

Myasthenia Gravis

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- neuromuscular transmission disorders cause abnormal WEAKNESS and FATIGABILITY.

CLASSIFICATION of Neuromuscular Transmission Disorders

I. Autoimmune

- myasthenia gravis
- Lambert-Eaton myasthenic syndrome (LEMS) see p. Mus2 >>

II. Congenital see p. Mus2 >>

- Pre-synaptic defects**
 - ACh resynthesis / packaging defect
 - paucity of synaptic vesicles and reduced quantal release
- Synaptic defect**
congenital end-plate AChE deficiency
- Post-synaptic defects: increased response to ACh**
slow-channel syndromes
- Post-synaptic defects: decreased response to ACh**
 - low-affinity fast channel syndromes
 - mode-switching kinetics of ACh receptors
 - ACh receptor deficiency without kinetic abnormality
- Partially characterized syndromes**
 - congenital myasthenic syndrome resembling LEMS
 - familial limb-girdle myasthenia
 - benign congenital myasthenic syndrome with facial malformations

III. Toxic

1. Drug-induced:

- D-penicillamine** (!!!) – induces anti-AChR antibody production → clinical manifestations similar to typical MG; antibodies disappear when drug is discontinued.
- curare**
- aminoglycosides** (esp. neomycin) - decrease both *presynaptic ACh release* (antagonism to Ca^{2+}) and *sensitivity of postsynaptic membrane to ACh* (curare-like effect);
H: calcium infusion, cholinesterase inhibitors, aminopyridines

Aminoglycosides are relatively contraindicated in both presynaptic and postsynaptic disorders of neuromuscular transmission!

- polypeptide antibiotics (colistin, polymyxin B)
- antiarrhythmics (quinidine, procainamide)
- Ca-channel blockers

2. Organophosphate intoxication see p. A35 >>

3. Venoms & toxins:

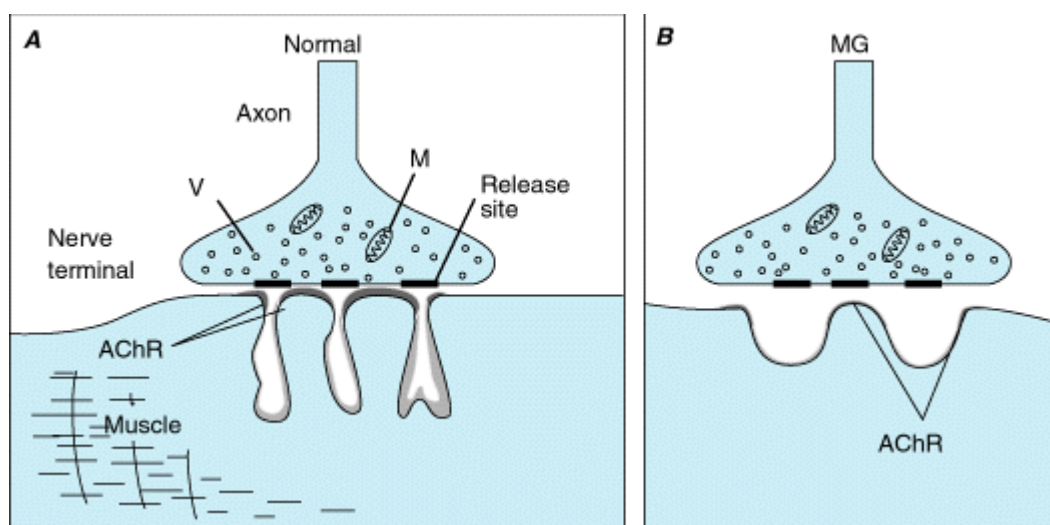
- botulism** see p. 227 (5-7) >>
- coral **snake**, **scorpion**, black widow **spider** see p. 2780 >>
- tick** paralysis see p. 2780 >>

MYASTHENIA GRAVIS

PATHOGENESIS & PATHOPHYSIOLOGY

Autoimmune acetylcholine receptor damage → postsynaptic destruction of neuromuscular junction (decreased numbers of muscle ACh receptors) → small end-plate potentials which may fail to trigger muscle action potentials.

- Sensitized T cells (**thymus** is unequivocally involved in pathogenesis!!!)
 - muscle-like (myoid) cells within thymus, which bear ACh receptors on their surface, may serve as source of autoantigen → trigger autoimmune reaction within thymus.
- Anti-acetylcholine receptor antibodies (anti-AChR)** - key to ACh receptor damage!; antibodies react with multiple determinants on AChR:
 - destruction of receptors** (complement-mediated lysis of junctional folds at motor end-plate).
 - acceleration of normal degradative processes** (e.g. cross-linking of receptors by Ab → endocytosis, lysosomal hydrolysis).
 - small percentage of anti-AChR interfere directly with binding of ACh - **functional blockade** of receptors (explains response to acetylcholinesterase inhibitors)



Histology

- decreased numbers of acetylcholine receptors
- simplification (flattening) of postsynaptic clefts
- widening of synaptic space
- immune deposits** at end plate (C3 localization is most convenient way to confirm suspected diagnosis).
- normal presynaptic nerve terminal - ACh is released normally!

- **thymic abnormalities:**
 - a) lymphoid **hyperplasia** (65-70%); in normal individuals, germinal centers are sparse in thymus.
 - b) **neoplasms** (10-15%) - usually locally invasive epithelial cell tumors (lymphoepithelial THYMOMAS* or rarely carcinomas); tend to occur in older patients.
 - *contain T-cells, but neoplastic elements are epithelial cells
- **lymphorrhages** in muscle ($\approx 50\%$) - focal clusters of lymphocytes near small necrotic foci without perivascular predilection.
- in severe cases - disuse changes with type 2 muscle fiber atrophy.

EPIDEMIOLOGY

- onset – any age.
- bimodal peak of INCIDENCE:
 - 1) **younger women** (2-3rd decades)
 - 2) **older men** (5-6th decades)
- PREVALENCE – 3-4 in 100,000
 - before age 40, disease is 3 times more common in women;
 - at older ages, both sexes are affected equally;
 - overall, ratio females : males = 3 : 2.
- **partial genetic predisposition** (case reports of families with various autoimmune conditions, incl. MG); disproportionate frequency of HLA haplotypes B8, DR3.

CLINICAL FEATURES

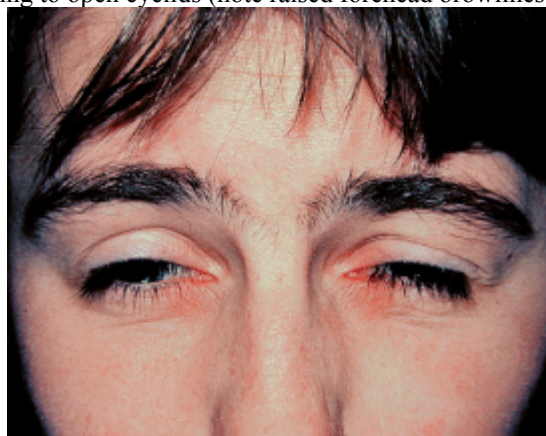
- **FATIGABILITY and WEAKNESS of skeletal muscles.** see p. Mus1a >>
- N.B. patients never complain of fatigue - myasthenic symptoms are **always due to WEAKNESS** not to rapid tiring!
- N.B. patients who complain of fatigue (if not anemic or oncologic) almost always have emotional problems (usually depression).
- in 10% MG is associated with another autoimmune disease.

Distribution

- 40% cases begin with **ocular muscles** with various combinations (diplopia + ptosis); often asymmetric; pupils are normal.
- **oropharyngeal** weakness - dysphagia and dysarthria; nasal regurgitations, aspirations; vocal cords are only exceptionally affected

ocular and **oropharyngeal** weakness occurs in virtually all patients (“expressionless facies with drooping eyelids and snarling smile”) - **diagnosis is doubtful if there are no cranial symptoms!**

patient is attempting to open eyelids (note raised forehead browlines reflecting effort):



- **limb & postural muscles** are generally less affected; **limbs** (upper > lower; proximal > distal; may be asymmetric) are never affected alone!
- weakness becomes **generalized** in majority (15% remain confined to ocular muscles); examination of **neck flexors** is most sensitive in demonstrating generalized disease (holding head up from surface of examining table while lying supine - gravity cannot be overcome for more than few seconds).
 - Deep tendon reflexes remain normal (even in weak muscles)!
- **muscular atrophy** (of variable degree) is found in only 10% cases - usually only in severely dysphagic patients with malnutrition; fasciculations do not occur!

Fluctuating Nature

- weakness varies in course of single day (sometimes within minutes), and *from day to day* (or over longer periods); constant weakness may occur.
- major prolonged variations are termed **remissions / exacerbations**.
- *during physical stress* (esp. respiratory infection, surgery) precipitous worsening may occur!
- symptoms are exacerbated by heat and improved by cold (e.g. ptosis may improve after cooling of eyelid with ice pack).

Myasthenic Crisis - RESPIRATORY FAILURE needing assisted ventilation.

- occurs in 10% patients.
 - mechanisms:
 - a) respiratory muscle weakness
 - b) oropharyngeal weakness → aspiration
- Failure of respiratory muscles** can be life threatening!

DISEASE SEVERITY:

- grade I** - ocular disease only;
- grade II** - generalized weakness of mild (IIa) or moderate (IIb) intensity;
- grade III** - severe generalized disease;
- grade IV** - myasthenic "crisis".

Transient neonatal MG - myasthenic syndrome from **passive transfer of maternal AChR-ab** (occurs to $\approx 12\%$ myasthenic mothers).

- impaired sucking, weak cry, limp limbs, and sometimes respiratory insufficiency (may require ventilatory assistance, exchange transfusion).
- symptoms begin in first 48 hours and resolve in 2 weeks.

DIAGNOSIS

Curare test is no longer used (patients are abnormally sensitive to curare).

N.B. **curariform medications are only drugs absolutely contraindicated** in MG!

Quantifiable timed endurance tasks:

- a) maintaining upward gaze
- b) holding forward outstretched arms in abduction
- c) vital capacities
- d) squats
- e) reading standard passage (measure time it takes for speech to become mushy and dysarthric)

- f) ergogram (repetitive measure of grip strength); N.B. simple grip dynamometry does not aid in evaluation.

“Normal neurologic examination is incompatible with diagnosis of symptomatic myasthenia gravis”

EDROPHONIUM CHLORIDE (TENSILON) injection → clinical weakness improvement.

- *first fatigue patient* with task that includes signs that can be easily clinically assessed (see above).
N.B. muscle that is clearly weak must be identified!
- initial test* dose 2 mg IV** → in 15 seconds additional 3 mg → in another 15 seconds final 5 mg (i.e. maximum of 10 mg).
* **monitor heart rate with ECG** - to avoid bradycardia and vasodepressor syncope; H: atropine.
** if definite improvement occurs (document with photo!), test is considered positive and is terminated.
- rapid improvement / recovery of fatigued muscles over subsequent 2 minutes is **positive test** → weakness returns within 5 minutes.
- test may be repeated in 30 minutes if necessary.
- **normal subjects** have no change in muscle strength; may transiently experience salivation, lacrimation, diaphoresis, fasciculations (perioral, periocular, or lingual).
N.B. false-negative and false-positive tests do occur!
N.B. subjective increase in general strength or relief of fatigue are *not* positive test!
- **EDROPHONIUM** (cholinesterase inhibitor) - rapid onset (30 s) and short duration (< 5 min) - preferred for **ocular** and other **cranial** muscles.
- **NEOSTIGMINE** (effect lasts up to 2 hours) - can be used for **limb** or **respiratory** muscles, which may require more time for testing.
- PLACEBO may be useful in evaluating limb weakness (placebos are not necessary in cranial muscle weakness because that cannot be simulated); placebo is difficult to “blind” because real cholinesterase inhibitor produces intestinal cramping and muscle fasciculations in eyelids.

Ice Pack test

- simple noninvasive bedside test *to evaluate ptosis*; lack of side effects.

- ice placed in surgical glove is placed lightly over eyelid.
- cooling of eyelid below 29° C is accomplished within 2 minutes.
- ptosis improves in ≥ 80% patients; test is at least as sensitive as edrophonium test.
- positive ice pack test strongly suggests ocular myasthenia gravis and alleviates any need for Tensilon test.
- in bilateral ptosis, more affected eye should be tested.
- normal individuals show no change in palpebral fissure.

Detection of AChR-ab in serum (commercially available test)

- sensitivity 50-70% (in ocular myasthenia) ÷ 88% (in generalized disease); only 25% in remission.
- specificity > 99.9% (definite diagnosis if positive; negative result does not exclude MG).
- titer does not match severity of symptoms (normal titer does not exclude diagnosis – so sensitivity is < 100%).

Repetitive nerve stimulation → **CMAP decrement** see p. D22 >>

- test at least 3 nerve-muscle systems (median-thenar; ulnar-hypothenar; accessory-trapezius).
- sensitivity ≈ 75% percent; virtually always present in generalized MG (clinically weak muscles are more likely to demonstrate decremental response).
- for patient comfort, *first perform on distal muscle* (if negative → proximal muscles).
- single dose of EDROPHONIUM may prevent or diminish this decremental reaction.

Single fiber EMG - progressively fewer fibers respond to arrival of nerve impulse → **increased "jitter", blockings** see p. D20 >>

- sensitivity – 80% (in ocular MG) ÷ 100% (in moderate generalized MG).
most sensitive test for MG!!!
- in 9% cases, this is only abnormal test.

AChR-ab + repetitive stimulation + single fiber EMG identifies all MG cases.

Microelectrode study - ↓ amplitude of miniature end-plate potentials (to ≈ 20% of normal).

Standard EMG is normal (occasionally shows myopathic pattern, and never denervation).

Pulmonary function tests (for respiratory muscle weakness); include *inspiratory & expiratory pressures* - may be abnormal before overt symptoms.

Search for Associated Conditions – tests indicated in all patients:

1. **Chest CT / MRI** - to screen for *thymoma / thymic hyperplasia*.
– detectable thymic tissue in patient > 40 yrs. - suspicion of thymoma.
2. **Thyroid function tests** (*hyperthyroidism* occurs in 3-8% MG patients!)
3. Blood tests for **rheumatoid factor & antinuclear antibodies** – for associated *other autoimmune disorders*.
4. **Head MRI** – for ocular myasthenia

DIFFERENTIAL DIAGNOSIS

- 1) **other disorders of neuromuscular transmission** (congenital myasthenic syndromes, botulism, Lambert-Eaton myasthenic syndrome)
- 2) **neurogenic weakness** (e.g. cranial nerve abnormalities)
- 3) chronic **progressive external ophthalmoplegia**
- 4) **drug-induced myasthenia, organophosphate intoxication**
- 5) **hyperthyroidism**, Graves' disease – occurs in 3-8% MG patients
- 6) **psychogenic weakness / fatigue** (neurasthenia)

TREATMENT

Lifelong immunomodulating therapy is often required!!!

SYMPTOMATIC TREATMENT

Acetylcholinesterase inhibitors - *symptomatic treatment* in all clinical forms *throughout disease course*.

- should be given as soon as diagnosis is made.
- three equally effective drugs - **NEOSTIGMINE****, **PYRIDOSTIGMINE***, **AMBENONIUM**.
*preferred - less severe GI side effects, longer duration of action (3-4 h).
**available for injections (1.0 mg is equivalent to 60 mg pyridostigmine).
- usual starting dose of pyridostigmine is 60 mg q4h orally while patient is awake;
 - *difficulty eating* – take doses 30 min before meal.
 - *difficulty on waking in morning* - give **prolonged-release** 180-mg tablet at bedtime (prolonged tablets should never be used for daytime because of variable absorption).
 - *muscarinic symptoms* - **ATROPINE** (0.4-0.6 mg) or **PROPANTHELINE** (15 mg) with each dose of pyridostigmine; **LOPERAMIDE** for diarrhea.
- **cholinergic toxicity** (transient weakness + muscarinic effects) can be difficult to distinguish from impending **myasthenic crisis** (no muscarinic effects + response to edrophonium in 1-mg increments); H: admission to ICU for transient cessation of cholinesterase inhibition.

N.B. *cholinergic drugs do not return function to fully normal* (e.g. some diplopia almost always persists)!

Plasma exchange (daily 2 liters), **intravenous pooled Ig** (400 mg/kg for 5 days; mechanism of action is not known) - effective short-term treatments (e.g. for MG crisis, stabilization prior to thymectomy).

PATHOGENETIC TREATMENT

THYMECTOMY - indicated for:

- GENERALIZED MYASTHENIA
 - THYMOMA (absolute indication at any age) - possibility of local tumor spread
- not usually recommended for pure OCULAR* myasthenia.
 - *thymectomy is so safe that it might be considered for truly disabling ocular myasthenia.
 - preoperative plasmapheresis improves care.
 - transsternal approach** is preferred; **transcervical approach** (by indirect mediastinoscopy - cosmetically more appealing) → higher risk of residual thymus tissue.
 - beneficial effects are delayed for months and occur in 1st year (but may be seen as late as 5 years from surgery) - 85% patients without thymoma show improvement / remission.

Corticosteroids - mainstay of immunotherapy (if patient is still seriously disabled after thymectomy).

- start with 40-60 mg **PREDNISONE** /d → taper to alternate-day dosing (e.g. 50-100 mg every other day).
 - with such dosage *initial exacerbation of weakness* occurs in many - hospitalization is advised!
- equally satisfactory response without exacerbation can be seen with lower starting dosage, but it takes longer time (e.g. with dose 25-40 mg, benefit may be seen in 2 to 3 months).
- 70-80% patients have complete remission.

Cytotoxic therapies – indicated in:

- patients who do not improve after 6 months of PREDNISONE.
 - patients who are not able to achieve sufficiently low doses of PREDNISONE.
 - significant steroid side effects.
- AZATHIOPRINE** - as adjunct to prednisone (some patients respond well enough to discontinue prednisone); earliest time for improvement onset is 3 months.
 - CYCLOSPORINE** is more effective & more toxic.
 - CYCLOPHOSPHAMIDE** is used occasionally for patients refractory to other drugs.

MYASTHENIC CRISIS

- principles of treatment are those of respiratory failure in general.

- cholinergic drug** is discontinued* once endotracheal tube has been placed and positive pressure respiration started.
 - * avoids uncertainties about overdosage (cholinergic crisis) + avoids cholinergic stimulation of pulmonary secretions.

N.B. *overmedication of myasthenic crisis can convert it into cholinergic crisis!!!*

- plasma exchange / intravenous Ig** may shorten crisis duration.
- vigorous infection treatment (myasthenic patient with fever and early infection should be treated like other immunocompromised patients!!!).
- crisis spontaneously subsides in few days or weeks.
- pulmonary intensive care is now so good that crisis is almost never fatal.

PREGNANCY

- course of MG may variably change during pregnancy (some women worsen).
- MG has no deleterious effect on uterine smooth muscle.
- frequent emesis** may interfere with absorption of any oral medication.
- growing fetus** may further restrict diaphragmatic movement.
- MgSO₄** can exacerbate weakness.
- cholinesterase inhibitors can be used (do not provoke uterine contractions).
- significant weakness may be adequately controlled with cholinesterase inhibitors and plasmapheresis.
- avoid immunosuppressive drugs.

PROGNOSIS

- myasthenia is not steadily progressive disease* - general nature is established within months after first symptoms:
 - if myasthenia is restricted to ocular muscles for 2-3 years, it will remain restricted;
 - spontaneous remission / progressive deterioration is more likely in first 2-3 years;
 - remissions are rarely complete or permanent.
- before 1958 - 1/3 patients died, 1/3 failed to improve, 1/3 improved spontaneously.
- currently - **mortality is zero** - most patients lead normal lives.

BIBLIOGRAPHY for ch. "Neuromuscular, Muscular Disorders" → follow this [LINK >>](#)