Myasthenia Gravis
Diagnosis and management

Dr. Thanin Asawavichienjinda, M.D.

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

JOAO 2004

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

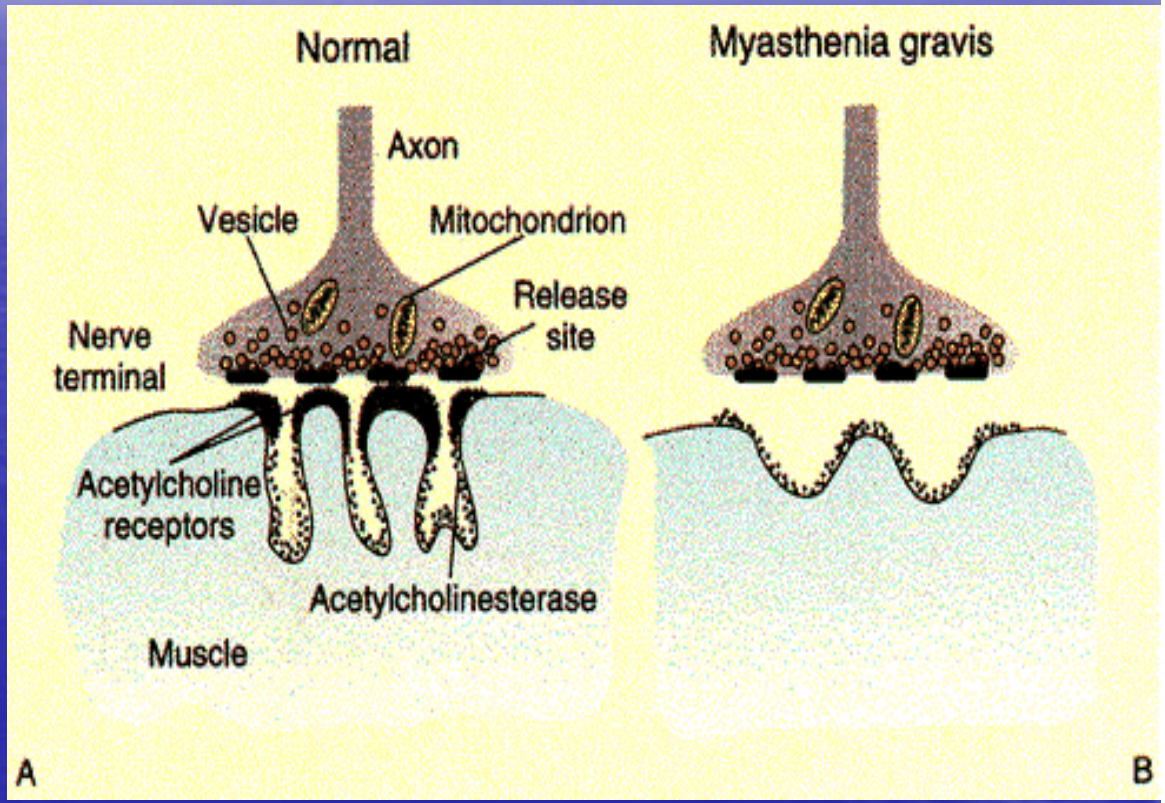
Myasthenia Gravis: Pathophysiology

- 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)

NEJM 1994; BJA 2002

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

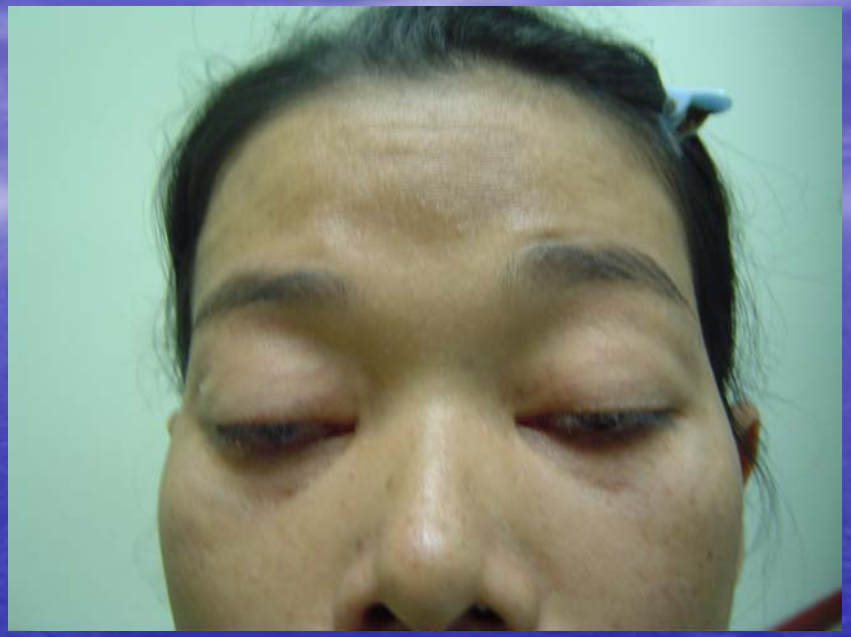
Myasthenia Gravis: Clinical Features

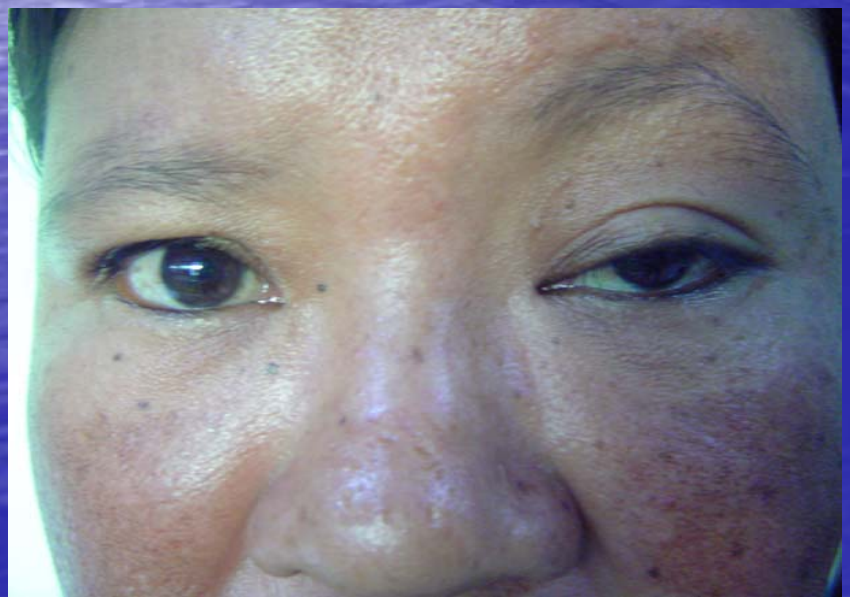
- Initial symptoms involve the ocular muscles in 60%
- All patients will have ocular involvement within 2 years of disease onset

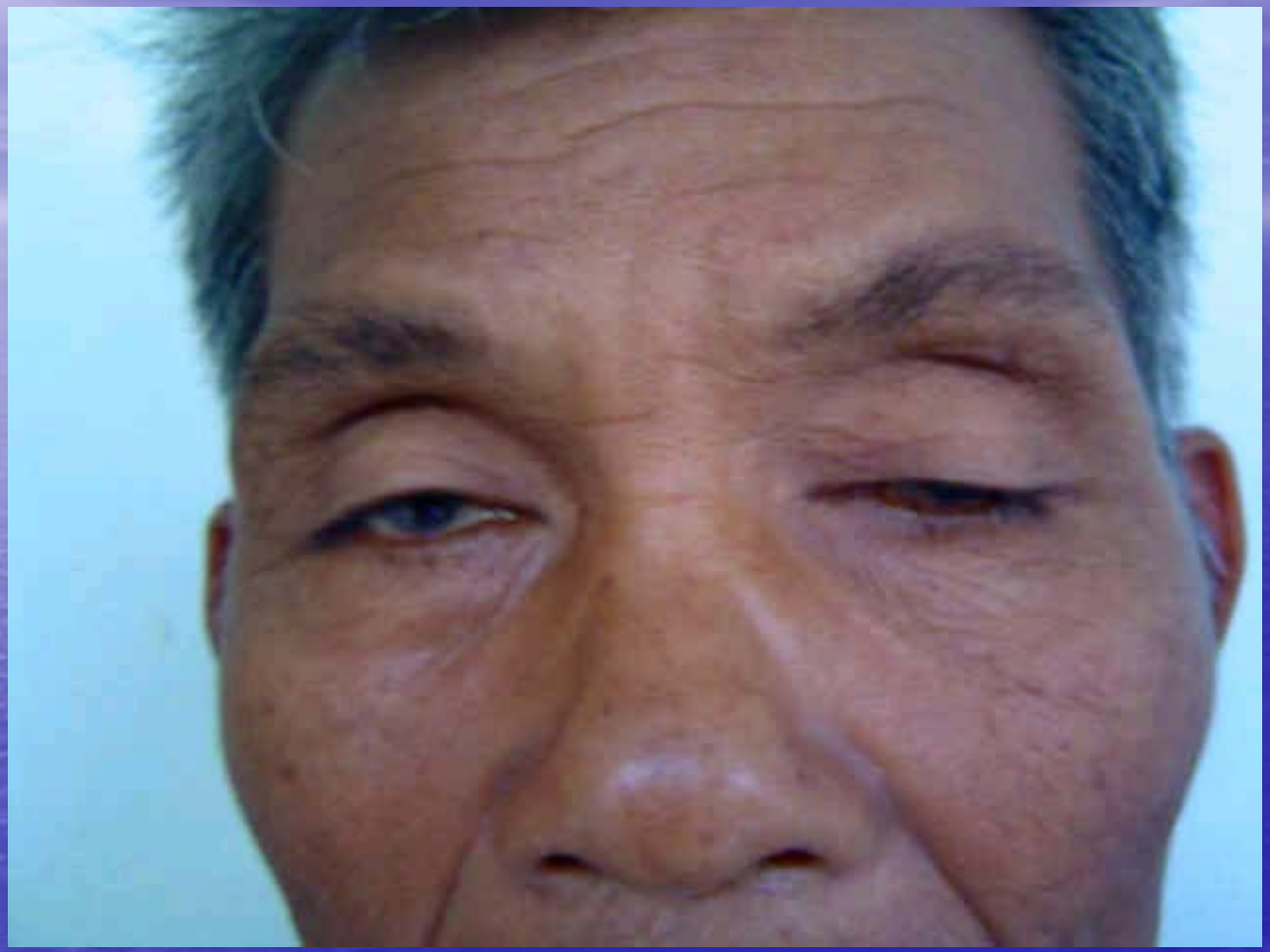
Myasthenia Gravis: Clinical Features

- Ocular manifestations
  - Ptosis, uni- or bilateral is very common and may occur while patients reading, or during long period of driving

Ptosis





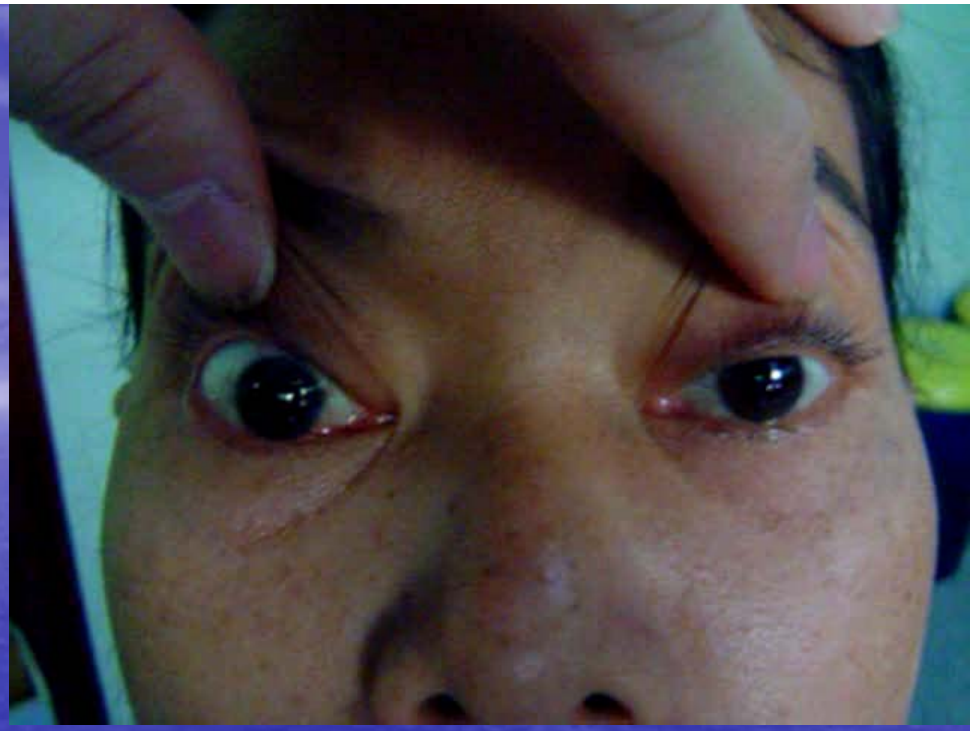


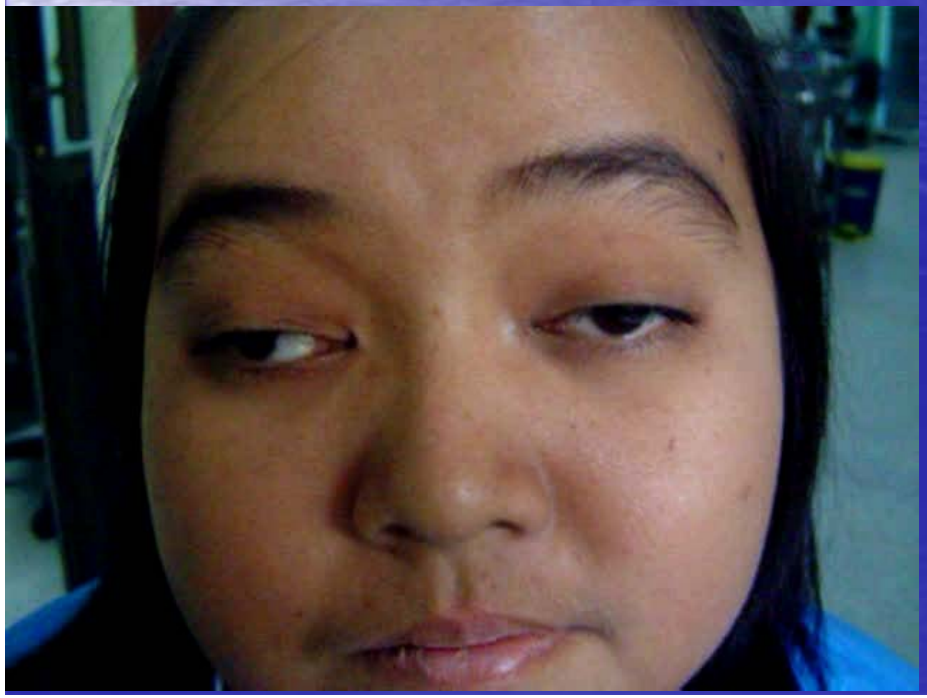
Ptosis and impaired orbicularis oculi

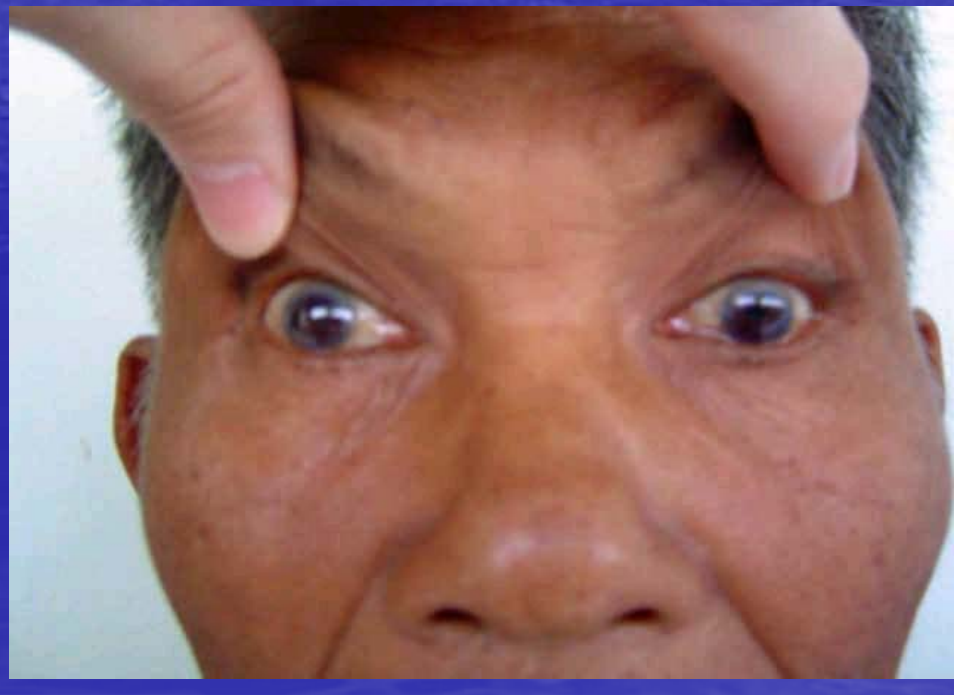
Myasthenia Gravis: Clinical Features

- Ocular manifestations
  - Diplopia: Extraocular muscle weakness may also present asymmetrically

EOM



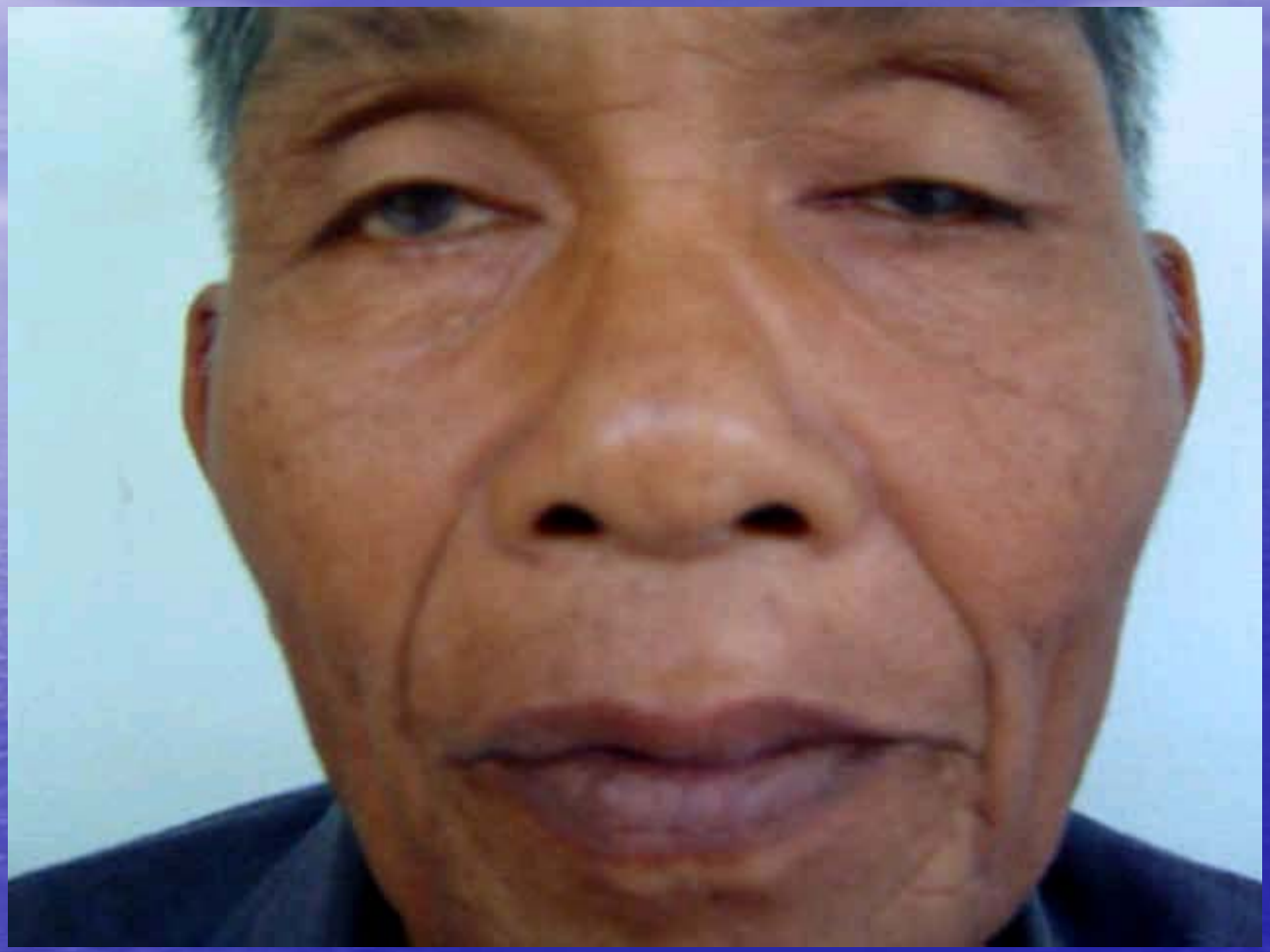




Myasthenia Gravis: Clinical Features

- 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

Neurologic clinics 1997; JOAO 2004



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

Neurologic clinics 1997; JOAO 2004

Myasthenia Gravis: Clinical Features

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

Neurologic clinics 1997

Myasthenia Gravis:

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

Neurologic clinics 1997

Medications induce or exacerbate MG

- Definite association
  - Penicillamine, corticosteroids
- Probable association
  - Anticonvulsants (phenytoin);
  - Anti-infectives (aminiglycosides, ciprofloxacin);
  - Beta-adrenergic receptor-blocking drugs;
  - Lithium carbonate;
  - Procainamide HCl

Archives of Internal Med 1997

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, trandermal nicotine)

Archives of Internal Med 1997

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

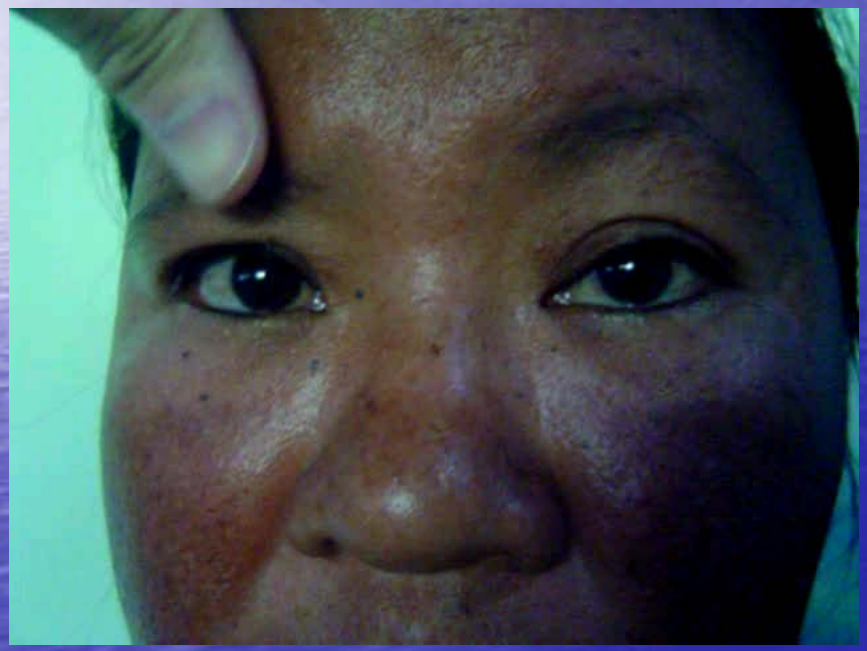
- Clinical course
  - Active stage (5-7 y): fluctuation and progression for several years: thymectomy benefit
  - Inactive stage (10 y) : fluctuation while intercurrent illness or other identifiable factors (drugs, pregnancy): thymectomy no benefit
  - Burnt-out stage: after 15-20 years; fixed weakness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

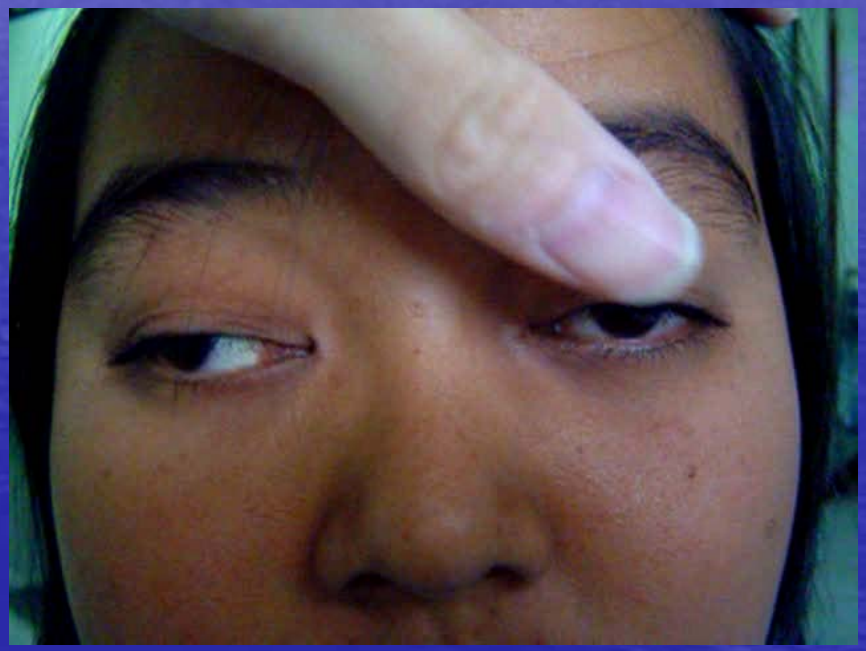
Neurologic clinics 1997

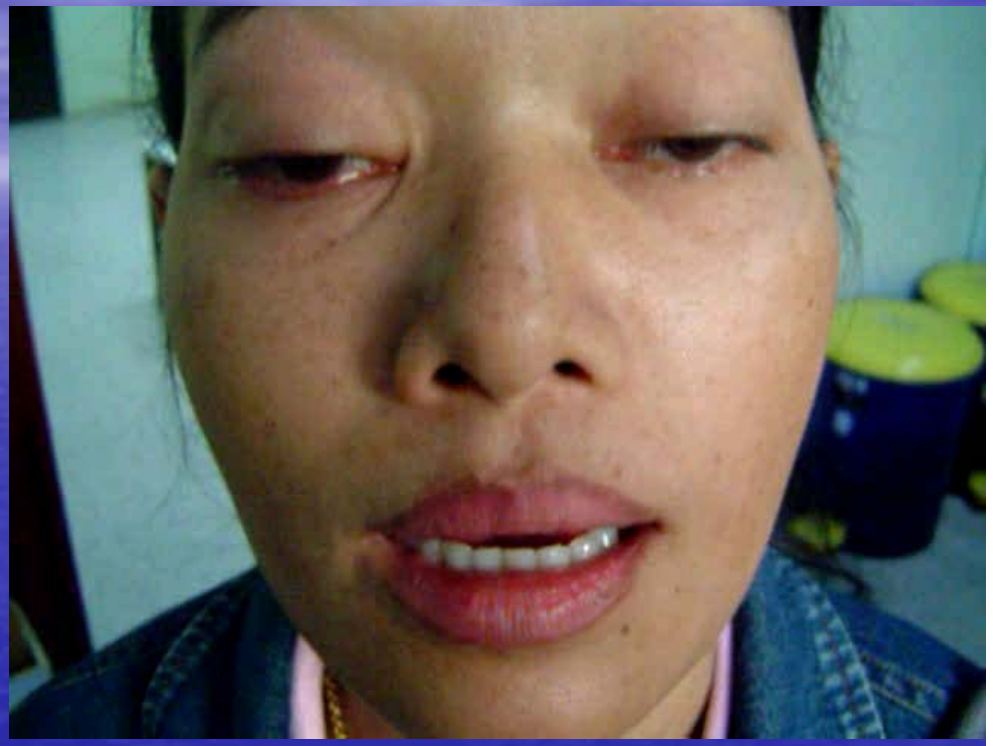
Myasthenia Gravis: Diagnosis

- 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)

Neurologic clinics 1997

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

Neurologic clinics 1997

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

Neurologic clinics 1997

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

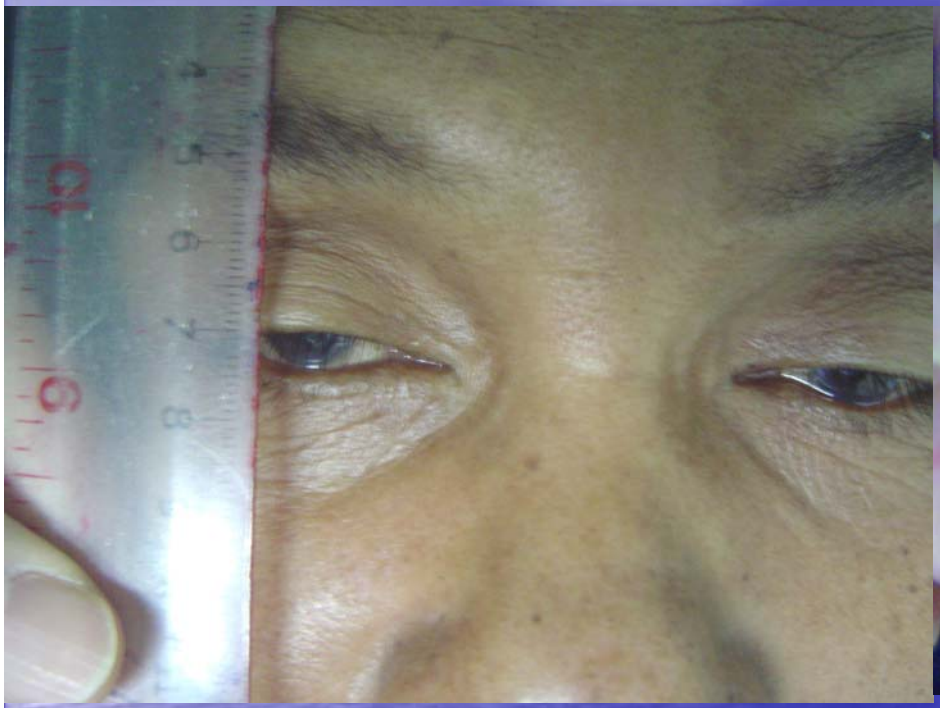
Myasthenia Gravis: Diagnosis

- Sleep test and rest test
  - Rest test for ocular (ptosis) type (AAO 2002)

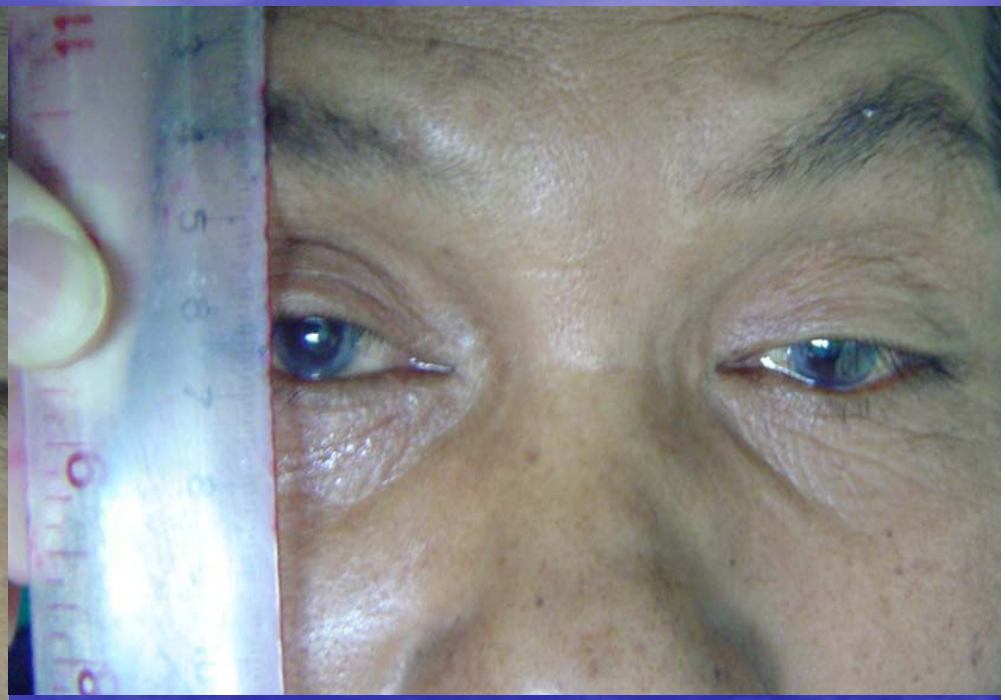
Myasthenia Gravis: Diagnosis

- 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)

ice test



rest test



Before ice test

After ice test

Myasthenia Gravis: Diagnosis

Ocular MG	Sensitive
• Tensilon test	86% (F +) (side effect)
• RNS (EOM)	48% (F+) (invasive)
• AchR-Ab:	45-65% (rare F +) (expensive)
• SFEMG (gold standard) (orbicularis oculi and frontalis)	95% (F +) (pain)
• Sleep test	simple and safe but takes time (30 mins.) and place
• Rest test	50% no F+ (AAO 2000)
• Ice test for ptosis:	95% no F+(Curr Opin Neurol 2001)

Neurologic clinics 1997; J med Assoc Thai 2001; JOAO 2004

Myasthenia Gravis: Diagnosis

Generalized MG	Sensitive
• Tensilon test	95
• RNS	higher than in ocular MG (F+)
• AchR-Ab:	90% (rare F +)
• SFEMG	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

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

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)

Neurologic clinics 1997

Recommended laboratory tests or procedures

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

Harrison 2001

Myasthenia Gravis: Treatment

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

JOAO 2004

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

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

Neurologic clinics 1994

Ocular MG

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

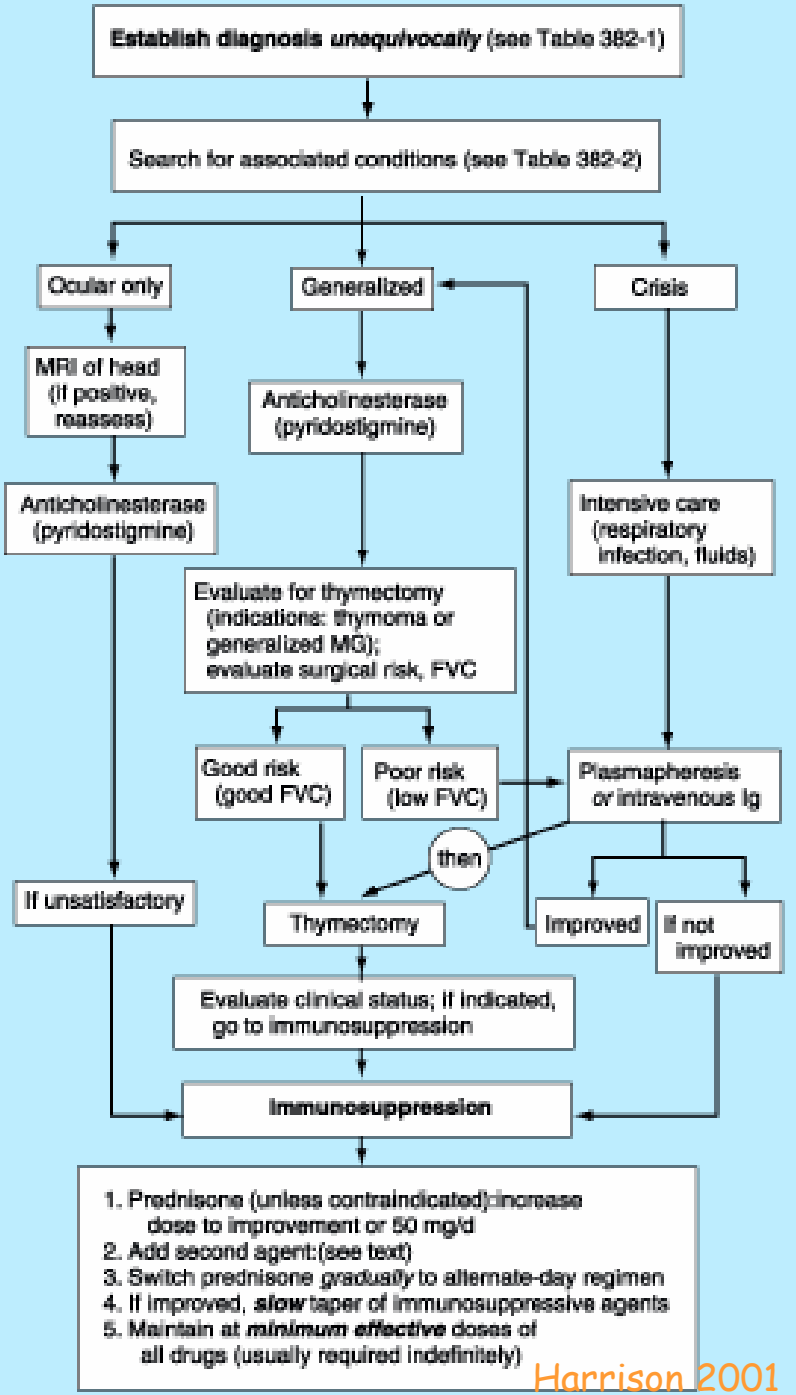
If spread out, in 2 y - thymectomy

If not response to pyridostigmine
Add prednisolone: 10-30 mg/d for 2-3 months or incrementing dose; after maximum benefit slow tapering

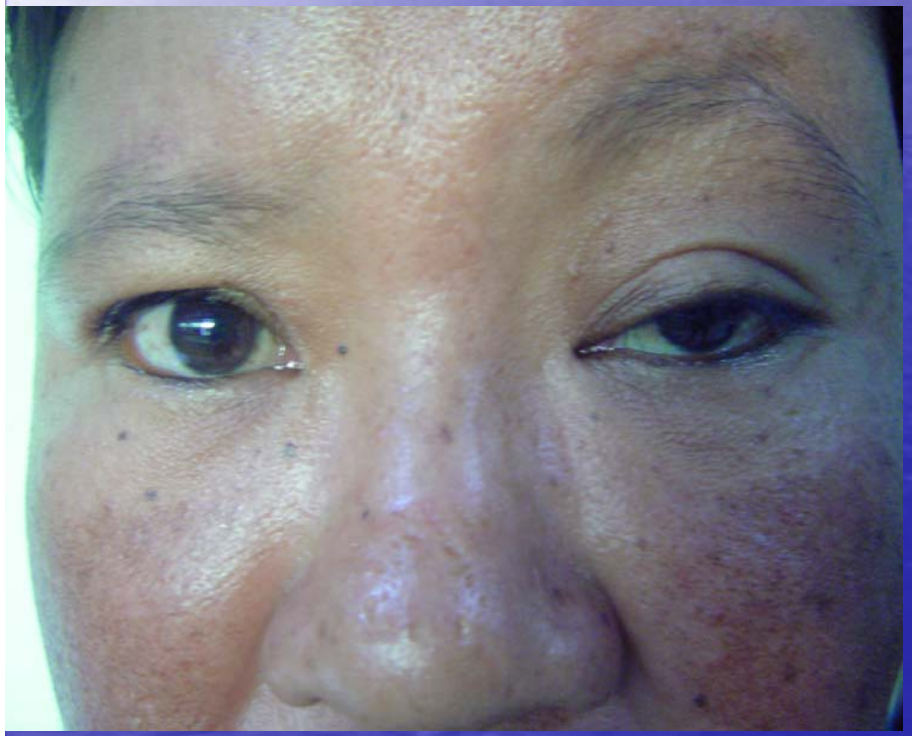
If not effective, getting along with dysfunction; maneuvers and simple mechanical devices used

Or high-dose daily prednisolone ± azathioprine or even thymectomy

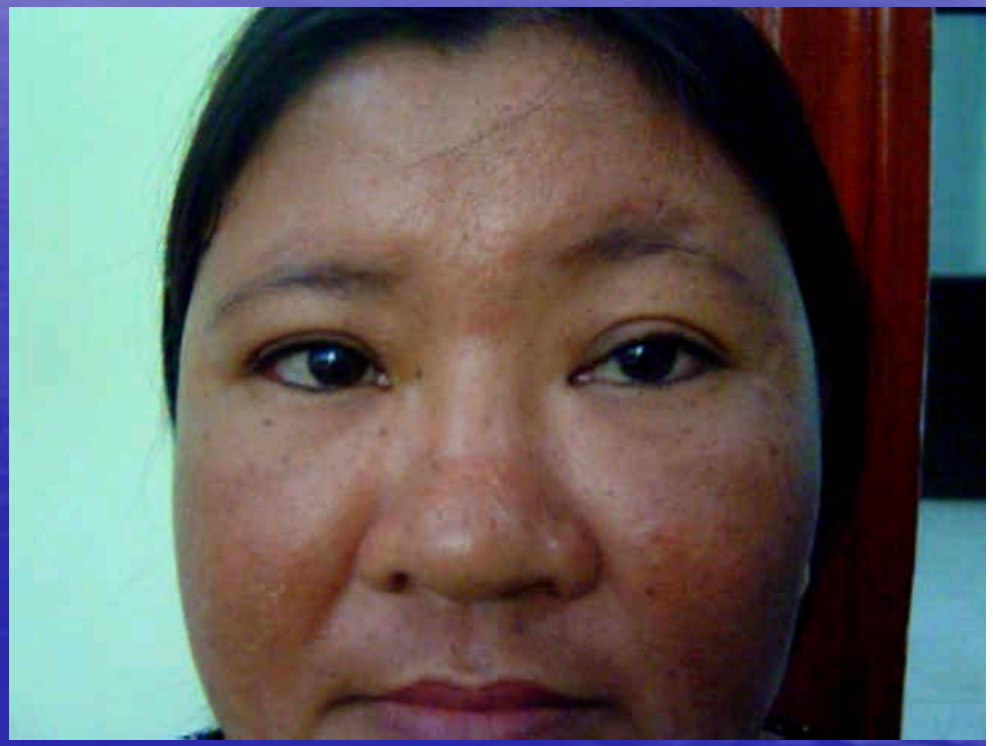
If ptosis is fixed; surgical shortening of the eyelid to be considered (JOAO 2004; Neurologic clinics 1994)



Harrison 2001



Before



After treatment

Generalized MG

No bulbar involvement: remission

Thymectomy: Indications

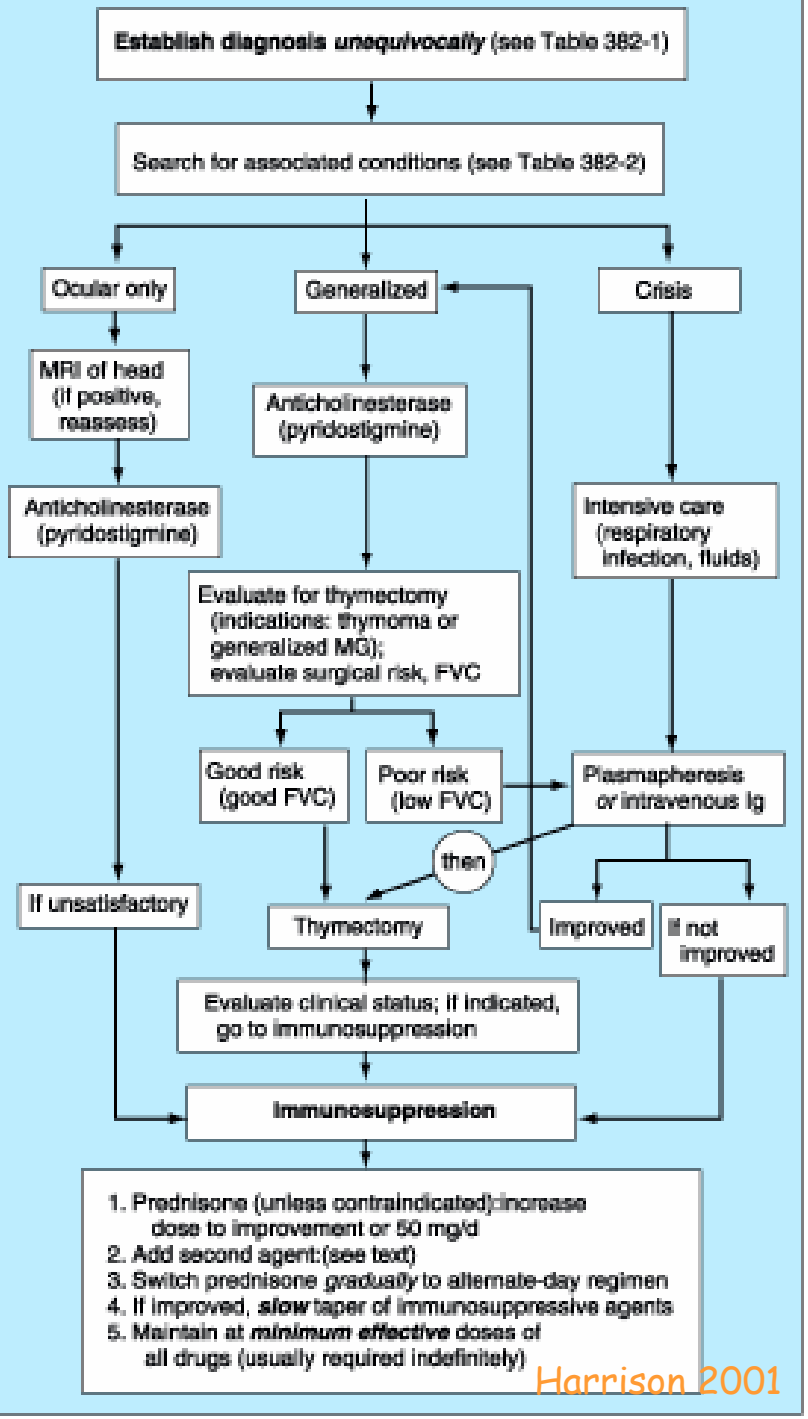
- Thymoma
- Those are medically stable and aged

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)



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

Neurologic clinics 1994

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

Neurologic clinics 1994

Myasthenic crisis

Sudden worsening of respiratory function ± profound muscle weakness

- Negative inspiratory force of less than -20 cmH_2O
- Tidal volume of less than 4mL/kg
- Force vital capacity < 15 mL/kg (normal 50-60 in female, 70 in male)

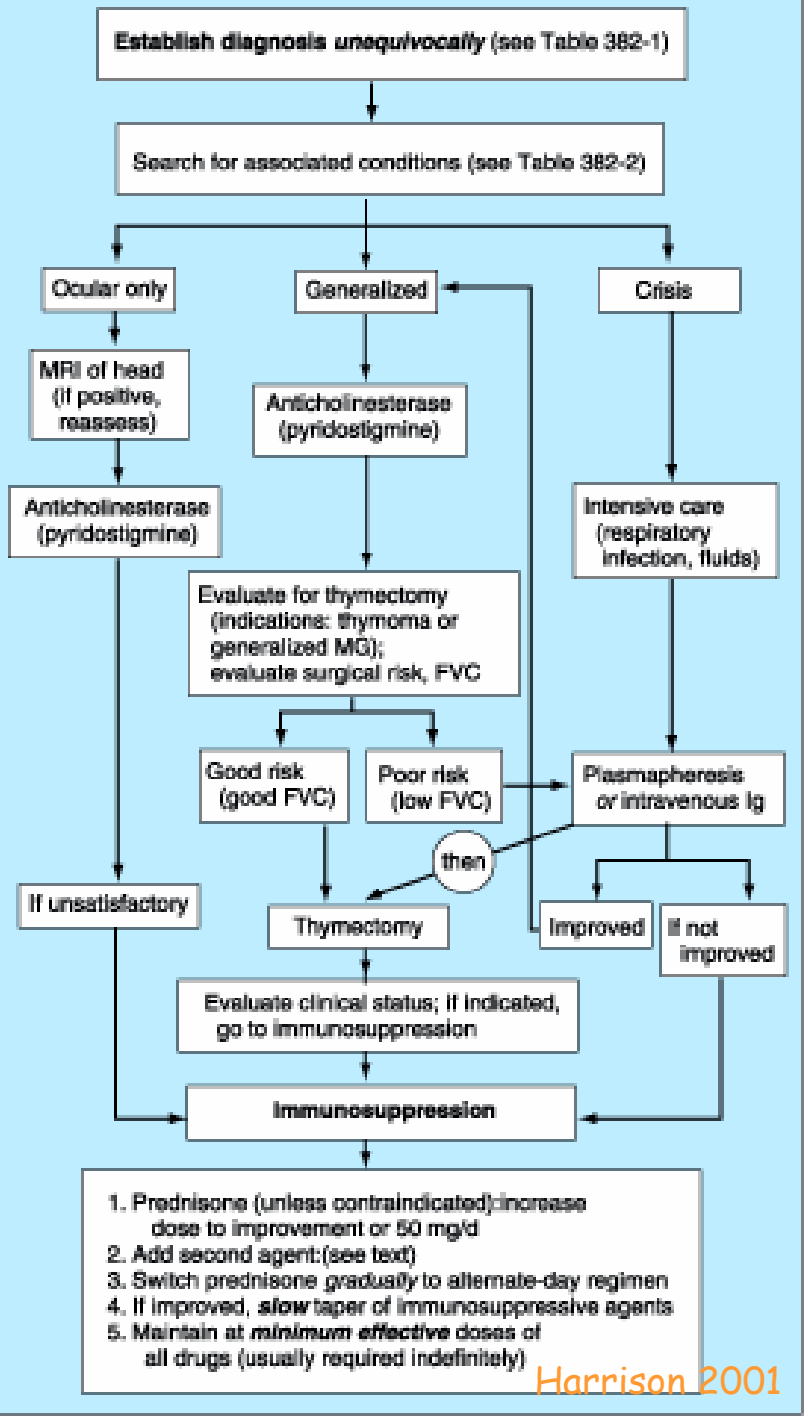
Neurologic emergency

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

DDx from cholinergic crisis: clinical and tensilon test

Management

-Stop every medications
-Assisted ventilation
-Treating ppf.
-If not improve
-IVIg or plasmapheresis (JOAO 2004)



Harrison 2001

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

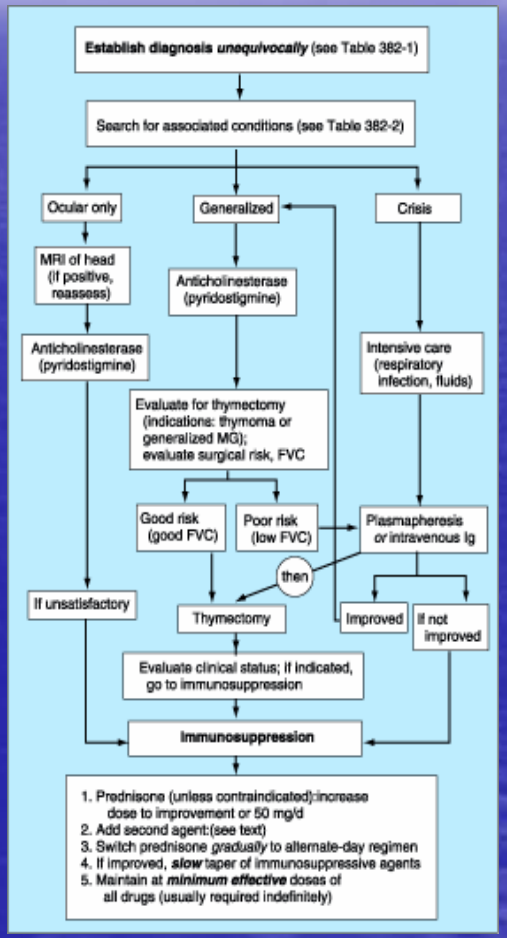
- Acetylcholinesterase inhibitors
  - Pyridostigmine bromide is used
    - Starting with 30 mg every 4 to 6 hours; titrated depending on clinical symptoms and patient tolerability
    - Cholinergic crisis if too much of this medication (max. Dose = 450 mg/d)
    - Lowest amount with maximum benefit
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

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

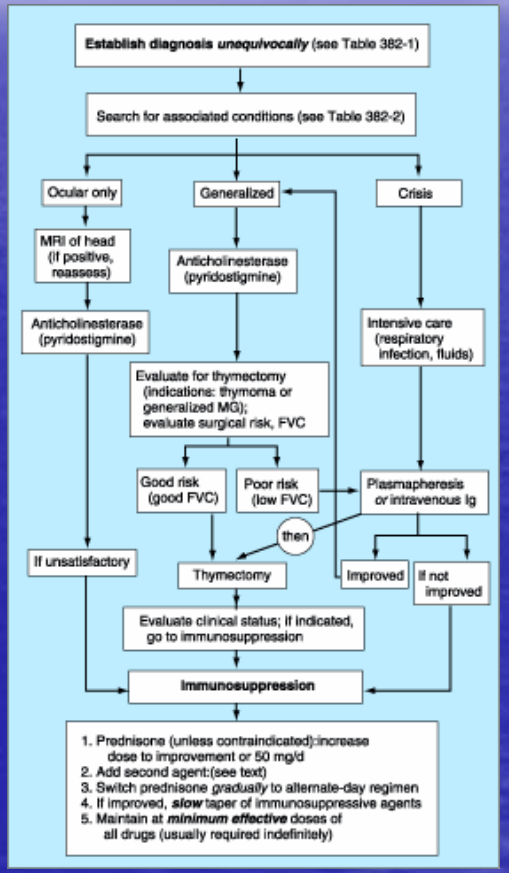
Myasthenia Gravis: Treatment

- 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



INDAPS 2004

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 compromized 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

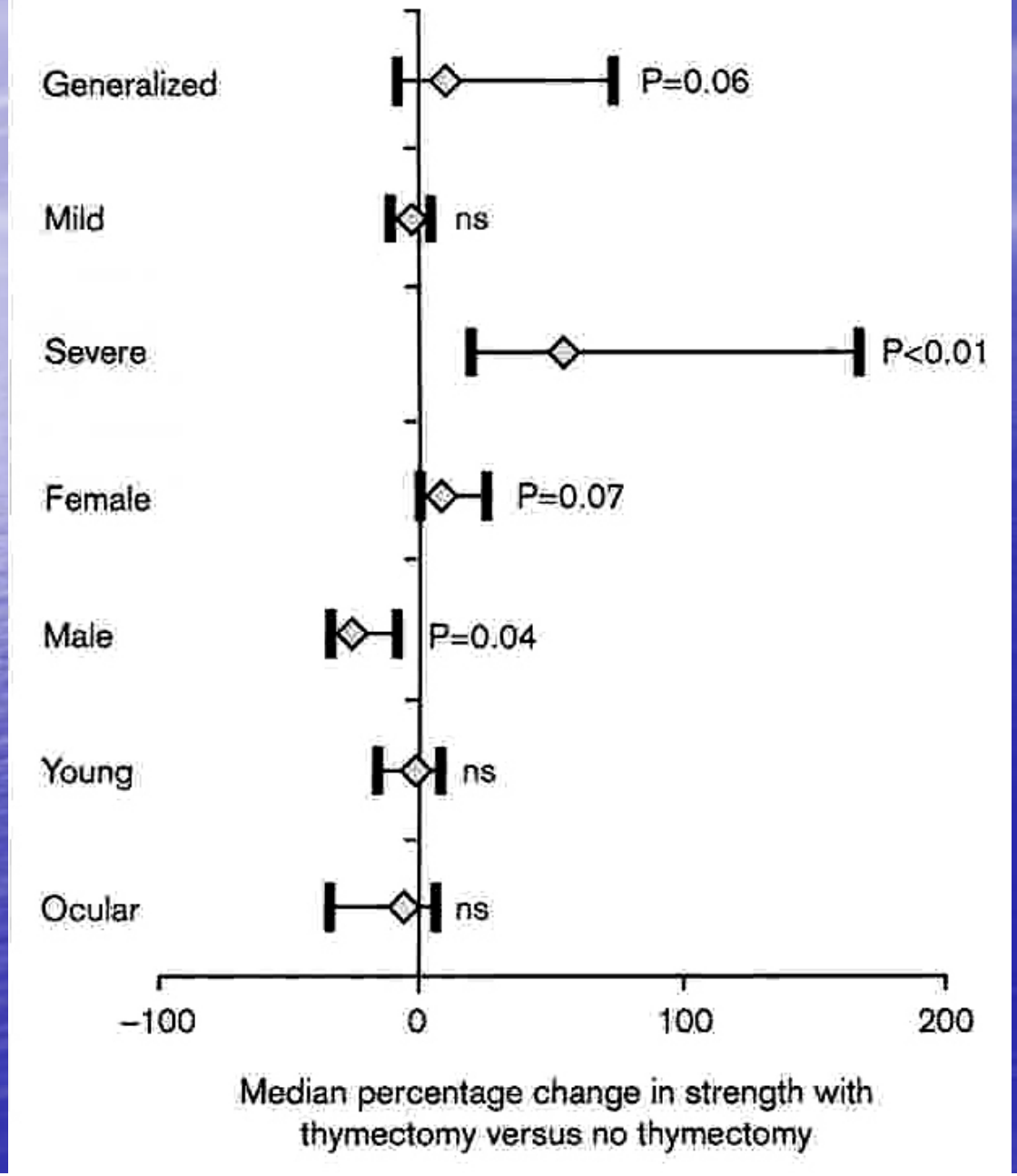
NEJM 1994

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



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

NEJM 1994

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

BJA 2002

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

BJA 2002

Anaesthetic management in MG

- Preoperative consideration: major elective surgical procedures
  - Sedative medications save if no respiratory comprimise
  - 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

BJA 2002

Anaesthetic management in MG

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

BJA 2002

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 reduce dose in the immediate post-operative period and increasing if necessary

BJA 2002

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)

Curr Opin Neurol 2001

Thymoma-associated MG

- Muscle antibodies predict the presence of thymoma

	Sens.	Spec.
– Ryanodine receptor Ab	70%	
– Titin Ab	95%	
– Both	70%	70%

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

Archives of Neurol 1999

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

BMC musculoskeletal disorders 2004

MG and pregnancy

- Use minimual dosage of drugs
- ChE-inhibitors: in creased 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

BMC musculoskeletal disorders 2004

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_2O
      - 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

CONDITION	SYMPTOMS AND CHARACTERISTICS	COMMENT
Congenital myasthenic syndromes	Rare; early onset; not autoimmune disorders	Sophisticated electrophysiologic and immunocytochemical tests required for diagnosis
Drug-induced myasthenia		
Penicillamine	Triggers autoimmune myasthenia	Recovery within weeks after drug withdrawal
Curare, procainamide, quinines, aminoglycosides	Weakness in normal persons; exacerbation of myasthenia	Recovery after drug withdrawal
Lambert–Eaton syndrome	Weakness; fatigue; areflexia; 60 percent of cases associated with oat-cell cancer	Incremental response on repetitive nerve stimulation; antibody to calcium channels present
Hyperthyroidism	Exacerbation of myasthenia; generalized weakness	Thyroid function abnormal
Graves' disease	Diplopia; exophthalmos	Thyroid-stimulating immunoglobulin present
Botulism	Generalized weakness; ophthalmoplegia	Incremental response on repetitive nerve stimulation; pupils are dilated
Progressive external ophthalmoplegia	Ptosis; diplopia; generalized weakness in some cases	Mitochondrial abnormalities
Intracranial mass compressing cranial nerves	Ophthalmoplegia; cranial-nerve weakness	Abnormalities on computed tomography or magnetic resonance imaging

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

Lancet 2001

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

NEJM 1997

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

JOAO 2004

- Rule out genetic MG, Lambert-Eaton myasthenic syndrome

Neurologic clinics 1994

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

Neurologic clinics 1994

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

NEJM 1994; JOAO 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

Drug	Usual Adult Dose	Time to Onset of Effect	Time to Maximal Effect	Variables to Monitor Drug Effects
Prednisone	15–20 mg/day gradually increasing to 60 mg/day and gradually changed to every other day	2–3 wk	3–6 mo	Weight Blood pressure Blood glucose Electrolytes Ophthalmic changes Bone density 24-hr urinary calcium
Azathioprine (Imuran)	2–3 mg/kg/day (total dose, 100–250 mg/day)	3–12 mo	1–2 yr	White-cell count ($<3500/mm^3$)* Differential count (<1000 lymphocytes/mm^3)* Mean corpuscular volume ($>100\ \mu m^3$)* Platelets Liver function
Cyclosporine (Sandimmune)	5 mg/kg/day given in 2 divided doses (total dose, 125–200 mg twice daily)	2–12 wk	3–6 mo	Blood pressure Serum creatinine Blood urea nitrogen Trough plasma cyclosporine level

*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

Neurologic clinics 1994

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

Myasthenia Gravis: Treatment

- Generalized MG with onset in childhood
  - Distiquishing 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

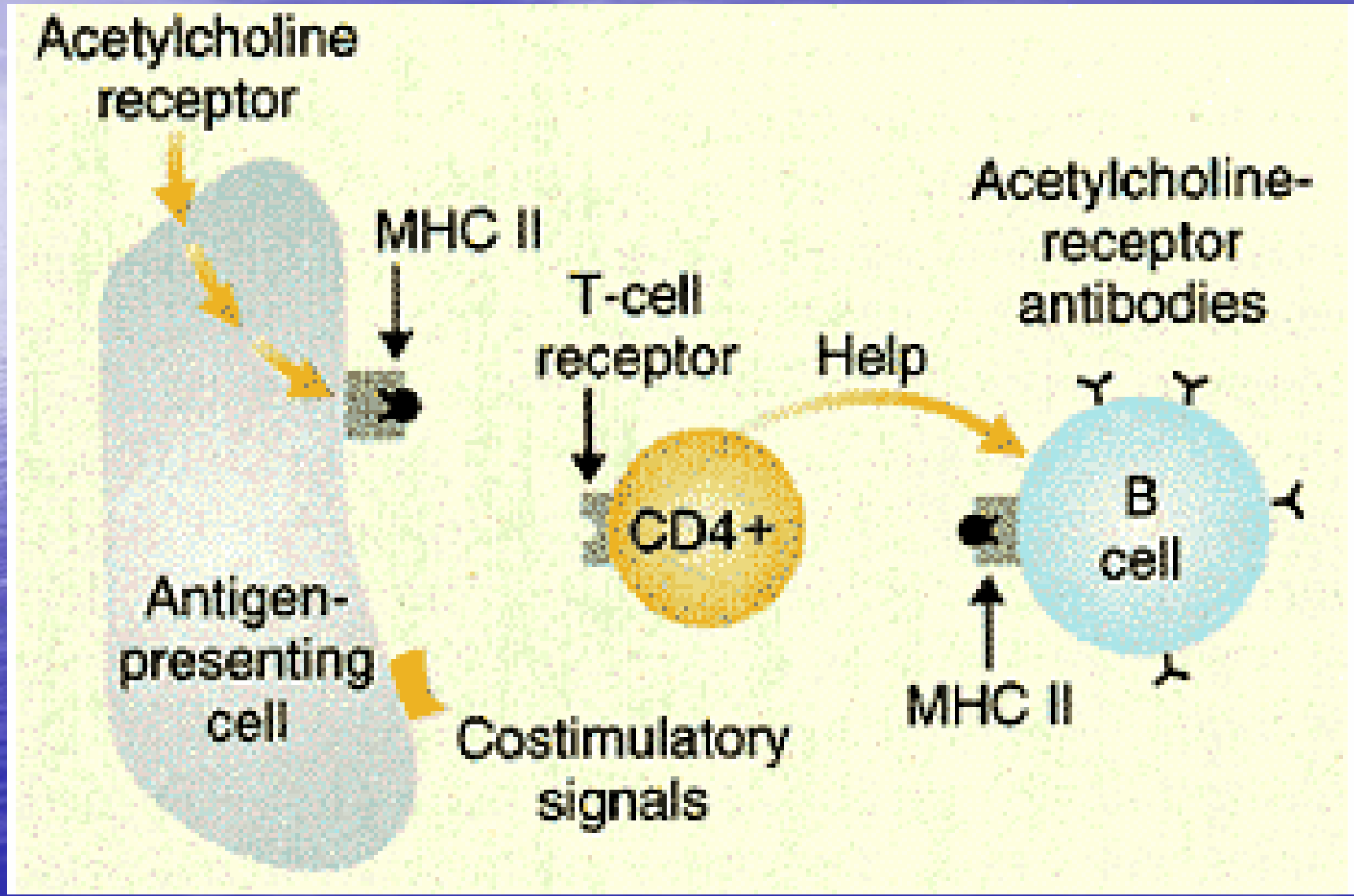
- Generalized MG
  - To reduce adverse steroid effects
  - Add with or switch to azathioprine

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



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

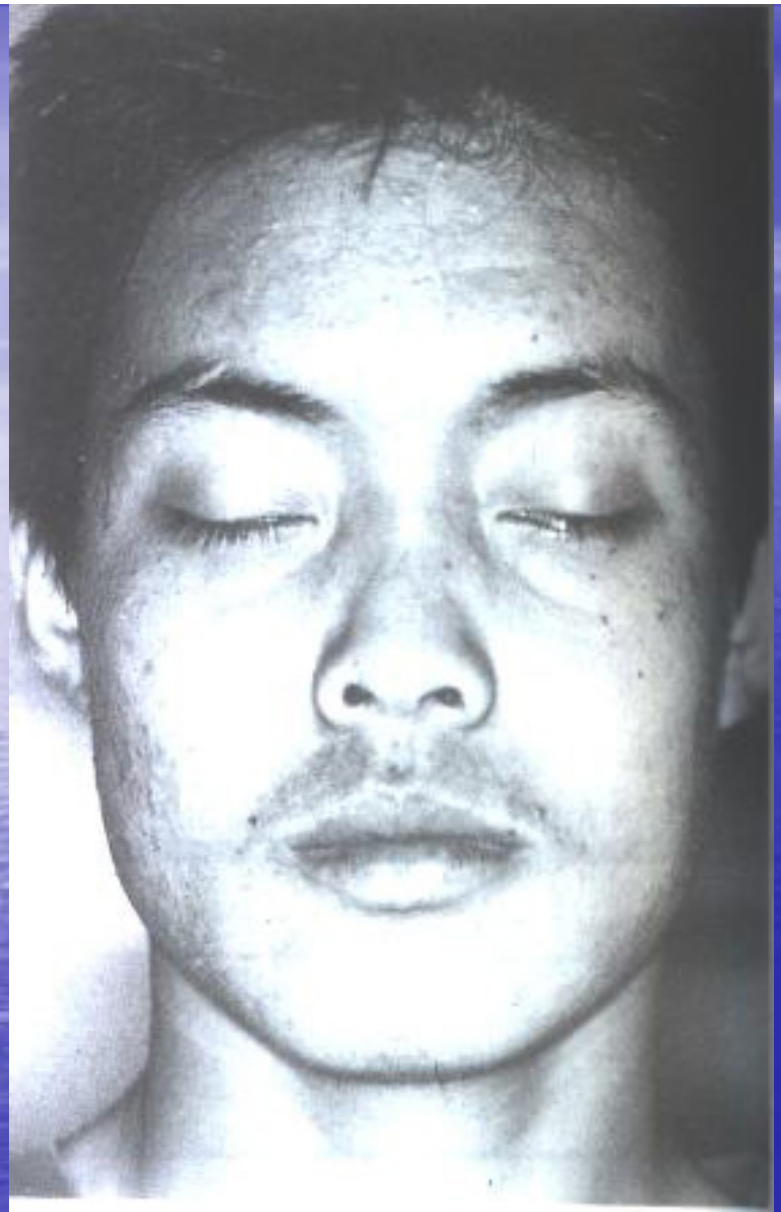
- Anti-infective Agents
  - Aminoglycosides
  - Kanamycin sulfate
  - Ampicillin sodium
  - Erythromycin
  - Ciprofloxacin HCL
  - Imipenem
  - Pyrantel

Medications induce or exacerbate MG

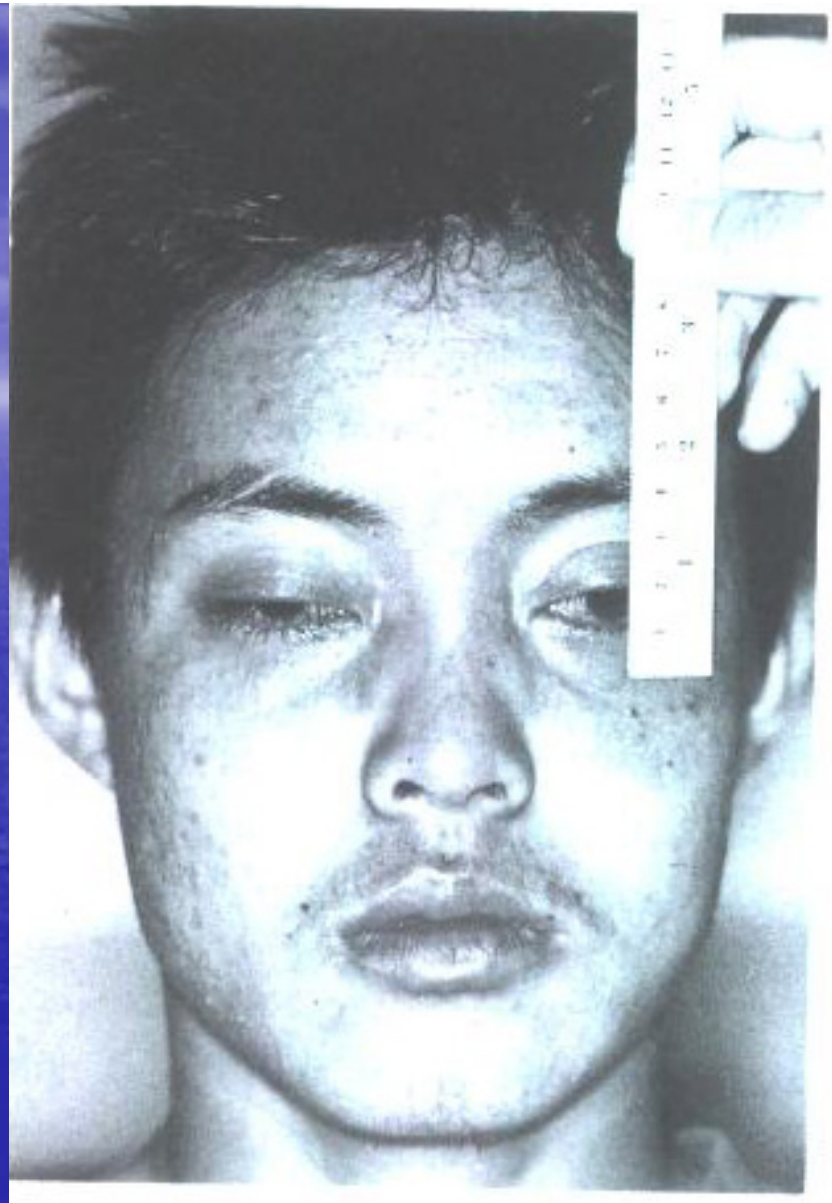
- Cardiovascular Agents
  - Propanolol HCL
  - Acebutolol HCL
  - Oxyprenolol HCL
  - Practolol
  - Timolol maleate (β blocker)
  - Quinidine (anti-arrhythmic)
  - Procainamide HCL (anti-arrhythmic)
  - Propafenone HCL (anti-arrhythmic)

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.



J med Assoc Thai 2001

Post ice test positive in ocular MG.

กลับสู่เมนูหลัก