Myasthenia Gravis

SV Khadilkar*, AO Sahni**, SG Patil**

Abstract
Myasthenia gravis is the prototype neuromuscular disease with immunological pathogenesis. The recognition and interpretation of the symptoms should be stressed as the diagnosis is initially achieved on clinical ground. Tests in the areas of immunology, electrophysiology and imaging further help the diagnosis, management and prognosis of the condition. The recent knowledge of immunology seems to point to variations in the immune abnormalities, but it remains to be seen whether the differences have clinical relevance. With the availability of intensive care units, the management of acute events in the myasthenic patients has improved considerably and the morbidity is reduced. Long term remissions are achievable in majority of patients, with supervised use of immunosuppression. In the modern times, the grave connotations of the name myasthenia gravis may be only rarely justified.

Myasthenia gravis (MG) is an important neuromuscular disorder and is one of the best understood autoimmune diseases. It presents to the clinician in a variety of ways, with symptoms that are varied and evanescent and hence it may be difficult to diagnose in the initial stages. This diagnosis is rewarding as the results of therapy are satisfactory in most patients. In the recent years, knowledge of immunopathology and therapy of MG has advanced and this review focuses on the pathogenetic, diagnostic and therapeutic aspects of MG.

PATHOGENESIS

Myasthenia gravis (MG) is an acquired autoimmune disease of the neuromuscular junction. In most cases, the target of the autoimmune attack is the nicotinic acetylcholine receptor (AChR) located in the postsynaptic muscle endplate membrane.1,2

In MG, the postjunctional muscle membrane is distorted and simplified, having lost its normal folded shape, the concentration of AChRs on the muscle endplate membrane is reduced, and antibodies and complement are attached to the membrane. ACh is released normally, but its effect on the postsynaptic membrane is reduced. The postjunctional membrane is less sensitive to applied ACh, and the probability that any nerve impulse will cause a muscle action potential is reduced.

The amount of ACh released per impulse normally declines on repeated activity (presynaptic rundown). In the myasthenic patient, the decreased efficiency of neuromuscular transmission combined with the normal rundown results in the activation of fewer and fewer muscle fibers by successive nerve impulses and hence increasing weakness, or myasthenic fatigue. This mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electrodiagnostic testing.

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane, first shown by the reduced binding of the radiolabelled specific AChR ligand, alpha-bungarotoxin (BuTx), a component of the venom of the banded krait.3

Mechanisms of acetylcholine receptor loss

Mechanisms by which anti-AChR antibodies cause AChR loss include complement-mediated lysis, cross-linking and down-regulation, and direct agonist block. Of these, complement-mediated lysis appears to be the most important.4

In addition to immune activation against acetylcholine receptors, there is functional blockade of postsynaptic receptors, which can in part explain the response to acetycholinesterase inhibitors and the relatively quick response to therapies that reduce the number of AChR-ab.1

Thymus abnormalities

The thymus is unequivocally involved in the pathogenesis of the disease, and its surgical removal often is associated with improvement in disease severity.2 The primary abnormality in MG appears to be a breakdown in immune tolerance toward self-antigens. The thymus is abnormal in approximately 75% of patients with MG; in about 65% the thymus is “hyperplastic”, with the presence of active germinal centers, while 10% of patients have thymic tumours (thymomas).5 The most striking change in the thymus is seen in the 60 per cent of patients who have early onset disease...
(age < 40 years). The late onset group of patients (age > 40 years), usually have a normal or atrophic thymus, as do those who are negative for anti-AChR antibody.

**Genetic factors**

Play a role in the pathogenesis of autoimmune MG, but monozygotic twins demonstrate a concordance rate of less than 50%. There is a moderate association with HLA antigens B8 and DRw3 in young women. The stronger association with HLA-DQw2 remains controversial. There is an unusually high incidence of other autoimmune diseases, such as SLE, rheumatoid arthritis, and thyroid diseases, in first-degree relatives of patients with MG, suggesting the presence of shared autoimmune genes. MG is not transmitted by Mendelian inheritance, but family members of patients are approximately 1000 times more likely to develop the disease than is the general population. From time to time more than one family member may have clinical myasthenia gravis.

**Clinical Presentation**

Age of onset is bimodal, with the first peak in the 20s and 30s, when it affects women more often than men, and a second peak in the sixth and seventh decades, when it affects men more often than women.1

Muscular weakness and fatigability are the hallmarks of MG. Patients with myasthenia gravis come to the physician complaining of specific muscle weakness and not of generalized fatigue. The severity of weakness fluctuates during the day, usually being least severe in the morning and worse as the day progresses, especially after prolonged use of affected muscles.

Ocular symptoms are often the first manifestation of MG (Table 1).7 The typical symptoms are ptosis, diplopia, or blurred vision. Ocular muscle weakness may be the first sign in up to 40% of patients, although 85% of patients with MG will eventually have ocular involvement. When present, ptosis is often worse toward the end of the day. In some patients, symptoms remain confined to the eye muscles (ocular myasthenia) and antibody titers are then usually low or absent. Weakness is restricted to the ocular muscles in about 10% of cases. The rest have progressive weakness during the first 2 years that involves oropharyngeal and limb muscles. Maximum weakness occurs during the first year in two-thirds of patients.

Oropharyngeal muscle weakness, difficulty in chewing, swallowing, or talking, is the initial symptom in one-sixth of patients, and limb weakness in only 10%. Facial weakness produces a “snarling” expression when the patient attempts to smile - ‘Myasthenic Snarl’. Weakness in chewing is most noticeable after prolonged effort. This symptom is important to recognize as there are very few other conditions like temporal arteritis which would have it. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric quality due to tongue weakness. Difficulty in swallowing occurs as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food.

Respiratory muscle weakness is rarely a presenting feature but can be a serious complicating factor in those with bulbar weakness.8

The signs of myasthenia gravis are confined to the motor system and, in mild cases, may be evident only after testing for fatigue. Double vision may increase with sustained gaze, and signs of ocular weakness may be asymmetrical. Fatigable ptosis is often present. Attempted elevation of the eyelid may result in an unsustained upward twitch (Cogan’s sign). Weakness of eye closure, facial expression, jaw opening or swallowing, or talking, is the initial symptom in one-sixth of patients, and limb weakness in only 10%. Facial weakness produces a “snarling” expression when the patient attempts to smile - ‘Myasthenic Snarl’. Weakness in chewing is most noticeable after prolonged effort. This symptom is important to recognize as there are very few other conditions like temporal arteritis which would have it. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric quality due to tongue weakness. Difficulty in swallowing occurs as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food.

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<table>
<thead>
<tr>
<th>Table 2: Disorders associated with myasthenia gravis and recommended laboratory tests</th>
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<tbody>
<tr>
<td><strong>Associated disorders</strong></td>
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<tr>
<td>● Disorders of the thymus : thymoma, hyperplasia</td>
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<tr>
<td>● Other autoimmune disorders : thyroiditis, Graves’ disease, rheumatoid arthritis, lupus erythematous, skin disorders.</td>
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<tr>
<td>● Disorders or circumstances that may exacerbate myasthenia gravis : hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (aminoglycoside antibiotics, quinine, antiarrhythmics)</td>
</tr>
<tr>
<td>● Disorders that may interfere with therapy : tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma.</td>
</tr>
<tr>
<td><strong>Recommended laboratory tests or procedures</strong></td>
</tr>
<tr>
<td>● CT or MRI of mediastinum</td>
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<tr>
<td>● Tests for lupus erythematous, antinuclear antibody, rheumatoid factor, antithyroid antibodies</td>
</tr>
<tr>
<td>● Thyroid-function tests and fasting blood glucose measurement</td>
</tr>
<tr>
<td>● Chest radiography</td>
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<tr>
<td>● Pulmonary function tests</td>
</tr>
<tr>
<td>● Bone densitometry in older patients.</td>
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<tr>
<td>[Table adapted from - RT Johnson, JW Griffin (eds) : Current Therapy in Neurologic Disease, 4th ed. St. Louis, Mosby Year Book, 1993, p 379.]</td>
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diagnosis, for example the Lambert-Eaton myasthenic syndrome.

Cardiac arrhythmias may occur occasionally, usually associated with ant cardiac muscle antibodies. Other autoimmune diseases, and other autoantibodies, occur more frequently than would be expected by chance. These include thyroid disease, systemic lupus erythematosus, polymyositis, insulin-dependent diabetes, and, rarely, the Lambert-Eaton myasthenic syndrome.

The course of disease

The course of MG is variable. Weakness remains restricted to the ocular muscles in approximately 10% of patients. The rest have progressive weakness during the first 2 years that ultimately involves oropharyngeal and limb muscles. Maximum weakness occurs during the first year in two thirds of patients. Before steroids were used for treatment, approximately one-third of patients had spontaneous improvement, one-third had progressive disease, and one-third died of the disease.

Factors that worsen myasthenic symptoms are emotional upset, systemic illness (especially viral respiratory infections), hypothyroidism or hyperthyroidism, pregnancy, the menstrual cycle, drugs affecting neuromuscular transmission and fever.

Drug-induced MG - A large number of drugs can alter the myasthenic status and hence it is important to be alert about such interactions (Table 3). D-penicillamine needs a particular myasthenic status and hence it is important to be alert about such interactions (Table 3). D-penicillamine needs a particular mention as it is the prototype of drug-induced MG.

Osserman Classification\(^6\) in Myasthenia Gravis
Grade 0 - Asymptomatic
Grade 1 - Ocular signs and symptoms
Grade 2 - Mild generalized weakness
Grade 3 - Moderate generalized weakness, bulbar dysfunction, or both
Grade 4 - Severe generalized weakness, respiratory dysfunction, or both

Table 3: Drug-induced myasthenia gravis

<table>
<thead>
<tr>
<th>Iatrogenic causes</th>
<th>Antibiotics</th>
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<tr>
<td>D-Penicillamine</td>
<td>Aminoglycoside</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Miscellaneous Drugs</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Clindamycin and lincomycin</td>
</tr>
<tr>
<td>Iodinated radiographic contrast</td>
<td>Colistin and polymyxin B</td>
</tr>
<tr>
<td>Intravenous sodium lactate</td>
<td>Other Drugs</td>
</tr>
<tr>
<td>Tetanus antitoxin</td>
<td>Quinidine and quinine</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>Cocaine use</td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Botulinum Toxin</td>
<td>Phenytoin</td>
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<tr>
<td>Ophthalmologic medications</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Timolol</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>General anesthetics</td>
</tr>
<tr>
<td>Echothiorphate</td>
<td>Neuromuscular blocking drugs</td>
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Diagnosis

The diagnosis of MG is essentially clinical. The clinical demonstration of fatigability is a reliable pointer to the diagnosis. Laboratory tests are adjunct to the diagnosis. The mainstays of diagnostic testing have been pharmacological, serological and electrodiagnostic.\(^1\) As a general rule, a firm diagnosis is based upon characteristic history and physical examination, and two positive diagnostic tests, preferably serological and electrodiagnostic.

**EDROPHONIUM CHLORIDE (TENSILON) TEST AND PROSTIGMINE TEST**

Patients, in whom weakness is caused by abnormal neuromuscular transmission characteristically improves after intravenous administration of edrophonium chloride. This response forms the basis of the Tensilon test, in which strength is examined before and after injection of the drug. The test should be performed in control settings of an ICU with monitoring and resuscitation.\(^7\)

Results of the Tensilon test are found to be positive in more than 90% of patients with MG. However, improved strength after edrophonium is not unique to MG. It may also be seen in motor neuron disease and in patients with lesions of the ocular motor nerves. A dose of 2 mg is injected intravenously, and the response is monitored for 60 seconds. Subsequent injection is of 8 mg. If improvement is seen within 60 seconds after any dose, no further injections are given. The total dose of edrophonium in children is 0.15 mg/kg administered incrementally. Subcutaneous administration can be used in newborns and infants, but the response may be delayed for 2-5 minutes. Some clinicians administer edrophonium in a blinded or double-blinded fashion to improve objectivity.

**Prostigmine test**

Patients whose MG does not respond to intravenous edrophonium may show a response to intramuscular neostigmine, which has a longer duration of action. Intramuscular neostigmine is particularly useful in infants and children whose response to intravenous edrophonium may be too brief for adequate observation. Prostigmine methylsulfate (Neostigmine) is administered intramuscularly at a dose of 0.04 mg/kg; if the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hours after the first dose (a typical dose is 0.5-1.5 mg). The peak effect is seen in 20-40 minutes. Intravenous prostigmine is not recommended because of risk of cardiac arrhythmias.

In some patients, a therapeutic trial of oral pyridostigmine for few days may produce improvement that cannot be recognized after a single dose of edrophonium or neostigmine.

**Utility of Tensilon test**

- Only useful in patients with objective, preferably measurable, findings on physical examination.
- Sensitivity for MG is relatively low (60%) compared to other diagnostic tests.
Anti-AChR antibodies occur in exclude the diagnosis. The concentration of AChR Abs cannot be used to predict the severity of disease in individual patients. Approximately 10% of patients who lack binding antibodies have antibodies that modulate the turnover of AChR in tissue culture. The concentration of binding antibodies may be low at symptom onset and rise later. Repeat studies are appropriate when initial values are normal. In general, finding AChR-binding antibodies in a patient with compatible clinical features confirm the diagnosis of MG, but normal concentrations do not exclude the diagnosis.

Anti-AChR antibodies occur in

- Adults with generalized MG: 85 to 90%
- Childhood MG: 50%
- Ocular MG: 50% to 70%
- MG and thymoma: Nearly 100%

AChR-binding antibody concentrations may be elevated rarely in patients with

- Systemic lupus erythematosus,
- Inflammatory neuropathy,
- Amyotrophic lateral sclerosis,
- Rheumatoid arthritis who are taking D-penicillamine, and
- Thymoma without MG
- In normal relatives of patients with MG.

Clinical correlations of MG and anti-AChR antibodies

- Absolute titer of antibodies - No relation with severity of MG
- Antibody blocking and modulation of AChRs - Some correlation with severity
- Change in titer of antibodies in individual patient - Improvement often seen with reduction of > 50%
- Neonatal MG: Transient and high anti-fetal/anti-adult muscle anti-AChR antibody ratio

Patients with MG but no anti-AChR antibodies

- Rule out hereditary MG
- Low frequency of thymic pathology and thymoma

More than one muscle is tested: Strong muscles often have less decrement

A decremental response to RNS is not specific for MG, decrements may also be seen in presynaptic disorders such as LEMS and motor neuron diseases.

SERUM ANTIBODIES

Anti-AChR antibodies are detectable in the serum of approximately 80% of all myasthenic patients. The serum concentration of AChR Abs cannot be used to predict the severity of disease in individual patients. Approximately 10% of patients who lack binding antibodies have antibodies that modulate the turnover of AChR in tissue culture. The concentration of binding antibodies may be low at symptom onset and rise later. Repeat studies are appropriate when initial values are normal. In general, finding AChR-binding antibodies in a patient with compatible clinical features confirm the diagnosis of MG, but normal concentrations do not exclude the diagnosis.

Antibodies to muscle-specific receptor tyrosine kinase have recently been described in patients with generalized MG who are seronegative for AChR antibodies. Repetitive Nerve Stimulation (RNS): 2 to 3 Hz

Repetitive nerve stimulation of a nerve supplying a symptomatic muscle is performed. Abnormality in MG is considered to be a reproducible 10% decrement in amplitude when the first stimulus is compared to the fourth or fifth, which is found in at least one muscles. Anticholinesterase medications should be withheld at least 12 hours before testing. RNS is positive in only 50% of patients with ocular MG.

RNS is positive in about 75% of patients with generalized MG, if

- Proximal and clinically involved muscles are tested
- Muscle is warm: Cooling reduces size of decrement
- More than one muscle is tested: Strong muscles often have less decrement

A decremental response to RNS is not specific for MG, decrements may also be seen in presynaptic disorders such as LEMS and motor neuron diseases.

SINGLE FIBER ELECTROMYOGRAPHY (SFEMG)

SFEMG is the most sensitive test for MG. Sensitivity is > 95% in generalized and ocular MG when the test site includes facial muscles. A normal jitter in a weak muscle conclusively rules out MG. Abnormal jitter is not specific for MG. May occur in other neuromuscular disorders, including ALS, polymyositis or LEMS. In MG, Jitter is greatest in weak muscles. Patients with mild or purely ocular muscle weakness may have increased jitter only in facial muscles. Studies to determine whether jitter in limb muscles predicts the development of generalized myasthenia in patients with purely ocular weakness show that at least one half of patients with persistent ocular myasthenia have increased jitter in the limb. Therefore increased jitter in a limb muscle does not predict the subsequent development of generalized myasthenia, and no threshold jitter value predicts the development of generalized weakness.

Ocular Cooling

Decrease in lid ptosis when the eye is cooled with an ice pack has been proposed as a simple and relatively sensitive technique to differentiate myasthenic from nonmyasthenic eyelid ptosis. The observed effect is due to a normal physiological response wherein cooling facilitates neuromuscular transmission. However its specificity for MG
has not been fully determined.

**TREATMENT**

There have been very few controlled clinical trials for treatment of MG. Most of the recommended regimens are empirical. The treatment decisions should be based on knowledge of the predicted course of disease in each patient and the predicted response to a specific treatment. Treatment goals must be individualized according to the severity of disease, the patient’s age and gender, and degree of functional impairment.

**Anticholinesterase medications**

Symptomatic management of autoimmune MG includes the cholinesterase inhibitors, especially pyridostigmine. Acetylcholinesterase inhibitors inhibit the enzymatic elimination of acetylcholine, increasing its concentration at the postsynaptic membrane. They play a supporting role in the management of symptoms throughout the disease course but do not affect the primary immune mechanism of the disease.

Cholinesterase inhibitor therapy, primarily with pyridostigmine, is usually effective early in the disease course or for patients with mild cases, presumably because there are still adequate numbers of AChRs present.

There is no substantial difference in efficacy among the various anticholinesterase drugs; oral pyridostigmine is the one most widely used.

The beneficial action of oral pyridostigmine begins within 15 to 30 min and lasts for 3 to 4 h, but individual responses vary. Treatment is begun with a moderate dose, e.g. 60 mg three to five times daily. The frequency and amount of the dose should be tailored to the patients individual requirements throughout the day.

Long-acting pyridostigmine tablets may help to get the patient through the night but should never be used for daytime medication because of their variable absorption. The maximum useful dose of pyridostigmine rarely exceeds 120 mg every 3 h during daytime.

Overdosage with anticholinesterase medication may cause increased weakness and other side effects. Muscarinic side effects of the anticholinesterase medication (diarrhea, abdominal cramps, salivation, nausea) may limit the dose tolerated. In such cases, propantheline bromide may be used to block the autonomic side effects. Loperamide is useful for the treatment of diarrhea. Bromism, presenting as acute psychosis, is a rare complication in patients taking large amounts of pyridostigmine bromide.

**Thymectomy**

Thymectomy is the classic long-term treatment. It is considered appropriate for patients between the ages of 15 to 60 years. The beneficial effects of thymectomy usually occur in the first year but may be seen as late as 5 years from the time of surgery. There is general consensus that thymectomy is helpful in the treatment of MG; however, a randomized controlled study has never been done. With thymoma, there is a clear role for thymectomy. For non-thymoma MG, thymectomy may increase the likelihood of disease remission of improvement. Typically, patients with generalized MG (Osserman stage 2b or worse) are selected for thymectomy.

Thymectomy for ocular MG (Osserman stage 1) has been supported by nonrandomized, uncontrolled data but remains a controversial issue. The trans-sternal approach is preferred because it allows for direct visualization and complete removal of the thymus and adipose tissue of the anterior mediastinum. In contrast, the transcervical approach by indirect mediastinoscopy is associated with a higher occurrence of residual thymus tissue, although this method is cosmetically more appealing. Controlled comparison of these two approaches has not demonstrated superiority of one over the other.

**Corticosteroids**

The current management of autoimmune diseases in general involves immunosuppressive medications. Therefore, the strategy usually translates into inducing a remission with high doses of the immunosuppressive agent.

When used appropriately, these medications are effective in inducing remission in at least 50%, and in as many as 80% of patients. Much of the improvement occurs in the first 6-8 weeks, but strength may increase to become total remission in the months that follow. The best responses occur in patients with recent onset of symptoms, but patients with chronic disease also may show improvement. The severity of disease does not predict the ultimate improvement. Patients with thymoma show an excellent response to prednisone before or after removal of the tumour. Initial studies of high-dose steroids demonstrated a worsening of the disease. It eventually became clear that the worsening occurred 7 to 14 days after initiation of the high doses but usually lasted less than 1 week. It appears that gradually increasing the dose of steroids over 1 to 2 months worsening of the disease. It eventually became clear that the worsening occurred 7 to 14 days after initiation of the high doses but usually lasted less than 1 week. It appears that gradually increasing the dose of steroids over 1 to 2 months reduces the risk of the early worsening of the disease.

The most predictable response to prednisone occurs when treatment begins with a daily dose of 1.5-2.0 mg/kg per day. This dose is given until sustained improvement occurs, which is usually within 2 weeks, and is then changed to an alternate-day schedule. This dose is gradually decreased over many months to the lowest dose necessary to maintain improvement, which is usually less than 20 mg every other day. If any weakness returns as the prednisone dose is reduced, the prednisone dose should be increased and another immunosuppressant should be added. Most patients who have a good response to prednisone become weak if the drug is stopped but may maintain strength with very low dosages (5-10 mg every other day).
The major disadvantages of chronic corticosteroid therapy are the side effects. Hypercorticism occurs in approximately one half the patients treated with the suggested regimen. Side effects are minimized when patients use a low-fat, low-sodium diet and take supplemental calcium. Postmenopausal women should also take supplementary vitamin D.

**Immunosuppressant drugs**

Several immunosuppressant drugs are effective in MG.

1. Azathioprine
2. Cyclosporine
3. Cyclophosphamide
4. Mycophenolate mofetil

Amongst the immunosuppressants, azathioprine is the drug most commonly used. Few studies have suggested that it is useful alone to induce a remission, but most studies have described its use in conjunction with corticosteroids.\(^{20,21}\)

A large double-blinded, randomized study has demonstrated its effectiveness as a steroid-sparing agent.\(^{22}\) The therapeutic dose of azathioprine is 2 to 3 mg/kg. (The initial dose should be 1 mg/kg with gradual increase to the therapeutic dose). It reverses symptoms in most patients, but the effect is delayed by 3-6 months. Improvement is maintained as long as the drug is given, but symptoms almost always recur 2-3 months after the drug is discontinued or the dose is reduced below therapeutic levels. Patients whose MG does not improve with corticosteroids may have a response to azathioprine, and the reverse is also true. Because the response to azathioprine is delayed, both drugs may be started simultaneously with the intent of rapidly tapering the dose of prednisone when azathioprine becomes effective.

Cyclosporine (CYA) is a potent immunosuppressant that inhibits predominantly T-lymphocyte-dependent immune responses. Cyclosporine A has been studied for patients with MG, primarily as a steroid-sparing mediation for steroid-dependent patients.\(^{23}\)

CYA is started at a daily dose of 5-6 mg/kg, given in two divided doses. Serum creatinine should be measured monthly. Renal toxicity and hypertension are the important adverse reactions of CYA.

Cyclophosphamide is a strong alkylating agent that acts on DNA, inhibiting cell proliferation. It is given intravenously in pulsed monthly doses and has been used effectively in severe, generalized MG that is refractory to other therapy.\(^ {24}\) The initial dose was 500 mg/m², which was subsequently titrated according to changes in strength and to reduce side effects. Cyclophosphamide can also be given orally, at a dose 150-200 mg per day to a total of 5-10 g, as required to relieve symptoms. The risks of the side effects of this medication are even greater than those of steroids. Alopecia is the major side effect. Other side effects are severe bone marrow suppression with risk of opportunistic infections, bladder toxicity, and a dose-related risk of neoplasms.

**Mycophenolate mofetil (MM) (CellCept)** - It is an inhibitor of the pathway for de novo purine synthesis by directly blocking the enzyme inosine monophosphate dehydrogenase. It is highly specific for proliferating lymphocytes, which do not make use of the purine salvage pathway.\(^ {25}\) A potential role for MM as a corticosteroid-sparing agent and as adjunctive therapy in refractory MG has recently been reported in an open-label pilot study.\(^ {26}\) The usual dose is 2 g per day, in divided doses 12 hours apart. Improvement has been reported as a early 2 weeks and is usually seen within 2 months in responding patients. The most common side effect is diarrhea, which can usually be managed by altering the dose schedule. The risk of leukopenia requires periodic blood counts, especially after therapy is begun. MM in patients with refractory MG and as a corticosteroid-sparing agent when azathioprine has produced intolerable side effects or has not been effective.

**Plasma exchange**

Almost all patients with MG show temporary improvement after plasma exchange.\(^ {27,28}\) It is used as a short-term intervention for patients with sudden worsening of myasthenic symptoms for any reason; to rapidly improve strength before surgery, concomitantly with starting high dose corticosteroids; and as a chronic intermittent treatment for patients whose MG is refractory to all other treatments. The need for plasma exchange and the timing of use are determined by the clinical response in individual patients.

A typical protocol of plasma exchange is to remove 2-3 liters of plasma three times a week until improvement plateaus, usually after five to six exchanges. Improvement usually begins after the second or third exchange. Maximum improvement may be reached as early as the first exchange or as late as the fourteenth. Improvement lasts for weeks or months and then the effect is lost unless the exchange is followed by thymectomy or immunosuppressive therapy. Most patients who have a response to the first course have a response again to subsequent courses. Repeated exchanges do not produce a cumulative benefit and should not be used as chronic maintenance therapy unless other treatments have failed or are contraindicated.

Adverse reactions to plasma exchange include transitory cardiac arrhythmias, nausea, lightheadness, chills, obscured vision, and pedal edema. The major complications are related to the route of access. Peripheral venipuncture should be used whenever possible to minimize the risk of thromboses, thrombophlebitis, and subacute bacterial endocarditis, as well as pneumothorax and brachial plexus injury when subclavian lines, arteriovenous shunts, or grafts are placed for vascular access. A flu-like illness has been reported in patients with reduced immunoglobulin levels.

**Intravenous immunoglobulin**

The process involves daily infusions of polyclonal human Ig, usually 0.4 g/kg/d for 5 consecutive days.\(^ {29}\) The precise mechanisms of action in MG are not known. In general, there appears to be modulation of the inhibitory pathways or down-regulation of production of antibodies against AChR. A
multicenter, randomized, controlled study comparing plasmapheresis with IV Ig has demonstrated equal efficacy but significantly fewer and less severe side effects for the IV Ig treatment. Improvement occurs in 50-100% of patients, usually beginning within 1 week and lasting for several weeks or months. Common adverse effects of IVIG are related to the rate of infusion and include headaches, chills, and fever. These reactions can be reduced by giving acetaminophen or aspirin with diphenhydramine before each infusion.

Severe reactions, such as alopecia, aseptic meningitis, leukopenia, and retinal necrosis, are rare but have been reported in patients receiving IVIG for diseases other than MG. Renal failure and headaches may occur. Reports of vascular occlusion have been made in patients receiving IVIG. Cerebrovascular and myocardial infarction have occurred, but the mechanism for this is not known, and it is unclear if it is related to the infusate rate, the immunoglobulin concentration by-products, or the osmolality of the preparation. Pre-existing arteriosclerosis appears to be a prerequisite for the occurrence of strokes or heart attacks. IVIG is contraindicated in patients with selective immunoglobulin (Ig)A deficiency because they may develop anaphylaxis to the IgA in IVIG preparations. IgA levels may be measured in all patients before IVIG therapy is started to detect this condition.

The indications for IVIG are similar to those for plasma exchange. IVIG is an effective alternative to plasma exchange, especially in patients with poor vascular access or when plasma exchange is not available. As with plasma exchange, IVIG should not be used as chronic therapy unless other treatments are contraindicated or have been ineffective.

**Myasthenic crisis**

Myasthenic crisis signifies rapid deterioration of the myasthenic status often with respiratory failure, is a potentially life-threatening complication that occurs in approximately 15 to 20% of patients. Myasthenic crisis is life-threatening and must be treated in intensive care unit. Maintenance of vital parameters with assistance, use of rapidly acting agents like immunoglobulins and plasmapheresis and treating the precipitating event are the mainstays of the therapy. Despite the rigorous, improved treatment of myasthenia gravis there is a small group of patients with myasthenia gravis that suffer from crises. Mortality in myasthenic crisis had declined from over 40% in the early 1960s to approximately 5% in the 1970s, due in large part to improvement in respiratory care and intensive care unit (ICU) management.

**References**

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Obituary

Homage to Prof. Sam GP Moses (1.6.1927 - 16.9.2004)

Prof. Sam GP Moses, "Father of Diabetes" expired on 16.9.2004 at Chennai. His sudden demise left a vacuum in the field of diabetes hard to fill up. His achievements are not mean right from his studentship onwards.

He was ranked first in B.Sc; MBBS and M.D. General medicine. He was instrumental in starting first Diabetic Clinic in the country in 1953 at Madras Medical College and General Hospital which earned him the popular title "Father of Diabetes". He was the youngest person to be promoted as Prof. of Medicine in 1957 at Madras Medical College and by the time he retired after 30 years of service in 1987, he won many laurels and awards from prestigious medical forums. To mention a few, he was the first Head of the Department of Diabetology at Madras Medical College, recipient of Fellowship of Royal College of Physicians, Hony. Doctorate from Dr. MGR Medical University, Gifted Teacher award from API and Lifetime Achievement Award in Endocrinology. Prof. Sam GP Moses was founder fellow of Indian College of Physicians, RSSDI, All India Institute of Diabetes and advisor to API, Chennai Chapter. He served as president of Diabetes Association of India in 1974, Chaired IDF and number of national and international conferences, presented first Indian paper on Malnutrition and Diabetes in 1971 besides many original papers and articles to his credit.

His professional knowledge, oratory skill with unmatched speed punctuated with humor, bound the audience to keenly follow without any diversion. He traveled widely sparing no city in India and also small towns and villages spreading the education on Diabetes. Many HODs in Chennai city hospitals are his students besides many scattered all over the world. His enviable knowledge and popularity crowned with simplicity endeared him to the medical fraternity. In his death not only the medical fraternity but also India as a whole lost a dedicated diabetologist at a time when services of such eminent persons are required to combat the disease which is acquiring monstrous proportion.

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