Myasthenia Gravis
Diagnosis and management

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Myasthenia Gravis

- A neuromuscular disorder characterized by weakness and fatigability of skeletal muscles
- The underlying defect: A decrease in the number of available acetylcholine receptors (AChRs) at neuromuscular junctions due to an antibody-mediated autoimmune attack.
- Preferable name: Autoimmune myasthenia
- Treatment now available for MG is highly effective, although a specific cure has remained elusive

Harrison 2001
Myasthenia Gravis: Epidemiology

- In the USA, the prevalence is 14.2 cases/1 million people
- Appear at any age
- In women, the onset between 20 and 40 years of age
- Among men, at 40-60
- Overall, women are affected more frequently than men, in a ratio of approximately 3:2.
- Familial occurrence is rare
Myasthenia Gravis: Epidemiology

- **Annual incidence:** 0.25-2/100,000
- **Spontaneous remission:** 20%
- **Without treatment, 20-30% die in 10 years**
- **MG is a heterogeneous disorder**
  - 90% no specific cause
  - Genetic predisposing factor: HLA association; HLA-BW46 in Chinese ocular MG
  - Thymic tumor: 10%

Lancet 2001
Myasthenia Gravis: Pathophysiology

- Autoimmune response mediated by specific anti-AChR antibodies
- Pathogenic antibodies are IgG and are T cell dependent, Sensitized T-helper cells
- Autoimmune response, the thymus appears to play a role
- 75%: thymus abnormal
  - 65%: hyperplasia
  - 10%: thymoma, rarely in children; often (20%) in patients aged 30-40 years

NEJM 1994; Neurologic clinics 1994; BJA 2002; JOAO 2004
Myasthenia Gravis: Pathophysiology

- Postsynaptic nicotinic acetylcholine receptor: reduce the number of functional receptors
  - loss of structural integrity of receptors: by Ab and complement
    - Morphologic changes of simplification of the pattern of postsynaptic membrane folding:
    - An increased gap between the nerve terminal and the post synaptic muscle membrane
  - Blockade
  - ↑ Turnover of AchRs: Accelerated degradation of acetylcholine receptors

NEJM 1994, 1997; Neurologic clinics 1997; BJA 2002; JOAO 2004
Myasthenia Gravis: Pathophysiology

- Reduced AchR density
  - results in end-plate potentials of diminished amplitude which fail to trigger action potentials in some fibers causing a failure in initiation of muscle fibre contraction - power of the whole muscle is reduced

- The amount of ACh released per impulse normally declines on repeated activity (termed presynaptic rundown)
Myasthenia Gravis: Clinical Features

- Fluctuating weakness of voluntary muscles (fatigability)
  - Worsen after exertion and improve with rest
- No abnormality of cognition, sensory function, or autonomic function
Myasthenia Gravis: Clinical Features

• Initial symptoms involve the ocular muscles in 60%
• All patients will have ocular involvement within 2 years of disease onset
Myasthenia Gravis: Clinical Features

• **Ocular manifestations**
  - Ptosis, uni- or bilateral is very common and may occur while patients reading, or during long period of driving
Ptosis
Ptosis and impaired orbicularis oculi
Myasthenia Gravis: Clinical Features

• **Ocular manifestations**
  - Diplopia: Extraocular muscle weakness may also present asymmetrically
EOM
Myasthenia Gravis: Clinical Features

• **Bulbar involvements**
  - Difficulty chewing, speaking, or swallowing: initial symptoms in 17% of patients
    • Fatigability and weakness during mastication
    • Unable to keep jaw closed after chewing
    • Slurred and nasal speech
Nasal voice
Myasthenia Gravis: Clinical Features

• **Limb muscles weakness:**
  - Initial symptoms in fewer than 10%
  - Upper extremities weakness is more common than lower extremities, asymmetrical
  - Involve proximal muscles than distal
  - Involve neck muscles: neck flexion weaker than neck extension
Myasthenia Gravis: Clinical Features

• Respiratory insufficiency
  - The initial presentation is rare
  - Occurring precipitously in a patient with recent worsening of symptoms
Myasthenia Gravis:

- Precipitating events
  - Systemic illness
  - Viral upper respiratory tract infection
  - Receiving general anesthesia
  - Receiving neuromuscular blocking agents
  - Pregnancy, menstrual cycle
  - Extreme heat
  - Stress
Medications induce or exacerbate MG

- **Definite association**
  - Penicillamine, corticosteroids

- **Probable association**
  - Anticonvulsants (phenytoin);
  - Anti-infectives (aminoglycosides, ciprofloxacin);
  - Beta-adrenergic receptor-blocking drugs;
  - Lithium carbonate;
  - Procainamide HCl
Medications induce or exacerbate MG

- Possible association
  - Anticholinergic drugs (artane);
  - Anti-infectives (ampicillin, imipenem, erythromycin, pyrantel);
  - Cardiovascular drugs (propafenone HCl, verapamil);
  - Cholroquine phosphate;
  - Neuromuscular-blocking drugs (vecuronium, succinylcholine);
  - Ocular drugs (proparacaine HCl, tropicamide);
  - Miscellaneous drugs (acetazolamide, carnitine, interferon alfa, transdermal nicotine)
MG: Classification

- **Osserman Classification**
  
  **Grade I:** involve focal disease (restricted to ocular muscle)
  
  **Grade II:** generalized disease
    
    IIa: mild
    
    IIb: moderate
  
  **Grade III:** severe generalized disease
  
  **Grade IV:** a crisis with life-threatening impairment of respiration

NEJM 1994
MG: Classification

- MG Foundation of America Clinical Classification

**Grade I:** Any ocular muscle weakness

**Grade II:** Mild weakness affecting other than ocular muscles
  - IIa: limb and/or axial weakness; less oropharyngeal involvement
  - IIb: oropharyngeal and/or respiratory weakness

**Grade III:** Moderate weakness affecting other than ocular muscles (a,b)

**Grade IV:** Severe weakness affecting other than ocular muscles (a,b)

**Grade V:** Defined by tracheal intubation

BMC musculoskeletal disorders 2004
Myasthenia Gravis: Clinical Features

• Clinical course
  – Most progress if no treatment
  – 66%: maximum weakness during the first year
  – Spontaneous improvement occurs early in the course
• Ocular type
  • 66% develop generalized disease in one year
  • 14% not progress after 2 years

Neurologic clinics 1997
Myasthenia Gravis: Clinical Features

• Clinical course
  - Active stage (5-7 y): fluctuation and progression for several years: thymectomy benefit
  - Inactive stage (10 y): fluctuation while intercurrent illness or other identifiable factors (drugs, pregnancy): thymectomy no benefit
  - Burnt-out stage: after 15-20 years; fixed weakness with atrophic muscles

Neurologic clinics 1997
Myasthenia Gravis: Diagnosis

• Clinical manifestations: chronic intermittent muscle weakness; fatigability

• Provocative test:
  – Physiologic:
    • Look up for several minutes; counting aloud to 100; repetitively testing the proximal muscles
  – Pharmacologic:
    • Curare test: to demonstrate generalized MG

(Neurologic clinics 1994)
Enhanced ptosis
Provocative test
Myasthenia Gravis: Diagnosis

• Pharmacological tests
Myasthenia Gravis: Diagnosis

• Tensilon test:
  - Using edrophonium chloride: short acting acetylcholinesterase inhibitor
  - 10 mg of edrophonium (0.15-0.2 mg/kg) used
    - A small test dose (2 mg) iv; after 1 min. no improvement and side effect, the remainder given slowly
  - The effect of edrophonium: in 30 sec. and last fewer than 10 min.
Myasthenia Gravis: Diagnosis

• Tensilon test:
  - Having false positive (LEMS, MND, MS, tumor, DM cranial neuropathy, mitochondrial myopathy) and false negative
  - Side effects: N/V, tearing, salivation, muscle fasciculation, abdominal cramp, bronchospasm, bradycardia, cardiac arrest
  - Cardiac monitoring
  - Atropine available: 0.6 mg IV
Myasthenia Gravis: Diagnosis

- Neostigmine test
  - Longer acting
  - 1.5 mg IM or 0.5 mg IV
  - Action begins in 15-30 mins and lasts up to 3 hours

Neurologic clinics 1997
Myasthenia Gravis: Diagnosis

- Electrophysiological tests
Myasthenia Gravis: Diagnosis

• Repetitive nerve stimulation
  - 3 Hz is used for 60 sec.
  - A greater than 15% decrement of the amplitude of CMAP is considered positive
  - The yield of the test increases if proximal nerves are stimulated
  - May be abnormal in ALS, peripheral neuropathy, radiculopathy, MS

Neurologic clinic 1997; JOAO 2004
Myasthenia Gravis: Diagnosis

- **SFEMG**
  - Signals are recorded only from muscle fibers close to the recording surface of the needle electrode
  - *Measure the relative firing (action potentials)* of adjacent muscle fibers from the same motor unit during voluntary activity
  - The variation (time) in firing between these firing is called jitter (µsec)
Myasthenia Gravis: Diagnosis

• SFEMG
  - Normal jitter ranges from 10-50 μsec
  - Increased jitter is seen in MG (100 μsec or greater)
  - Neuromuscular block occurs as end-plate potentials fail to reach adequate threshold to generate action potential
  - Time for end-plate potential to reach the threshold for action potential generation is longer
Myasthenia Gravis: Diagnosis

- **SFEMG**
  - Most sensitive
  - Difficult to perform
  - Need experience of the EMGer
Myasthenia Gravis: Diagnosis

• SFEMG
  – May be abnormal (F+) in neuropathies, mitochondrial myopathies, nerve injury, anterior horn cell disorders
  – May have false negatives in mild affected, or on immunosuppressive treatment
Myasthenia Gravis: Diagnosis

• Immunological tests
Myasthenia Gravis: Diagnosis

- Antibody to acetylcholine receptor
  - Present in almost all patients with thymoma
  - Absent in ocular type
  - Absent in 20% of generalized MG

JOAO 2004
Myasthenia Gravis: Diagnosis

- Sleep test and rest test
  - Rest test for ocular (ptosis) type (AAO 2002)
Myasthenia Gravis: Diagnosis

• **Ice test**
  - Muscles in MG function better in a lower temperature
    • Decreased acetylcholinesterase activity
    • Increased depolarizing effect of acetylcholine at motor endplates
  - Applying ice pack on the eyelid during closing for 2 mins.
  - Positive: lid fissure increases by 2 mm or more from baseline *(Curr Opin Neurol 2001)*
Before ice test

After ice test

ice test

rest test
Myasthenia Gravis: Diagnosis

**Ocular MG**
- Tensilon test
- RNS (EOM)
- AchR-Ab:
- SFEMG (gold standard)
  (orbicularis oculi and frontalis)
- Sleep test simple and safe but takes time (30 mins.) and place
- Rest test
- Ice test for ptosis:

**Sensitive**
- 86% (F+) (side effect)
- 48% (F+) (invasive)
- 45-65% (rare F+) (expensive)
- 95% (F+) (pain)
- 50% no F+ (AAO 2000)
- 95% no F+ (Curr Opin Neurol 2001)

Neurologic clinics 1997; J med Assoc Thai 2001; JOAO 2004
Myasthenia Gravis: Diagnosis

**Generalized MG**
- Tensilon test
- RNS
- AchR-Ab:
- SFEMG

**Sensitive**
- 95
- higher than in ocular MG (F+)
- 90% (rare F+)
- 100% (F+)
Myasthenia Gravis: Differential Diagnosis

• From generalized MG
  - ALS: Asymmetric muscle weakness and atrophy
  - Other NMJ disorders
    • Lambert Eaton myasthenic syndrome
    • Congenital myasthenic syndrome
    • Neurotoxins
      - Botulism: Generalized limb weakness
      - Venoms: snakes, scorpions, spiders
  - Inflammatory demyelinating diseases
    • GBS: ascending limb weakness
    • Miller Fisher syndrome
    • Chronic
  - Inflammatory muscle disorders: Painful proximal symmetric limb weakness; no ocular involvement
  - Periodic paralysis: Intermittent generalized muscle weakness; no ocular involvement

JOAO 2004
Myasthenia Gravis: Differential Diagnosis

- **From Bulbar Myasthenia**
  - Brainstem stroke
  - Pseudobulbar palsy

- **From Ocular Myasthenia**
  - *MS*: UMN; bilateral internuclear ophthalmoplegia
  - Mitochondrial cytopathy (*chronic progressive external ophthalmoplegia*)
  - Oculopharyngeal muscular dystrophy
  - Thyroid ophthalmopathy

JOAO 2004
Myasthenia Gravis

- **Management**
  - Diagnosis
  - Searching for associated diseases
  - Treatments
  - Avoiding and treating precipitating factors
Myasthenia Gravis:

- Associated diseases
  - Thymoma
  - Nonthymus neoplasm in 3%
  - DM in 7%
  - Thyroid disease in 6%
  - Rheumatoid arthritis in fewer than 2%
  - Pernicious anemia, pancytopenia, thrombocytopenia and SLE in fewer than 1%
  - Polymyositis, dermatomyositis, psoriasis, scleroderma (BJA 2002)
Recommended laboratory tests or procedures

Magnetic resonance imaging or computed tomography of mediastinum
Tests for lupus erythematous: antinuclear antibody, rheumatoid factor, antithyroid antibodies
Thyroid-function tests
Tuberculin test
Chest radiography
Fasting blood glucose measurement
Pulmonary-function tests
Bone densitometry in older patients
Myasthenia Gravis: Treatment

• The goal is to achieve remission
  – Symptoms free and taking no medication
    • By increased neuromuscular transmission
    • Reduce autoimmunity

• Others: having a normal quality of life even if some signs remaining and cholinesterase inhibitors taking

JOAO 2004

Neurologic clinics 1994
Myasthenia Gravis: Treatment

• No single treatment is ideal for all patients
  – Each patient needs an individual plan
  – Treatment may have to be changed time to time

• Obtain the best response while keeping the risk and side effects as low as possible
**Ocular MG**

15% never spread out *(Neurologic clinics 1994)*  
Spontaneous remission *(JOAO 2004)*  
Good response to pyridostigmine

**If spread out, in 2 y - thymectomy**  
If not response to pyridostigmine  
Add prednisolone: 10-30 mg/d for 2-3 months or incrementing dose; after maximum benefit slow tapering  
If not effective, getting along with dysfunction; maneuvers and simple mechanical devices used  
Or high-dose daily prednisolone + azathioprine or even thymectomy  
If ptosis is fixed; surgical shortening of the eyelid to be considered *(JOAO 2004; Neurologic clinics 1994)*

*Harrison 2001*
**Generalized MG**

**No bulbar involvement: remission**

**Thymectomy: Indications**

- Thymoma
- Those are medically stable and aged 60 years or younger (puberty) (Neurologic clinics 1994; NEJM 1994)

35% have clinical remission; 50%: improvement (Neurologic clinics 1994; NEJM 1994)

**Clinical improvement in 6-12 m. after** (JOAO 2004)

1-2 years after surgery, immunosuppressive therapy to be considered if functional limitations (Neurologic clinics 1994)

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**Establish diagnosis unequivocally (see Table 362-1)**

**Search for associated conditions (see Table 362-2)**

- **Ocular only**
- **Generalized**
- **Crisis**

**MRI of head** (if positive, reassess)

**Anticholinesterase (pyridostigmine)**

- **Evaluate for thymectomy** (indications: thymoma or generalized MG; evaluate surgical risk, FVC)
  - **Good risk** (good FVC)
  - **Poor risk** (low FVC)

**Plasmapheresis or intravenous Ig**

**If unsatisfactory**

- **Thymectomy**

**Immunosuppression**

1. Prednisone (unless contraindicated): increase dose to improvement or 50 mg/d
2. Add second agent: (see text)
3. Switch prednisone gradually to alternate-day regimen
4. If improved, slowly taper of immunosuppressive agents
5. Maintain at minimum effective doses of all drugs (usually required indefinitely)

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Harrison 2001
Myasthenia Gravis: Treatment

• Generalized MG with onset in childhood
  – More benign than in adult; less associated with thymoma, and remit spontaneously
  – ChE inhibitors only apply otherwise disabling signs exist, steroid will be recommended
  – Thymectomy if not respond to prednisolone
Myasthenia Gravis: Treatment

• Generalized MG with late-life onset
  – Less likely to improve after thymectomy
  – Surgery carries greater risk
  – Treatment with ChE inhibitors
  – Severe cases worth to use prednisolone and azathioprine
**Myasthenic crisis**

Sudden worsening of respiratory function ± profound muscle weakness

- Negative inspiratory force of less than -20 cmH₂O
- Tidal volume of less than 4mL/kg
- Force vital capacity < 15 mL/kg (normal 50-60 in female, 70 in male)

**Neurologic emergency**

**Causes:** concurrent infection, medications, drug withdrawal (JOAO 2004)

**DDx from cholinergic crisis:** clinical and tensilon test

**Management**

- Stop every medications
- Assisted ventilation
- Treating pff.
- If not improve
- IVIg or plasmapheresis (JOAO 2004)
Myasthenia Gravis: Treatment

- Acetylcholinesterase inhibitors
  - Symptomatic improvement for a period of time
  - Initial therapy
  - Onset in 30 mins.
  - Peak effect at 2 hrs.
  - Half life approximately 4 hrs.
  - Lower risks and side effects than others: abdominal cramping, n/v increased salivation, and diarrhea

NEJM 1994; Neurologic clinics 1997
Myasthenia Gravis: Treatment

• Acetylcholinesterase inhibitors
  – Benefit most patients but incomplete after weeks or months treatment; require further therapeutic measures
  – No fixed dosage schedule suits all patients
  – The need for ChE inhibitors varies from day-to-day and during the same day
  – A sustained-release preparation used only at bedtime

NEJM 1994; Neurologic clinics 1997
Myasthenia Gravis: Treatment

- **Acetylcholinesterase inhibitors**
  - Pyridostigmine bromide is used
    - **Starting with 30 mg every 4 to 6 hours; titrated depending on clinical symptoms and patient tolerability**
    - **Cholinergic crisis if too much of this medication (max. Dose = 450 mg/d)**
    - **Lowest amount with maximum benefit**
    - **30 minutes before eating for patients with oropharyngeal weakness**

60 mg pyridostigmine = 15 mg neostigmine
Dose im form (2 ml = 5 mg) = 1/30 of oral dose

Neurologic clinics 1997; JOAO 2004
Myasthenia Gravis: Treatment

- Immunosuppressive therapy
  - Indications
    - Not adequately controlled by anticholinesterase drugs and sufficiently distressing to outweigh the risks of possible side effects of immunosuppressive drugs in ocular MG
    - Severe but not ready to have surgery
    - Not improve after thymectomy: may delay 3 y after surgery
    - Crisis not respond to plasma exchange or IVIg
    - In inactive and burnt-out stage

NEJM 1994
Myasthenia Gravis: Treatment

• **Immunosuppressive therapy**
  – Steroid: reduce AchR-Ab titer
    • Most use
    • Typical dosage is 1 mg/kg daily as a single oral dose
Myasthenia Gravis: Treatment

• **Immunosuppressive therapy**
  
  – **Steroid:**
    
    • Start on a low dose and gradually titrate the dose up
      
      – 5 mg daily and increased by 5 mg every 4-7 days until clinical benefit achievement;
      
      – Remain on this dose for 2 mo.
      
      – Then, switch to alternate-day therapy
      
      – Once, the condition stable, taperd downward by 5 mg every month
      
      – Patients may relapse after tapered off
      
      – Most patients require long-term low-dose

JOAO 2004
Myasthenia Gravis: Treatment

• **Immunosuppressive therapy**
  - **Steroid:**
    - Have benefit in 6 to 8 weeks after initiation
    - Adverse effects: acne, bruising, cataracts, electrolyte imbalance, hirsutism, hyperglycemia, HT, avascular necrosis of the femoral head, obesity, osteoporosis, myopathy
  - **High-dose daily prednisolone (60-80 mg; 1-1.5 mg/kg/d)**
    - Rapid improvement
    - Institution in the first 2-3 weeks
    - Exacerbation of weakness managed by ChE-inhibitors or plasmapheresis

JOAO 2004
Myasthenia Gravis: Treatment

- **Immunosuppressive therapy**
  - **Azathioprine:**
    - Most use
    - To reduce adverse steroid effects
    - To whom steroids are contraindicated
    - Starting dose is 50 mg daily for the first week, then increased 50 mg every week
    - Titrating up to a maximum of 2-3 mg/kg/d in two or three divided doses

NEJM 1994; JOAO 2004
Myasthenia Gravis: Treatment

- **Immunosuppressive therapy**
  - **Azathioprine:**
    - Clinical benefit shown in 4-6 months or longer (max effect 12-24 mos.)
    - Once improvement; maintain as long as 4-6 mos.
    - Adverse effects: neutropenia, hepatotoxicity; increase risk of malignancy; idiosyncratic influenza-like reaction

NEJM 1994; JOAO 2004
Myasthenia Gravis: Treatment

- Plasmapheresis (plasma exchange) and IVIg: Indications
  - Severe MG and exacerbations
  - Preparing for thymectomy or post operative period
  - Covering period before immunosuppressive therapy becomes fully active
Myasthenia Gravis: Treatment

• Plasmapheresis (plasma exchange): double filtration plasma exchange and immunoadsorption plasmaphoresis
  - Undergoing a 2-week course of 5-6 exchanges (1 plasma volume = 40-50 ml/kg; 2-3 liters each)
  - Effective but transient in its response: Improvement in the third exchange and lasts 6-8 weeks
  - To remove the circulating immune complexes and AchR-Ab

NEJM 1994; Neurologic clinics 1997; JOAO 2004
Myasthenia Gravis: Treatment

- **Plasmapheresis (plasma exchange):**
  - Limitation: too small or fragile venous access
  - **Complications (catheters):** pneumothorax, bleeding, sepsis,
  - **Adverse effects:** hypotension, hypercoagulation, hypoalbuminemia, hypocalcemia, pulmonary embolism, arrhythmia, (frequent exchanges) anemia, low platelets

NEJM 1994; Neurologic clinics 1997; JOAO 2004
Myasthenia Gravis: Treatment

• IVIg therapy
  - Dose: 2 g/kg over 2-5 days
  - Clinical improvement in 1-2 weeks and lasts weeks to months

NEJM 1994; Neurologic clinics 1997; JOAO 2004
Myasthenia Gravis: Treatment

• IVIg: Side effect profile(some product contain IgA)
  – Allergic response: low grade fever, chills, myalgia
  – Diaphoresis, fluid overload, HT
  – Nausea, vomiting, rash, neutropenia
  – Headache, aseptic meningitis
  – Hyperviscosity: stroke, MI, ATN (most serious with compromised renal glomerular filtration; DM)

NEJM 1994; Neurologic clinics 1997; JOAO 2004
Myasthenia Gravis: Treatment

• IVIg: Side effect profile
  – Anaphylactic reaction: with IgA deficiency
  – Transmission with (very low)
    • Hepatitis
    • HIV

NEJM 1994; Neurologic clinics 1997; JOAO 2004
Myasthenia Gravis: Treatment

- **Surgical intervention**
  - Thymectomy
    - Acetylcholine-receptor antibody levels fall after thymectomy
    - **Mechanisms**
      - Eliminate a source of continued antigenic stimulation
      - Subside immune response
      - Correct a disturbance of immune regulation
Myasthenia Gravis: Treatment

- Surgical intervention
  - Thymectomy
    - Not recommended in
      - Patients with purely ocular MG
      - Childhood, some do not recommended because of less severity than in adults and common remission spontaneously
      - Late-onset

Neurologic clinics 1994; NEJM 1994
Effect of thymectomy on strength in myasthenia gravis

- Generalized: $P=0.06$
- Mild: ns
- Severe: $P<0.01$
- Female: $P=0.07$
- Male: $P=0.04$
- Young: ns
- Ocular: ns

Median percentage change in strength with thymectomy versus no thymectomy

Curr Opinion in Neurol 2001
Myasthenia Gravis: Treatment

• **Future treatment**
  - B-cell-directed approaches
    • B-cells produce pathogenic antibodies
  - T-cell-directed approaches
    • Pivotal role in autoimmune antibody response

NEJM 1994
Preparation for thymectomy
Preparation for thymectomy

- No emergency performance of thymectomy
- Preoperative preparation
  - Optimized strength and respiratory function
  - Avoided immunosuppressive agents (risk of infection)
  - If VC < 2 liters, plasmapheresis carried out
Preparation for thymectomy

- **Postoperative management**
  - May have weakness
    - Pain
    - Myasthenic crisis: ChE-Is withdrawal
    - Cholinergic crisis: disease improvement
    - May test with tensilon
  - ChE inhibitors may be reduced for a few days after thymectomy
  - Postoperative ChE medication given IV at a dose of $\frac{3}{4}$ of the preoperative requirement

NEJM 1994
Anaesthetic management in MG
Anaesthetic management in MG

- Local and regional anaesthesia should be employed
- GA requires meticulous pre and perioperative care
Anaesthetic management in MG

- Preoperative consideration: major elective surgical procedures
  - Admitted 48 hrs prior to surgery
  - Assessment and monitoring of respiratory (FVC) and bulbar function
  - Adjustment of ChE inhibitors and steroid if indicated
  - Chest physiotherapy started
  - Plasma exchange or IvIg if necessary

BJ A 2002
Anaesthetic management in MG

• Preoperative consideration: major elective surgical procedures
  – Sedative medications save if no respiratory compromise
  – Antimuscarinic agents helpful in reducing secretions
  – Steroid continued pre-operatively
  – Hydrocortisone administered on the day of surgery
  – ChE inhibitors withheld on the morning of surgery
Anaesthetic management in MG

- Induction and maintenance of anaesthesia
  - Routine monitoring
  - Supplement with invasive blood pressure measurement
  - Nasotracheal tube is preferred
  - Patients more sensitive to neuromuscular blocking agents
Anaesthetic management in MG

- Postoperative management
  - Nursed in a high dependency area and adequate analgesia provided: NSAID and parenteral opioids
  - ChE inhibitors restarted at a reduced dose in the immediate post-operative period and increasing if necessary
Seronegative MG
Seronegative MG

- Found in approximately 15% of patients with generalized MG
- Clinically indistinguishable from AchR-Ab-positive patients
- Be diagnosed using SFEMG
- 70% of SNMG patients have Ab to the muscle-specific receptor tyrosine kinase (MuSK)
Thymoma-associated MG

- Muscle antibodies predict the presence of thymoma
  - Ryanodine receptor Ab 70%
  - Titin Ab 95%
  - Both 70% 70%

Sens. Spec.

Curr Opin Neurol 2001
Late-onset MG
Late-onset MG

- Onset after the age of 50
- Male = female
- Most are nonthymoma
- More severe than early-onset MG
- Having circulating Ab to AchR but lower conc. than in early-onset MG
- Titin Ab associates with severity
- Difficulty in treatment

Archives of Neurol 1999
Late-onset MG

• Difficulty in treatment
  - Temporary response to ChE-inhibitors
  - Plasma exchange produces more complications
  - Thymectomy gives poorer results
  - Steroids give many complications
  - Treatment has to be tailored
MG and pregnancy
MG and pregnancy

- Pregnancy is associated with physiologic immunosuppression: depress leukocyte function
- Pregnancy aggravates MG
- So, clinical course unpredictable: rule of three
- One pregnancy not predict the course in subsequent pregnancies
- Exacerbation occur equally in all trimesters
- Therapeutic termination not demonstrate a consistent benefit in cases of first trimester exacerbation
MG and pregnancy

- Use minimal dosage of drugs
- ChE-inhibitors: increased uterine contraction
- Avoid other immunosuppressive drugs except steroid
- Normal delivery done
- No problems in breast feeding
- Transient neonatal myasthenia:
  - Found by 9-30%
  - Good response to ChE-inhibitors
  - Complete recovery in 2-4 mo
Myasthenic crisis
Myasthenic crisis

- Rarely at the initial presentation
- Known MG may reach a crisis
- Defined as sudden worsening of respiratory function and/or profound muscle weakness
- Being a neurologic emergency
- Causes: concurrent infection, medications, drug withdrawal
Myasthenic crisis

• **DDx from cholinergic crisis**
  - Abdominal pain, diarrhea, hypersecretion, pinpoint pupil
  - Negative or worse by tensilon test
    • Hold ChE-Is
    • Atropine 2 mg/hr
  - Tensilon test to consider the need of ChE-Is
Myasthenic crisis

• **Management**
  - Stop every medications
  - Assisted ventilation
    • Respiratory support required if
      - Negative inspiratory force of less than -20 cm H$_2$O
      - Tidal volume of less than 4mL/kg
      - Force vital capacity < 15 mL/kg (normal 50-60 [f], 70 [m])
  - Treating ppf.
  - Tensilon test to estimate ChE-Is requirement
  - If not improve
    • IVIg or plasmapheresis

JOAO 2004
<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms and Characteristics</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital myasthenic syndromes</td>
<td>Rare; early onset; not autoimmune disorders</td>
<td>Sophisticated electrophysiologic and immuno-cytochemical tests required for diagnosis</td>
</tr>
<tr>
<td>Drug-induced myasthenia</td>
<td>Triggered autoimmune myasthenia</td>
<td>Recovery within weeks after drug withdrawal</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Weakness in normal persons; exacerbation of myasthenia</td>
<td>Recovery after drug withdrawal</td>
</tr>
<tr>
<td>Curare, procainamide, quinines,</td>
<td>Weakness; fatigue; areflexia; 60 percent of cases associated with oat-cell cancer</td>
<td>Incremental response on repetitive nerve stimulation; antibody to calcium channels present</td>
</tr>
<tr>
<td>aminoglycosides</td>
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<tr>
<td>Lambert-Eaton syndrome</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Exacerbation of myasthenia; generalized weakness</td>
<td>Thyroid function abnormal</td>
</tr>
<tr>
<td>Graves' disease</td>
<td>Diplopia; exophthalmos</td>
<td>Thyroid-stimulating immunoglobulin present</td>
</tr>
<tr>
<td>Botulism</td>
<td>Generalized weakness; ophthalmoplegia</td>
<td>Incremental response on repetitive nerve stimulation; pupils are dilated</td>
</tr>
<tr>
<td>Progressive external ophthalmoplegia</td>
<td>Ptosis; diplopia; generalized weakness in some cases</td>
<td>Mitochondrial abnormalities</td>
</tr>
<tr>
<td>Intracranial mass compressing cranial</td>
<td>Ophthalmoplegia; cranial-nerve weakness</td>
<td>Abnormalities on computed tomography or magnetic resonance imaging</td>
</tr>
</tbody>
</table>
Differential diagnosis of myasthenia gravis

Generalised myasthenia
Other neuromuscular junction disorders:
  Lambert-Eaton myasthenic syndrome
  Congenital myasthenic syndromes
  Neurotoxins
  Botulism
  Venoms (snakes, scorpions, spiders)
Idiopathic inflammatory demyelinating polyradiculoneuropathies
  Acute (Guillain-Barré)-motor type
  Miller Fisher syndrome
  Chronic
  Many myopathies (idiopathic inflammatory, metabolic, dystrophies [rarely])
Bulbar myasthenia
  Brain stem stroke
  Motor-neurone disease (pseudobulbar palsy)
Ocular myasthenia
  Mitochondrial cytopathy (chronic progressive external ophthalmoplegia)
  Oculopharyngeal muscular dystrophy
  Thyroid ophthalmopathy
  Other causes of ptosis eg, contact-lens syndrome
  Brain-stem lesions
Myasthenia Gravis: Etiology

- **Immunopathogenesis**
  - MG is due to antibody-mediated processes
    - Ab is present
    - Ab interacts with the target antigen, acetylcholine receptor
    - Passive transfer reproduces disease feature
    - Immunization with the antigen produces a model disease
    - Reduction of antibody levels ameliorates the disease
Associated disorders

Disorders of the thymus: thymoma, hyperplasia
Other autoimmune disorders: thyroiditis, Graves’ disease, rheumatoid arthritis, lupus erythematosus, skin disorders, family history of autoimmune disorder
Disorders or circumstances that may exacerbate myasthenia gravis: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (aminoglycoside antibiotics, quinine, antiarrhythmic agents)
Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis
Myasthenia Gravis: Investigation

- For associated diseases
  - Autoimmune thyroiditis
  - Grave’s disease
  - SLE
  - CXR
  - CT chest scan: may miss small thymoma nodules

- Rule out genetic MG, Lambert-Eaton myasthenic syndrome
Myasthenia Gravis: Treatment

• Ocular MG
  - Good response to pyridostigmine
  - Starting with 30 mg every 4 to 6 hours
  - Titrated depending on clinical symptoms and patient tolerability
  - Adverse effects: abdominal cramping, increased salivation, nausea and diarrhea
  - Lowest amount, maximum benefit
  - Usually spontaneous remission
Myasthenia Gravis: Treatment

• Ocular MG
  - If spread out, will occur in 1-2 years after onset
  - So, closed follow up in the first 2 years is necessary to detect weakness early - thymectomy is recommended
Myasthenia Gravis: Treatment

- **Immunosuppressive therapy**
  - **Cyclosporine**
    - Inhibits T-cell activation
    - For failure to respond to combination therapy with prednisolone and azathioprine or intolerability of azathioprine
    - Starting dose: 25 mg twice daily
    - Titrating up to 3-6 mg/kg/d

NEJM 1994; JOAO 2004
Myasthenia Gravis: Treatment

- **Immunosuppressive therapy**
  - **Cyclosporine**
    - Combination therapy is more efficacious; reduced dosage and fewer adverse effects
    - Time to onset of effect: 2-12 wk
    - Time to maximal effect: 3-6 mo
    - Adverse effects: nephrotoxicity, HT

References:

NEJM 1994; J OAO 2004
Myasthenia Gravis: Treatment

- **Immunosuppressive therapy**
  - *Cyclophosphamide*
    - Used only others failed or not tolerated
    - **Starting dose:** 25 mg daily
    - Gradually increased up to 2-5 mg/kg/d
    - **Adverse effect:** hemorrhagic cystitis
Myasthenia Gravis: Treatment

- **Immunosuppressive therapy**
  - **Mycophenolate Mofetil**
    - Novel agent, benefit in transplantation medicine
    - Starting at 250 mg twice daily
    - Standard daily dosage: 1-2 g.
    - CBC checked every week for the first month; every two weeks for the next 6-8 weeks; and monthly thereafter
<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dose</th>
<th>Time to Onset of Effect</th>
<th>Time to Maximal Effect</th>
<th>Variables to Monitor Drug Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>15–20 mg/day gradually increasing to 60 mg/day and gradually changed to every other day</td>
<td>2–3 wk</td>
<td>3–6 mo</td>
<td>Weight</td>
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<td>Blood pressure</td>
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<td>Blood glucose</td>
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<td>Electrolytes</td>
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<td>Ophthalmic changes</td>
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<td></td>
<td>Bone density</td>
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<td>24-hr urinary calcium</td>
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<tr>
<td>Azathioprine</td>
<td>2–3 mg/kg/day (total dose, 100–250 mg/day)</td>
<td>3–12 mo</td>
<td>1–2 yr</td>
<td>White-cell count (&lt;3500/mm³)*</td>
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<tr>
<td>(Imuran)</td>
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<td>Differential count (&lt;1000 lymphocytes/mm³)*</td>
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<td></td>
<td></td>
<td>Mean corpuscular volume (&gt;100 μm³)*</td>
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<td></td>
<td>Platelets</td>
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<td>Liver function</td>
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<td>Blood pressure</td>
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<td>Serum creatinine</td>
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<td></td>
<td>Blood urea nitrogen</td>
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<td>Trough plasma cyclosporine level</td>
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<tr>
<td>Cyclosporine</td>
<td>5 mg/kg/day given in 2 divided doses (total dose, 125–200 mg twice daily)</td>
<td>2–12 wk</td>
<td>3–6 mo</td>
<td></td>
</tr>
</tbody>
</table>

*Values in parentheses are desirable levels.
Myasthenia Gravis: Treatment

• Generalized MG with onset in adult life
  – Mild: no symptoms related to breathing, coughing and swallowing
    • ChE inhibitors
    • If optimal dosage, thymectomy to be considered
    • Or additional prednisolone, if no remission in 1 year - thymectomy
  – Balbar involvement
    • ChE inhibitors + high dose prednisolone
    • Thymectomy to be considered
Myasthenia Gravis: Treatment

• **Generalized MG**
  – Combination with pyridostigmine and prednisolone
    • Starting with low dose
    • Starting with high dose: 1-1.5 mg/kg/d
      – Patients be worse
      – Should be admitted for 2 weeks
      – Clinical benefit in 1-2 months afterward
      – Adverse effects: acne, bruising, cataracts, electrolyte imbalance, hirsutism, hyperglycemia, HT, avascular necrosis of the femoral head, obesity, osteoporosis, myopathy

JOAO 2004
Myasthenia Gravis: Treatment

- Generalized MG with onset in childhood
  - Distinguishing acquired autoimmune MG from genetic MG – not respond to immunotherapy
  - Seronegative in acquired MG possible
  - Positive treatment response with plasma exchange, IvIg is autoimmune disease; but negative not excluded
  - More benign than in adult; less associated with thymoma, and remit spontaneously
  - ChE inhibitors only apply otherwise disabling signs exist, steroid will be recommended
  - Thymectomy if not respond to prednisolone

Neurologic clinics 1994
Myasthenia Gravis: Treatment

• Generalized MG
  – To reduce adverse steroid effects
  – Add with or switch to azathioprine
Myasthenia Gravis: Treatment

• **Ocular MG**
  
  - If not good response to pyridostigmine: not lead to normal social and working life
    
    • Add low dose prednisolone: 10-30 mg/d for 2-3 months or incrementing dose; after maximum benefit slow tapering
    
    • If not effective, getting along with dysfunction; maneuvers and simple mechanical devices used
    
    • Or high-dose daily prednisolone with/without azathioprine or even thymectomy
    
    • If ptosis is fixed; surgical shortening of the eyelid to be considered

JOAO 2004; Neurologic clinics 1994
Myasthenia Gravis: Pathophysiology

Diagram showing the involvement of acetylcholine receptors, MHC II, CD4+, costimulatory signals, T-cell receptor, B cells, and antibodies in the pathophysiology of Myasthenia Gravis.
Myasthenia Gravis: Pathophysiology

- Serum concentration of acetylcholine-receptor antibody not correlate with the clinical severity
- Degree of reduction of acetylcholine receptors correlate with the severity

NEJM 1997
Myasthenia Gravis: Pathophysiology

• Immunopathogenesis
  – Antibody negative MG
    • Found in 10-20%
    • Causes:
      – Too low an affinity for detection in the soluble assay system
      – Antibody may be directed at epitopes not present in the soluble acetylcholine-receptor extract

NEJM 1997
Medications induce or exacerbate MG

- **Anti-infective Agents**
  - Aminoglycosides
  - Kanamycin sulfate
  - Ampicillin sodium
  - Erythromycin
  - Ciprofloxacin HCL
  - Imipenem
  - Pyrantel
Medications induce or exacerbate MG

- **Cardiovascular Agents**
  - Propanolol HCL
  - Acebutolol HCL
  - Oxyprenolol HCL
  - Practolol
  - Timolol maleate (β blocker)
  - Quinidine (anti-arrhythmic)
  - Procainamide HCL (anti-arrhythmic)
  - Propafenone HCL (anti-arrhythmic)
Medications induce or exacerbate MG

- **Other Agents**
  - Chloroquine
  - Corticosteroids
  - D-penicillamine
  - Interferon α
  - Mydriatics
  - Phenytoin sodium
  - Trihexyphenidyl HCL (artane)
  - Trimethadione
  - Verapamil HCL
Pre ice test in ocular MG.

Post ice test positive in ocular MG.