ال pupil كان سليم عند حالتها في فاست

- MG is an autoimmune disorder characterized by weakness and fatigability of skeletal muscles due to dysfunction of the neuromuscular junction.
- Auto-immune disease with production of antibodies against acetylcholine receptors of neuromuscular junction, leading to their destruction.
- Thymic dysfunctions lead to production of these acetylcholine receptors antibodies.

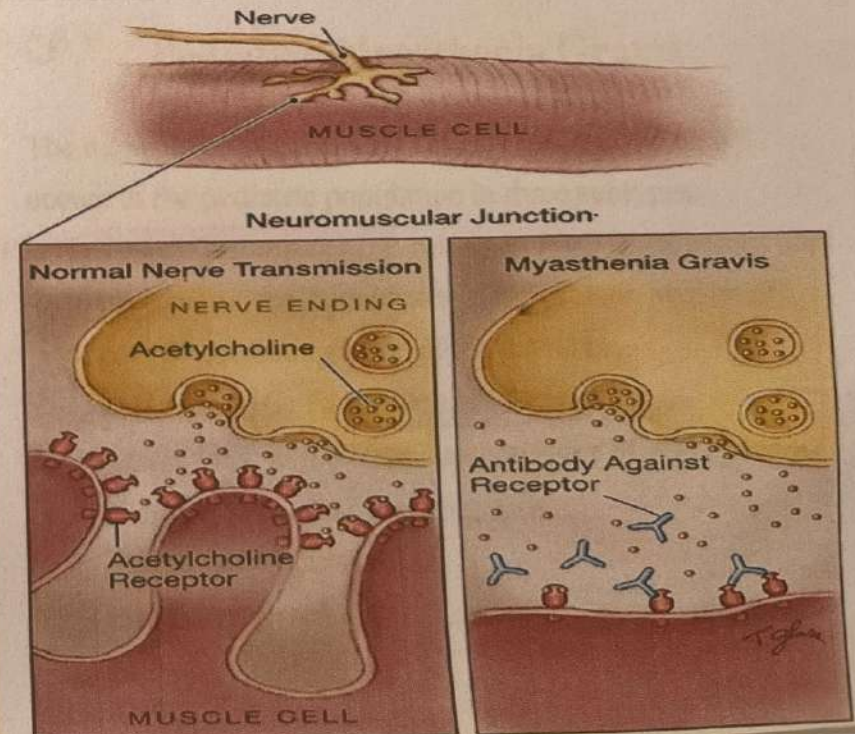
* ال T-cell بتعلم عند المدرسة : Thymus ، بتكونها ال Ag الجسم ، فلما تكون خرابة مش حلتاقي ال ال ال ال فيبتحن ال الرنا ، وصطلع ال AB ضد AChR ..



Normal neuromuscular junction



Neuromuscular junction in myasthenia gravis



Myasthenia Gravis- Epidemiology

- An annual incidence of 10 to 20 new cases per million people
- Typical MG may begin at any age, but is most in the second to fourth decade. It less frequent before age 10 or after age 65 years. *هناك ضعف عي، زائد الحالة اول الحائض كان عمرها 5*
- Women are affected more than men with a female-to-male ratio of 3:2, but at older ages both sex are equally affected.

Myasthenia Gravis: Clinical Subdivisions

- Class 1-** Ocular muscles only
- Class 2-** Mild generalized weakness
- Class 3-** Moderate generalized and mild to moderate ocular-bulbar weakness
- Class 4-** Severe generalized and ocular-bulbar weakness
- Class 5-** Myasthenic crisis

Myasthenia Gravis: Etiology

- Autoimmune disease
- Thymic abnormality
- There is an association between MG and SLE, thyroid disease and rheumatoid disease

← Pediatric Myasthenia Gravis *في الاطفال MG عند الاطفال*

The majority of patients with MG are adults MG also occurs in the pediatric population in three subtypes:

*AB هتدي ص الدم
للطفه عبر المشيمة*

- 1. Transient neonatal MG:** occurs in 10-20% of babies born to myasthenic mothers (due to passive transmission of abnormal antibodies through the placenta).
- 2. Congenital MG:** Familial infantile myasthenia.
- 3. Juvenile MG:** is the most common type of pediatric MG.

MG presents as one of two variants:

- ✓ a. Isolated ocular MG
- ✓ b. Generalized MG

Ocular Myasthenia Gravis

- Over 50% of patients with MG initially present with isolated ptosis, diplopia and squint. *... ptosis symptom دا بيكون فيها*
- Approximately 15% of all patients with MG have isolated ocular variant. *لديهم عبارة عن smooth m.*
- **Sparing of the intraocular muscle function.**
- Patients with ocular MG are more likely to be seronegative for acetylcholine receptor antibodies. *له يعني الـ AB - عديم*

General Characteristics of Myasthenic Symptoms

The symptoms of MG have three general characteristics:

1. **Fluctuation of muscle weakness and fatigability** (worse in late afternoon or evening, and after exercise). *بعض كويش لو غدا لفره بتعب*
2. Distribution of muscle weakness and fatigability: **ocular muscles are affected first** in about 50% of patients, and in 85% of patients with general myasthenia. *خاصة ptosis*
3. Clinical response to **cholinergic** (anticholinesterase) drugs. *له يعني لو أعطيناهم ايام هنعفوا*

Generalized Myasthenia Gravis

- More than **50%** of patients **present with ocular symptoms** of ptosis and/or diplopia, about half will develop generalized variant within two years. *بيبدأوا مع بعض بقتل الـ ptosis*
- Many of the patients develop ptosis or diplopia at some point in the course. *له يعني الـ ocular symptom, الـ general symptom*
- About **15%** of patients present with **bulbar symptoms** (dysarthria, dysphagia, and fatigable chewing).
- Less than **5%** present with **proximal limb weakness alone**.
- Less common presentations include isolated **neck weakness**, **isolated respiratory muscle weakness**, and distal limb weakness.

Drug-induced myasthenia-like syndrome

- **Antibiotics** (ciprofloxacin, erythromycin, ampicillin, polymyxins, aminoglycosides)
- **Anticholinergics** (eg, trihexyphenidyl) → *use in Parkinson*
- **Beta-adrenergic receptor blocking agents** (propranolol, oxprenalol)
- **Cardiac drugs** (procainamide, verapamil, quinidine)
- **Antimalaria** (chloroquine)
- **Anticonvulsant** (phenitoin, gabapetine)
- **Antipsychotic** (lithium, chlorpromazine, phenothiazine)
- **Neuromuscular blockers and muscle relaxants** (magnesium sulfate, botulinum toxin)
- **Ophthalmologic drugs** (betaxolol, timolol, trpocamide)

Myasthenia Gravis and Pregnancy

- The **first trimester** and the **early postpartum** period are times of **highest risk** for exacerbation of MG.
- **Exacerbation** of MG may occur **after abortion**.
- **Pyridostigmine** is the **first-line treatment** for MG in pregnancy.
- **Magnesium sulfate** is relatively **contraindicated** in patients who have MG.
- **Valproic acid or phenobarbital** can be used for seizure, but **phenytoin** can potentially exacerbate weakness and fatigability.

طبيب لو كانت preclampsia لازم نعطها Mg sulfate و في عيناها MG شو نل؟ نعطها ايام ب بقله dose adjust
 و نعط pyridostigmine من oral ل IV ... هيك عيناها من
 exp. failure ممكن نعط لو اخذت Mg.sulf طاب بيوتن intubation كلة

Myasthenia Gravis- Diagnostic Approach

Bedside Test:

- Ice pack test:** the ice pack test can be used in patients with ptosis. Positive in about 80% of patients with ocular M.
- Tensilon (Edrophonium) test:** (10 mg/mL) with an initial 2 mg test dose given intravenously. This can be followed by another 2 mg dose every 60 seconds up to a total dose of 10 mg.

* اذا مش موجود ال edrophonium هنعط Neostigmine

Neostigmine bromide test 0.04 mg/kg given i.m

To avoid cholinergic side effect, atropine (0.4 to 0.6 mg) or (0.01 mg/Kg) should be given i.v. before the edrophonium is administered.

نلا
 بيوغنا
 بقسونا

Myasthenia Gravis- Diagnostic Approach

- CBC,
- Full Blood Chemistry,
- TFTs, (Thyroid Function test)
- CRP, RF, rheumatoid factor
- ANA
- DNA (ds) antibodies,
- HBsAg, HCV, HIV
- Blood culture

Serological Test

- Acetylcholine receptors (AChR) antibodies:** results are positive in about 85-90% of patients with **generalized MG** and in **50%** of those with pure ocular MG.

False-positive anti-AChR antibodies test occurs in cases with:

- ❖ Thymoma without myasthenia gravis
- ❖ Lambert-Eaton myasthenic syndrome
- ❖ Small cell lung cancer ~ 2nd M.G. دونه
- ❖ Rheumatoid arthritis, SLE
- ❖ In 1-3% of the population older than 70 years

باعتدوا ايا كانوا عندهم

ABO

دبوتو

AChR
 AB
 to detect M.G

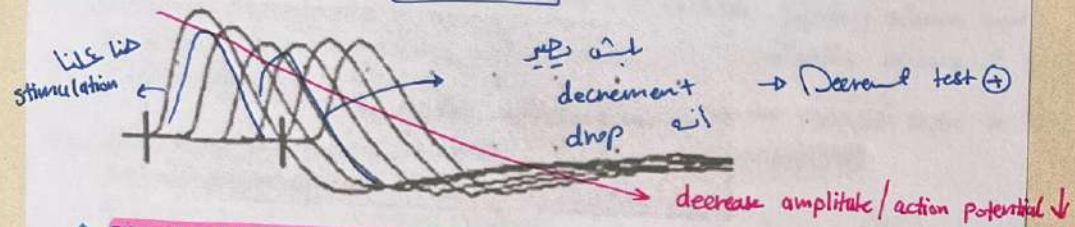
- Muscle-specific kinase (MuSK) antibodies:** are present in 50% of those with generalized MG who are **AChR-Ab negative**

- Striated muscle (SM) antibodies:** they are present in 30% of patients with **myasthenia**, but in **80%** of those with **thymoma**.

باعتدوا نط لتشفية اياهم اذ عندهم Thymoma

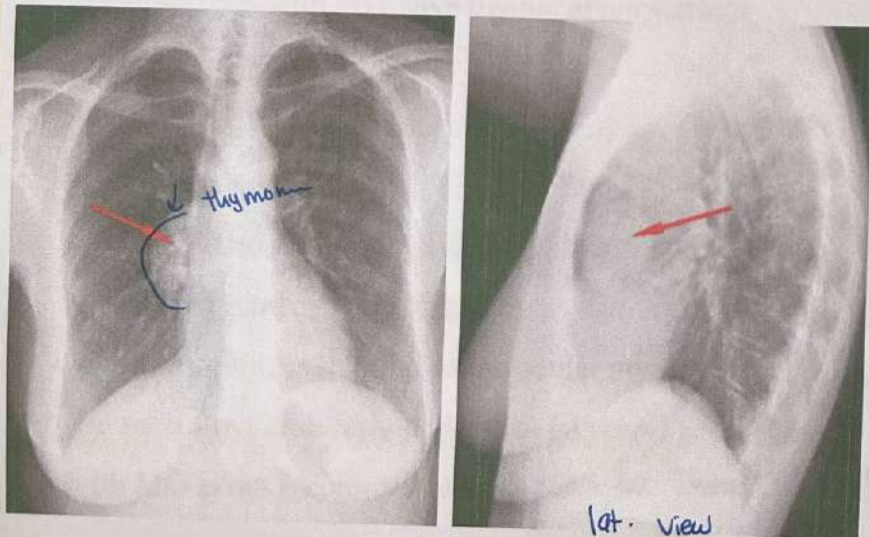
3. Electrophysiological Confirmation

- ❖ **Repetitive nerve stimulation:** progressive decrement in the amplitude of muscle action potentials after repetitive nerve stimulation at 3 or 5 Hz.



- ❖ **Single-fiber electromyography (SFEMG):** is the most sensitive diagnostic test for MG. **Positive** in greater than **95%** of those with **generalized MG** and in **90%** with **ocular MG**.

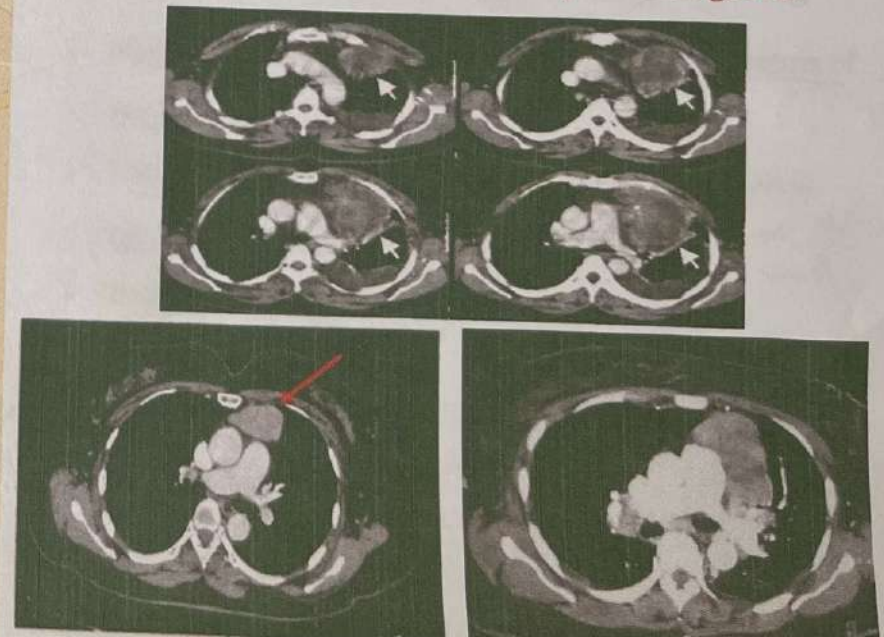
Chest X-Ray showing an anterior mediastinal mass (thymoma) in a patient with myasthenia gravis



Radiological Studies

- ❖ **Brain MRI:** to exclude brain stem malignancy.
- ❖ **Chest X-Ray:** provide evidence of thymomas in about 15% of all patients with thymomas.
- ❖ **Chest CT & MRI:** for detection of thymus and lung tumors. 75% of patients with MG have thymic abnormalities (85% thymic hyperplasia and 15% thymic tumors). MRI is not more sensitive than CT for detection of thymoma.
 Thymom - الـ ثيموما
 Contrast ← Chest CT →

CT scan of chest showing an anterior mediastinal mass (thymoma) in a patients with myasthenia gravis



Differential Diagnosis of Myasthenia Gravis

The differential diagnosis of myasthenia gravis includes conditions that mimic **ocular MG**:

- ❖ Thyroid ophthalmopathy
- ❖ Myotonic dystrophy and oculopharyngeal dystrophy
- ❖ Brainstem and cranial nerve pathology
- ❖ Pseudotumor cerebri → fundus exam to exclude papillary edema and idiopathic intracranial HIN
- ❖ Thyroid gland disease
- ❖ Cavernous sinus thrombosis
- ❖ Tolosa-Hunt syndrome → painful ophthalmoplegia → pain يكون المرافق بينا

The differential also includes conditions that mimic **generalized MG**:

- ❖ Motor neuron disease (ALS)
- ❖ Lambert-Eaton myasthenic syndrome
- ❖ Botulism
- ❖ Penicillamine-induced myasthenia → Wilson وبأخذها
- ❖ Congenital myasthenic syndromes → Penicillin ...

Thymectomy for Myasthenia Gravis

- Most patients with MG have thymic abnormalities: hyperplasia or thymoma
- Thymectomy for all patients with thymomas and MG is recommended. كل واحد عنده thymoma أو MG لازم نزيلها
- The benefit and use of thymectomy in patients without thymoma is still **controversial** لا في جرح نزيل Thymus في حال كان ب hyperplasia أو نفي (الاستجابة منها)
- Most neurologists limit its use in ocular myasthenia → يعنى ب ocular
- Thymectomy for elderly patients (>60 years) and children with MG is **not recommended** ثيمكتومي كبار Thymus مرة لا يطلع رنا عمر

Treatment of Myasthenia Gravis

There are four basic therapies used to treat MG:

1. Symptomatic treatments (anticholinesterase agents):

Pyridostigmine (Mestinon) is the usual choice.

Neostigmine is available but not commonly used.

2. Chronic immunomodulating treatments:

corticosteroids and other immunosuppressive drugs (azathioprine and cyclosporine)

3. Rapid immunomodulating treatments: plasmapheresis and/or intravenous immune globulin

4. Surgical treatment: (thymectomy)

80-100mg prednisone

Lambert-Eaton Myasthenic-Myopathic Syndrome (LEMS)

➤ Non-metastatic manifestation of small-cell carcinoma of the bronchus

➤ Fatigability of muscles tends to improve after muscle contraction and exercise بعض المصيح مكي لقابن لما يتحركه

➤ Increment test positive by EMG بقت

➤ Treatment: زيان و P. action

➤ 3,4-diaminopyridine "The mechanism of action is a significant prolongation of the nerve terminal membrane depolarization, which enhances calcium entry and improves the release of acetylcholine"

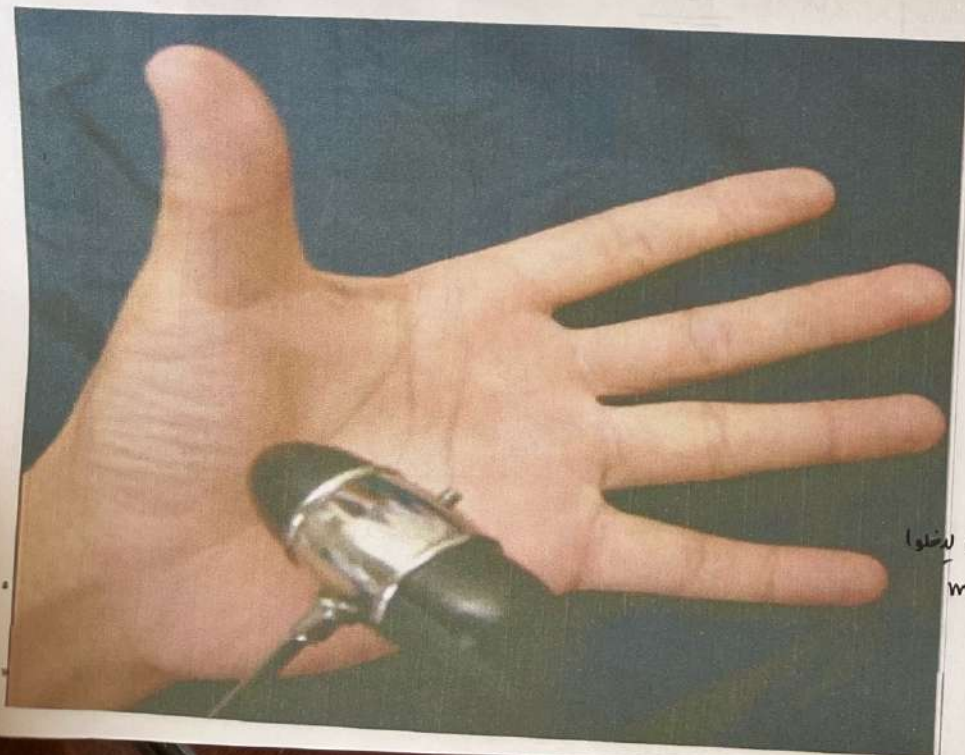
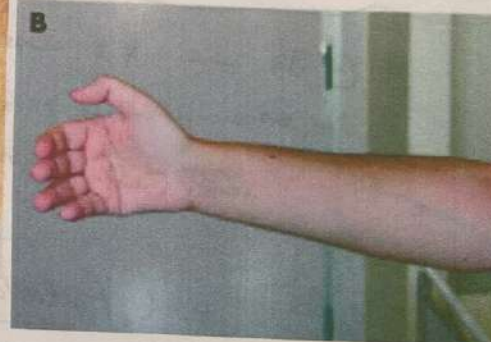
➤ Surgical.

Myotonia

لو نعلت عليه بيخيل
طارد وماسك في ايدك

There are characterized by delayed relaxation of skeletal muscle After cessation of voluntary movement.

- **Voluntary stimulation:** patient is unable to open hand except very late.
- **Mechanical (percussion):**
 - Tap of the thenar eminence, leads to adduction of thumb with delayed abduction.
 - Tap of the tongue leads to dimple formation
- **Electrical stimulation:** 2-3 milliampere are enough to produce muscle contracture (normally 6 milliampere is needed) 2-3 ب ١٢ m. contraction → hypercontractility rate عكس م. ٦
- **Cold, K, cholinergic drugs:** increased myotonic phenomen



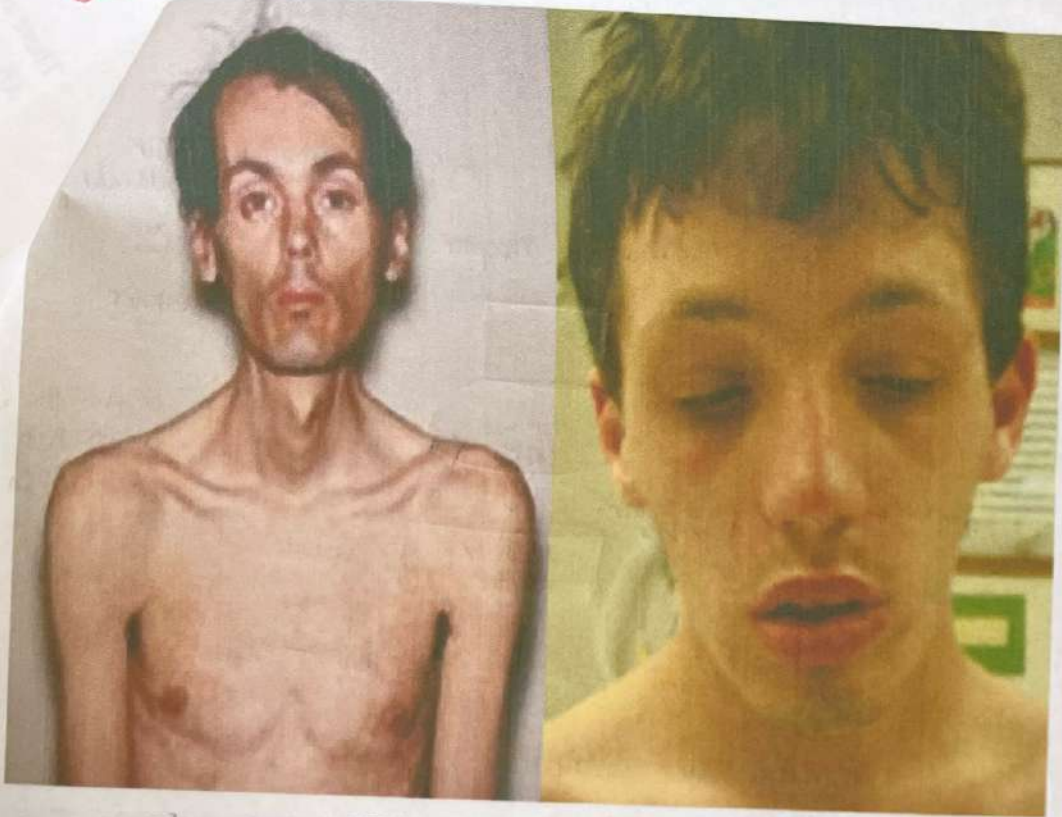
Dystrophia (Atrophica) Myotonia

- Autosomal dominant
- Common in **males** (20-50 years)
- Myotonia associated with muscle atrophy (myopathic face, ptosis and progressive shoulder and distal muscle wasting) → inferilitis
- Cataract, frontal boldness, hypogonadism, glucose intolerance, mild intellectual impairment and cardiomyopathy
- **Muscle pain** Cardiac block or arrhythmia or Cardiac arrest
- **EMG:** positive myotonic pattern (2-3 milliampere)
- **Treatment:** Phenytoin or procinamide Relaxation

لنتم قوله الطبيب عيون

مذاكرو ال Contractility لشلوا m. Cramp

Relaxation



Myotonia Congenita or Hypertrophica (Thomsen's Disease)

- An isolated **autosomal dominant**
- Common in **females** (in **childhood**)
- Myotonia associated with muscle **diffuse muscle hypertrophy**
(**real or pseudohypertrophy**)

fat deposition لا تاج عا

M.G (B&B)

Myasthenia crisis

rapid, life threatening worsening of weakness.

⇒ crisis is treated with surgery, infection, or drugs.

(hydroxychloroquine, B blocker, aminoglycoside, fluoroquinolones)

(intubation or noninvasive ventilation):

weak bulbar m. ⇒ weak resp. muscle ⇒ airway obs. ⇒ m. of head/neck ⇒

Plasma exchange or IVIG

or oral prednisone → glucocorticoid

mylophenolol, atropine, cyclosporine

immuno suppress

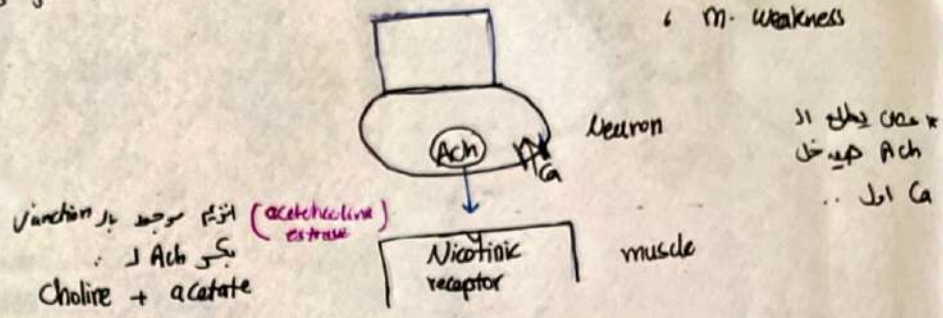
Most M.G have → abnormal thymus
 ↳ hyperplasia 85%
 ↳ Thymoma 15%

M.G is cured with Thymectomy

• Lymphomatous M.G can also be cured with thymectomy
 • = thymectomy then done ptn < 60.

• CT or MRI (imaging of mediastinum)
 ↳ ant. median mass

nicotinic Ach receptors are blocked by AB: 60%
 * neuromuscular junction disorder
 ح ال Ach ال receptor 60%
 6 m. weakness



ACh is released from the neuron into the synaptic cleft.

* Bimodal age distribution:

- women: 20-30 y
- men: 60-80 y

* repeated stimulation → ↓ ACh release
 m. weaken with use

* Diplopia, ptosis:

extraocular m. weak
 50% ptn present with eye complaints

* 15% present with "bulbar symptom"
 Chewing, swallowing
 speech problem.

②

Drug contraindical in M.G

- Antibiotic $\rightarrow$ amino., fluoro.
- Na channel block $\rightarrow$ IV local anesthetic (lidocaine)
 - $\rightarrow$ Procainamide
 - $\rightarrow$ Quinidine
- BB

* M.G لا ايجى دى حد اغلب اى بعدى الحمل ع جز
 Postpartum م.ج من الحمل اى
 1st month Post-Partum 1st trimester بلا Flare =

* Chronic T. $\rightarrow$ (Acetylcholinesterase Inhibitor)

Pyridostigmine : 1st line
 $\downarrow$ Ach metabolism
 $\uparrow$ Ach level in junction

- $\rightarrow$ immunosuppressed
- $\rightarrow$ Thymectomy in appropriate pts.

BB #

signal fiber EMG

test : لو لى
 ABO , $\oplus$ حيا
 [Sens $\ominus$ M.G]
 more, بكون اى ocular manifest اى

CS - 0 medium dose
 (20 - 40 mg)

high dose لى حيزد اى
 exacerbation دى gravis

aminoglycoside main exacerbating دى M.G

1st T. دى exacerbating M.G :

Plasmapheresis or W/G

azathioprine : دى عيشى ع
 or rituximab

Pyridostigmine ع حيزد اى
 medium dose CS

life long drug

Notes ip. M.G #

Cambert-Eaton Myasthenic \$

BB, Notes from ... #

②

* هنا يحس M.G. ما يتولد بـ

m. use → improve symptoms.

نبت M.G. اى حكة بـ Ach. receptor

هنا نوزودنا القوة بين زودنا depolarization

↑ motor action potential.

* هنا يحس M.G. hyporelexia

* شئ الاشياء الـ unique الـ LEM\$

• autonomic dysfunction common

↓ dry mouth " ↓ salivation "

• erectile dysfunction, constipation.

• impaired pupillary light response.

* ①: (Amitampridine)

• دة حشيد

Presynaptic neuron K channel efflux

prolong depolarization

• خـ: (guanidine) فـ الـ mechanism

Pyridostigmine: شـ الـ

• لو الـ severe

• ونباع لو في لاسر ... بـ

①

• دة دة less common

(الفق) • عـ الـ Ach الـ الـ Ca

presynaptic Ca channel

• Ach الـ present

• Paraneoplastic الـ الـ

• Small cell lung cancer lung CT
• Ovarian, breast cancer (CT الـ)

* for dx: VGCC AB
Voltage gated Ca channel

* clinical features:-

• Slow onset symmetric proximal m. weakness
hip / shoulder

myositis

m. Pain

no myalgia CK level

* مشكلة الـ M.G. Post synaptic Ach receptor
Pre synaptic LEM\$ Ca channel

LEM \$

Myasthenia

Cause	Ca Channel AB	Ach R. AB
m. use	improve	worsen
eye symptom	less common	classic
Proximal m.	common	rare
autonomic symptom	"	absent
reflex	hyporeflexia	normal