**Myasthenia Gravis**

Last updated: September 5, 2017

**CLASSIFICATION OF NEUROMUSCULAR TRANSMISSION DISORDERS**

1. Autoimmune: 1) myasthenia gravis

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

**II. Congenital** see p. Mus2 >>

1. Presynaptic defects 1) ACh reuptake / packaging defect

2. Postsynaptic defect 1) congenital end-plate AChE deficiency

3. Post-synaptic defects: increased response to ACh

   1. slow-channel syndromes

   2. Postsynaptic defective: decreased response to ACh

   1. low-affinity fast channel syndromes

   2. mode-switching kinetics of ACh receptors

3. Partially characterized syndromes

   1. congenital myasthenic syndrome resembling LEMS

   2. familial limb-girdle myasthenia

   3. benign congenital myasthenic syndrome with facial malformations

**III. Toxic**

1. Drug-induced: 1) D-penicillamine (***)) - induces auto-AChR antibody production → clinical manifestations similar to typical MG; antibodies disappear when drug is discontinued.

2. curare

3. AChE inhibitors: (esp. neomycin) - decrease both presynaptic ACh release (antagonism to Ca++) and sensitivity of postsynaptic membrane to ACh (curare-like effect);

4. calcium infusion, cholinesterase inhibitors, aminopyridines

5. Ca-channel blockers

2. Organophosphate intoxication see p. A35 >>

3. Venoms & toxins: 1) botulinum toxin see p. 227 (5-7) >>

2) coral snake, scorpion, black widow spider see p. 2780 >>

3) 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.

1. 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 autotrogen → trigger autoimmune reaction within thymus.

2. Anti-acetylcholine receptor antibodies (anti-AChR) - key to ACh receptor damage!; antibodies react with multiple determinants on AChR.

   1. destruction of receptors (complement-mediated lysis of junctional folds at motor end-plate)

   2. acceleration of normal degradative processes (e.g. cross-linking of receptors by Ab → endocytosis, lysosomal hydrolysis).

   3. 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 postynaptic clefts

• widening of synaptic space

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* * *
MUS1(2) - MYASTHENIA GRAVIS

**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.
  - 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.
- **oopharyngeal 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!

**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).

**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".

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

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!

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MYASTHENIA GRAVIS

Clinical Manifestations

- 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!

Transient neonatal MG - Myasthenic syndrome from passive transfer of maternal AChR antibodies (occurs to ≈ 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).

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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) Reading standard passage (measure time it takes for speech to become mushy and dysarthric)
d) Squats
f) 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.

Placero 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 25°C is accomplished within 2 minutes.
Corticosteroids

Plasma exchangepersists!

Acetylcholinesterase inhibitors

Search for Associated Conditions

Pulmonary function tests

Standard EMG

Microelectrode study - amplitudes of miniature end-plate potentials (to > 20% of normal).

Pathogenic TREATMENT

Myasthenia Gravis

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.

equally severe in the side effects, longer duration of action (3-4 h).

detectable in thymic tissue in up to 80% of cases; symptoms of thymoma.

Thymectomy is so safe that it might be considered for truly disabling ocular myasthenia.

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:

1) thymic hyperplasia
2) thymoma
3) congenital myasthenic syndromes, botulism, Eaton-Lambert myasthenic syndrome
4) neostigmine**, pyridostigmine**, edrophonium
5) diagnostic:
   - edrophonium test
   - standard EMG
   - ocular myasthenia
6) thymectomy
7) thymoma / thymic hyperplasia
8) chest CT / MRI

H: admission to ICU for transient cessation of cholinesterase inhibition.

for MG crisis, stabilization prior to thymectomy.

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

Muscle weakness / fatigue (neurasthenia)

Towards A New Treatment

Detection of AChR

Repetitive nerve stimulation

Simple fiber EMG:

In 9% cases, this is only abnormal test.

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

Tensilon test.

Tensilon test.

D: 1) thymoma / thymic hyperplasia
2) Graves' disease
3) thymectomy
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MYASTHENIA GRAVIS

Mus1 (5)

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 vary 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 >>

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