MYASTHENIA GRAVIS

DEPARTMENT OF GENERAL MEDICINE

CLINICAL FEATURES

- The cardinal features of MG are weakness and fatigability of muscles.
- The weakness increases during repeated use and may improve following rest or sleep.
- The course of MG is often variable.
- Exacerbatations and remissions may occur, particularly during the first few years after the onset of the disease.
- Remissions are rarely complete or permanent.
- Unrelated infections or systemic disorders often lead to increased myasthenic weakness and may precipitate crisis.

- The distribution of muscle weakness often has a characteristic pattern.
- The cranial muscles particularly the lids and extra ocular muscles are often in world early in the course and diplopia and ptosis are common initial complaint.
- Facial weakness produces a snarling expression when the patient attempts to smile.
- Weakness in chewing is most noticeable after prolonged effort as in chewing meat.
- Speech may have a nasal timbre caused by weakness of the palate or a dysarthric “mushy” quality due to tongue weakness

- Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food.
- In ~ 85% of patients, the weakness becomes generalized, affecting the limb muscles as well.
- The limb weakness in MG is often proximal and may be asymmetric.
- Despite the muscle weakness, deep tendon reflexes are preserved.
- If weakness of respiration becomes so severe as to require respiratory assistance, the patient is said to be I crisis.

DIAGNOSIS AND EVALUATION

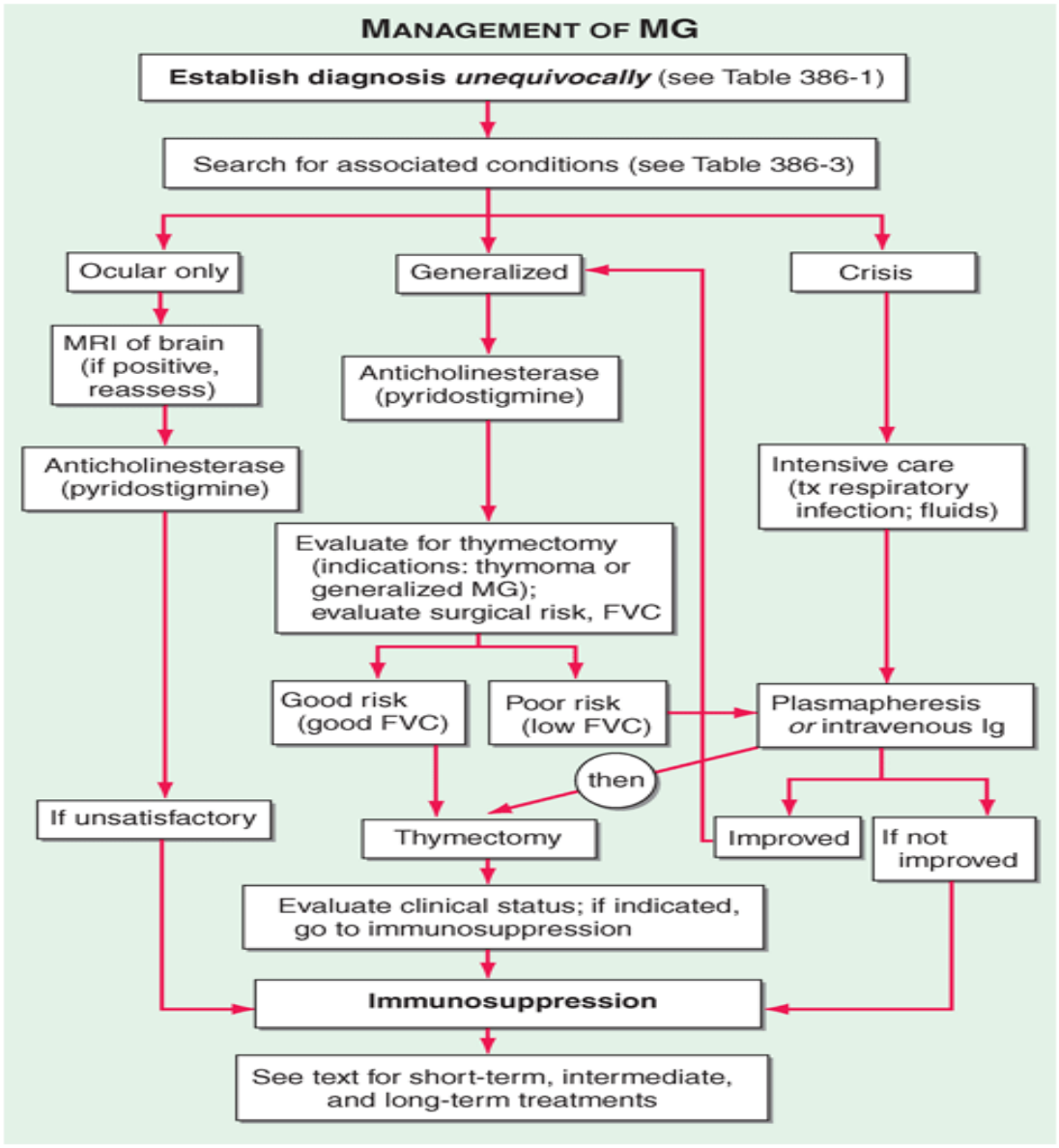
- The diagnosis is suspected on the basis of weakness and fatigability in the typical distribution described above, without loss of reflexes or impairment of sensation or other neurologic function.
- The suspected diagnosis should always be confirmed definitively before treatment is undertaken; this is essential because:
- (1) treatable conditions may closely resemble MG
- (2) treatment of MG may involve surgery and the prolonged use of drugs with adverse side effects.

Table 386-1 Diagnosis of Myasthenia Gravis (mg)
History
Diplopia, ptosis, weakness
Weakness in characteristic distribution
Fluctuation and fatigue: worse with repeated activity, improved by rest
Effects of previous treatments
Physical examination
Ptosis, diplopia
Motor power survey: quantitative testing of muscle strength
Forward arm abduction time (5 min)
Vital capacity
Absence of other neurologic signs
Laboratory testing
Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG. ~40% of AChR antibody–negative patients with generalized MG have anti-MuSK antibodies.
Repetitive nerve stimulation: decrement of >15% at 3 Hz: highly probable
Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific
Edrophonium chloride (Tensilon) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive
For ocular or cranial MG: exclude intracranial lesions by CT or MRI

Table 386-3 Disorders Associated with Myasthenia Gravis and Recommended Laboratory Tests
Associated disorders
Disorders of the thymus: thymoma, hyperplasia
Other autoimmune disorders: Hashimoto's 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 (see Table 386-4)
Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity
Recommended laboratory tests or procedures
CT or MRI of mediastinum
Tests for lupus erythematosus, antinuclear antibody, rheumatoid factor, antithyroid antibodies
Thyroid-function tests
PPD skin test
Chest radiography
Fasting blood glucose measurement, hemoglobin A1c
Pulmonary-function tests
Bone densitometry in older patients

Table 386-4 Drugs with Interactions in Myasthenia Gravis (mg)
Drugs that may exacerbate MG
Antibiotics
Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin
Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin
Macrolides: e.g., erythromycin, azithromycin,
Nondepolarizing muscle relaxants for surgery
D-Tubocurarine (curare), pancuronium, vecuronium, atracurium
Beta-blocking agents
Propranolol, atenolol, metoprolol
Local anesthetics and related agents
Procaine, Xylocaine in large amounts
Procainamide (for arrhythmias)
Botulinum toxin
Botox exacerbates weakness
Quinine derivatives
Quinine, quinidine, chloroquine, mefloquine (Lariam)
Magnesium
Decreases ACh release
Penicillamine
May cause MG
Drugs with important interactions in MG
Cyclosporine
Broad range of drug interactions, which may raise or lower cyclosporine levels.
Azathioprine
Avoid allopurinol—combination may result in myelosuppression.

TREATMENT



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Thymectomy

(1)surgical removal of thymoma, and (2) thymectomy as a treatment for MG

Immunosuppression

- immediate improvement is essential either because of the severity of weakness or because of the patient's need to return to activity as soon as possible, IVIg should be administered or plasmapheresis should be undertaken.
- intermediate term, glucocorticoids and cyclosporine or tacrolimus generally produce clinical improvement within a period of 1–3 months. The beneficial effects of azathioprine and mycophenolate mofetil usually begin after many months (as long as a year), but these drugs have advantages for the long-term treatment of patients with MG

- occasional patient with MG a course of high-dose cyclophosphamide may induce long-lasting benefit .

Glucocorticoid Therapy

- Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the great majority of patients.
- The initial dose should be relatively low (15–25 mg/d) to avoid the early weakening that occurs in about one-third of patients treated initially with a high-dose regimen.
- The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 2- to 3-day intervals), until there is marked clinical improvement or a dose of 50–60 mg/d is reached

- This dose is maintained for 1–3 months and then is gradually modified to an alternate-day regimen over the course of an additional 1–3 months.

Other Immunosuppressive Drugs

- Mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, and occasionally cyclophosphamide are effective in many patients, either alone or in various combinations.
- Mycophenolate mofetil has become one of the most widely used drugs in the treatment of MG because of its effectiveness and relative lack of side effects. A dose of 1–1.5 g bid

- The calcineurin inhibitors cyclosporine and tacrolimus (FK506) are approximately as effective as azathioprine and are being used increasingly in the management of MG. Their beneficial effect appears more rapidly than that of azathioprine.
- The usual dose of cyclosporine is 4–5 mg/kg per d, and the average dose of tacrolimus is 0.07–0.1 mg/kg per d, given in two equally divided doses (to minimize side effects.
- The therapeutic range for the trough level of cyclosporine is 150–200 ng/L, and for tacrolimus it is 5–15 ng/L.
- Cyclophosphamide is reserved for occasional patients refractory to the other drugs
- Rituximab, a monoclonal antibody that depletes CD20 B cells, has been used with variable—sometimes dramatic—success in the treatment of MG, especially in patients with anti-MuSK antibody.

Plasmapheresis and Intravenous Immunoglobulin

- A course of five exchanges (3–4 L per exchange) is generally administered over a 10- to 14-day period.
- Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients.
- It is useful as a temporary expedient in seriously affected patients or to improve the patient's condition prior to surgery (e.g., thymectomy).
- Improvement occurs in 70% of patients, beginning during treatment, or within a week, and continuing for weeks to months.

Management of Myasthenic Crisis

- Myasthenic crisis is defined as an exacerbation of weakness sufficient to endanger life; it usually consists of respiratory failure caused by diaphragmatic and intercostal muscle weakness
- Treatment should be carried out in intensive care units staffed with teams experienced in the management of MG, respiratory insufficiency, infectious disease, and fluid and electrolyte therapy.
- The most common cause of crisis is intercurrent infection.
- This should be treated immediately.
- The myasthenic patient with fever and early infection should be treated like other immunocompromised patients. Early and effective antibiotic therapy, respiratory assistance (preferably noninvasive, using BiPap), and pulmonary physiotherapy are essentials of the treatment program