

Test & Diagnostic methods

In addition to a complete medical and neurological evaluation, a number of tests may be used to establish a diagnosis of MG. A characteristic of MG is that patients have weakness that comes on with activity and improves following rest. To examine for weakness with activity, a clinician might have a patient do a sustained task, such as looking upwards (which induces the eyelids to remain elevated) to see if the eyelids start to droop (referred to clinically as ptosis) when the eyelids are open for several minutes. To test for recovery of strength after rest, a clinician may examine muscle strength and then have the patient suspected to have MG rest or rest a part of the body and then retest muscle strength after rest to see if strength improves. For example if a person who is suspected to have MG has droopy eyelids, the physician might have the patient lay down with his/her eyes closed for several minutes, perhaps with a cool pack over the eyelids, to see if eyelid function improves after rest.

A diagnosis can be confirmed in several ways, including the following:

Anti-MuSK Antibody testing----a blood test for the remaining 15% of MG patients who have tested negative for the acetylcholine antibody. These patients have seronegative (SN) MG. About 40% of patients with SNMG test positive for the anti-MuSK antibody. The remaining patients have unidentified antibodies causing their MG.

Office Tests—Sleep, Ice Pack and Edrophonium tests are examinations performed by specialists to evaluate an improvement in strength that may be consistent with MG.

Electromyography— (EMG) studies can provide support for the diagnosis of MG when characteristic patterns are present. Repetitive Nerve Stimulation is used to check for a pattern of response that is characteristic of MG.

Single Fiber EMG— studies can provide support for the diagnosis of MG when characteristic patterns are present. The single fiber EMG and AChR antibody test are primary tests used to confirm a clinical diagnosis of MG.

Acetylcholine Receptor Antibody— a blood test for the abnormal antibodies can be performed to see if they are present. Approximately 85% of MG patients have this antibody and, when detected with an elevated concentration the AChR antibody test is strongly indicative of MG.

Sometimes all of these tests are negative or equivocal in someone whose story and examination still seem to point to a diagnosis of MG. A clinician skilled in recognizing MG and distinguishing MG from other conditions would need to determine if such a patient has MG or another disorder.

There are many effective treatments for myasthenia gravis. Spontaneous improvement and even remission (although uncommon) may occur without specific therapy.

Anti-acetylcholinesterase agents (e.g., Mestinon®) allow acetylcholine to remain at the neuromuscular junction longer than usual so that more receptor sites can be activated.

Corticosteroids (e.g., prednisone) and immunosuppressant agents (e.g., Imuran®) may be used to suppress the abnormal action of the immune system that occurs in MG. Thymectomy (surgical removal of the thymus gland) is another treatment used in some patients. The thymus gland lies behind the breastbone and is an important part of the immune system. When there is a tumor of the thymus gland (in 10-15% of patients with MG), it is always removed because of the risk of malignancy. Thymectomy may lessen the severity of the MG weakness after some months to years. In some people the weakness may completely disappear. This is called a remission. The degree to which the thymectomy helps varies with each patient.

Plasmapheresis, or plasma exchange, may be useful in the treatment of MG also. This procedure removes the abnormal antibodies from the plasma of the blood. The improvement in muscle strength may be striking, but is usually short-lived, since production of the abnormal antibodies continues. When plasmapheresis is used, it may require repeated exchanges. Plasmapheresis may be especially useful during severe MG weakness or prior to surgery.

Intravenous immune globulins (IVIg) are sometimes used to affect the function or production of the abnormal antibodies also.

Newer treatments with monoclonal antibodies (rituximab, eculizumab) are under active clinical trials and may be available in the near future as another tool in the treatment of MG.

Treatment decisions are based on knowledge of the natural history of MG in each patient and the predicted response to a specific form of therapy. Treatment goals are individualized according to the severity of the MG weakness, the patient's age and sex, and the degree of impairment.

**What is the prognosis for those with MG?**

The current treatments for MG are sufficiently effective that the outlook for most patients is bright. Although the treatments may not cure MG, most patients will have improvement in their muscle strength. In some cases MG may go into remission during which treatment can be modified or reduced.. There is much that can be done, but still much to understand. New drugs to improve treatments are needed. Research plays an important role in finding new answers and treatments for MG.

**Clinical Overview of MG**

MYASTHENIA GRAVIS - A SUMMARY
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Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission. The usual cause is an acquired immunological abnormality, but some cases result from genetic abnormalities at the neuromuscular junction. Much has been learned about the pathophysiology and immunopathology of myasthenia gravis during the past 20 years. What was once a relatively obscure condition of interest primarily to neurologists is now the best characterized and understood autoimmune disease. A wide range of potentially effective treatments are available, many of which have implications for the treatment of other autoimmune disorders.

**Epidemiology**

The prevalence of myasthenia gravis in the United States is estimated at 14 to 20 per 100,000 population, approximately 36,000 to 60,000 cases in the United States. However, myasthenia gravis remains underdiagnosed and the prevalence is probably higher. Previous studies have shown that women are more often affected than men. The most common age at onset is the second and third decades in women and the seventh and eighth decades in men. As the population ages, the average age at onset has increased correspondingly, and now males are more often affected than females, and the onset of symptoms is usually after age 50. A 2015 study in acetylcholine receptor antibody (AChR-Abs) positive Caucasian has demonstrated that there is no specific causal gene for myasthenia gravis there are specific regulatory genes that influence immune regulation. In addition, about 3% of the study population had a primary relative with myasthenia gravis suggesting a small but distinct but not direct genetic influence.

**Clinical Presentation**

Patients with myasthenia gravis come to the physician complaining of specific muscle weakness and not of generalized fatigue. Ocular motor disturbances, ptosis or diplopia, are the initial symptom of myasthenia gravis in two-thirds of patients; almost all had both symptoms within 2 years. Oropharyngeal muscle weakness, difficulty chewing tough, chewy or fibrous foods, swallowing, or talking, is the initial symptom in one-sixth of patients, and limb weakness in only 10%. Initial weakness is rarely limited to single muscle groups such as neck or finger extensors or hip flexors. 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.

The course of disease is variable but usually progressive. Weakness is restricted to the ocular muscles in about 10% to 40% 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. In the era before corticosteroids were used for treatment, approximately one-third of patients improved spontaneously, one-third became worse, and one-third died of the disease. Spontaneous improvement frequently occurred early in the course. Symptoms fluctuated over a relatively short period of time and then became progressively severe for several years (active stage). The active stage is followed by an inactive state in which fluctuations in strength still occurred but are attributable to fatigue, intercurrent illness, or other identifiable factors. After 15 to 20 years, weakness often becomes fixed and the most severely involved muscles are frequently atrophic (burnt-out stage). 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 increases in body temperature.

**Pathophysiology of Myasthenia Gravis**

The normal neuromuscular junction releases acetylcholine (ACh) from the motor nerve terminal in discrete packages (quanta). The ACh quanta diffuse across the synaptic cleft and bind to receptors on the folded muscle end-plate membrane. Stimulation of the motor nerve releases many ACh quanta that depolarize the muscle end-plate region and then the muscle membrane causing muscle contraction. In acquired myasthenia gravis, the post-synaptic muscle membrane is distorted and simplified, having lost its normal folded shape. The concentration of ACh receptors on the muscle end-plate membrane is reduced, and antibodies are attached to the membrane. ACh is released normally, but its effect on the post-synaptic membrane is reduced. The post-junctional membrane is less sensitive to applied ACh, and the probability that any nerve impulse will cause a muscle action potential is reduced.

**The Thymus in Myasthenia Gravis**

Thymic abnormalities are clearly associated with myasthenia gravis but the nature of the association is uncertain. Ten percent of patients with myasthenia gravis have a thymic tumor and 70% have hyperplastic changes (germinal centers) that indicate an active immune response. These are areas within lymphoid tissue where B-cells interact with helper T-cells to produce antibodies. Because the thymus is the central organ for immunological self-tolerance, it is reasonable to suspect that thymic abnormalities cause the breakdown in tolerance that causes an immune-mediated attack on AChR in myasthenia gravis. The thymus contains all the necessary elements for the pathogenesis of myasthenia gravis: myoid cells that express the AChR antigen, antigen presenting cells, and immunocompetent T-cells. Thymus tissue from patients with myasthenia gravis produces AChR antibodies when implanted into immunodeficient mice. However, it is still uncertain whether the role of the thymus in the pathogenesis of myasthenia gravis is primary or secondary. Most thymic tumors in patients with myasthenia gravis are benign, well-differentiated and encapsulated, and can be removed completely at surgery. It is unlikely that thymomas result from chronic thymic hyperactivity because myasthenia gravis can develop years after thymoma removal and the HLA haplotypes that predominate in patients with thymic hyperplasia are different from those with thymomas. Patients with thymoma usually have more severe disease, higher levels of AChR antibodies, and more severe EMG abnormalities than patients without thymoma. Almost 20% of patients with myasthenia gravis whose symptoms began between the ages of 30 and 60 years have thymoma; the frequency is much lower when symptom onset is after age 60.

**Diagnostic Procedures**

The diagnosis of MG is often delayed months or even years (in the mildest cases). The unusual distribution and fluctuating symptoms often suggests psychiatric disease. Patients with drooping eyelids, double vision and difficulty with speech or swallowing symptoms suggest intracranial pathology and often lead to an evaluation for stroke, brain tumor or multiple sclerosis. Patients with anti-MuSK-antibody positive MG may have focal or regional weakness and muscle atrophy that are more suggestive of motor neuron or muscle membrane (myopathy) disease.

**The Edrophonium Chloride (Tensilon®) Test**

Weakness caused by abnormal neuromuscular transmission characteristically improves after intravenous administration of edrophonium chloride, commonly referred to as the Tensilon® Test. Some patients who do not respond to intravenous edrophonium chloride may respond to intramuscular neostigmine, because of its longer duration of action. Intramuscular neostigmine is particularly useful in infants and children whose response to intravenous edrophonium chloride may be too brief for adequate observation. In some patients, a therapeutic trial of daily oral pyridostigmine may produce improvement that can't be appreciated after a single dose of edrophonium chloride or neostigmine.

**Serum Antibodies in Myasthenia Gravis**

Several types of antibodies are found in the majority of patients with MG and include forms directed against the acetylcholine receptor (AChR) and muscle-specific receptor tyrosine kinase (MuSK). Ten percent of patients with acquired, presumably immune-mediated MG do not have detectable serum antibodies to AChR or MuSK. In these seronegative patients, the diagnosis is based on the clinical presentation, the response to cholinesterase inhibitors and electrodiagnostic findings.

Anti-striational muscle antibodies (Str-Abs), which react with contractile elements of skeletal muscle, are not pathogenic. They are found in more than 90% of MG patients with thymoma, and in one-third of patients with thymoma who do not have MG. One-third of MG patients without thymoma also have these antibodies; they are more frequent in older patients and in those with more severe disease. Str-Abs are also elevated in other disorders including autoimmune liver disease and infrequently in Lambert-Eaton syndrome and in primary lung cancer. Str-Abs are rarely, if ever, elevated in MG in the absence of acetylcholine receptor antibodies and are therefore of limited use in confirming the diagnosis. The main clinical value of Str-Abs is in predicting thymoma: 60% of patients with MG with disease onset before age 50 who have elevated Str-Abs acetylcholine receptor antibodies (AChR-Abs) have thymoma.

At least 85% of patients with acquired generalized myasthenia and 54% with ocular myasthenia have serum antibodies that bind human acetylcholine receptor (AChR) although there is wide variation in reported studies. The serum concentration of AChR antibody varies widely among patients with similar degrees of weakness and its level cannot predict the severity of disease in individual patients. Approximately 10% of patients who do not have binding antibodies, have other antibodies that modulate the turnover of AChR in tissue culture. The concentration of binding antibodies may be low or absent at symptom onset and become elevated later. AChR binding antibodies concentrations are sometimes increased in patients with systemic lupus erythematosus, inflammatory neuropathy, amyotrophic lateral sclerosis, rheumatoid arthritis taking D-penicillamine, thymoma without myasthenia gravis, and in normal relatives of patients with myasthenia gravis. False positive tests are reported when blood is drawn within 48 hours of a surgical procedure involving the use of general anesthesia and muscle relaxants. In general, an elevated concentration of AChR binding antibodies in a patient with compatible clinical features confirms the diagnosis of myasthenia gravis, but normal antibody concentrations do not exclude the diagnosis.

Antibodies to muscle-specific receptor tyrosine kinase (MuSK), a surface membrane component essential in the development of the neuromuscular junction, have recently been identified and are found in up to 40% of MG patients who are seronegative for AChR antibodies. Another small percentage of these seronegative patients have antibody to the agrin receptor low-density lipoprotein receptor–related protein 4 (LRP4). These patients typically will have prominent weakness of the neck, oro-bulbar and sometimes respiratory musculature, are often poorly responsive to cholinesterase inhibitors.

**Electromyography**

**Repetitive Nerve Stimulation (RNS)**

The amplitude of the compound muscle action potential (CMAP) elicited by repetitive nerve stimulation is normal or only slightly reduced in patients without MG. The amplitude of the fourth or fifth response to a train of low frequency nerve stimuli falls at least 10% from the initial value in myasthenic patients. This decrementing response to RNS is seen more often in proximal muscles, such as the facial muscles, biceps, deltoid, and trapezius than in hand muscles. A significant decrement to RNS in either a hand or shoulder muscle is found in about 60% of patients with myasthenia gravis.

**Single Fiber EMG (SFEMG)**

Voluntary SFEMG is done with the patient making minor contraction of the muscle with the physician using either a standard single fiber electrode or a concentric needle EMG electrode with the smallest recording surface. The third technique, axonal micro-stimulation, requires the terminal nerve branch to be activate with a small amount of electrical current while recording with the electrode. All of the techniques are technically demanding. Each have specific normative values to which the patient’s study can be compared if the same methodology is used. The latter technique is very useful in sedated infants and children.

**Comparison of Diagnostic Techniques**

Intravenous edrophonium chloride is often diagnostic in patients with ptosis or ophthalmoparesis, but is less useful when other muscles are weak. Elevated serum concentrations of AChR binding and probably MuSK antibodies virtually assures the diagnosis of myasthenia gravis, but normal concentrations do not exclude the diagnosis. Repetitive nerve stimulation confirms impaired neuromuscular transmission but is not specific to myasthenia gravis and is frequently normal in patients with mild or purely ocular disease. The measurement of jitter by SFEMG is the most sensitive clinical test of neuromuscular transmission and is abnormal in almost all patients with myasthenia gravis. A normal test in a weak muscle excludes the diagnosis of myasthenia gravis, but an abnormal test can occur when other motor unit disorders cause defects in neuromuscular transmission.

**Treatment**

A controlled clinical trial has never been reported for any medical or surgical modality used to treat myasthenia gravis. All recommended regimens are empirical and experts disagree on treatments of choice. Treatment decisions should be based on knowledge of the natural history of disease in each patient and the predicted response to a specific form of therapy. Treatment goals must be individualized according to the severity of disease, the patient's age and sex, and the degree of functional impairment. The response to any form of treatment is difficult to assess because the severity of symptoms fluctuates. Spontaneous improvement, even remissions, occur without specific therapy, especially during the early stages of the disease.

**Cholinesterase Inhibitors**

ChE inhibitors retard the enzymatic hydrolysis of ACh at cholinergic synapses, so that ACh accumulates at the neuromuscular junction and its effect is prolonged. ChE inhibitors cause considerable improvement in some patients and little to none in others. Strength rarely returns to normal. Pyridostigmine bromide (Mestinon) and neostigmine bromide (Prostigmin) are the most commonly used ChE inhibitors. No fixed dosage schedule suits all patients. The need for ACh inhibitors varies from day-to-day and during the same day in response to infection, menstruation, emotional stress, and hot weather. Different muscles respond differently; with any dose, certain muscles get stronger, others do not change, and still others become weaker. Adverse effects of ChE inhibitors may result from ACh accumulation at muscarinic receptors on smooth muscle and autonomic glands and at nicotinic receptors of skeletal muscle. Central nervous system side effects are rarely seen with the doses used to treat myasthenia gravis. Gastrointestinal complaints are common; queasiness, loose stools, nausea, vomiting, abdominal cramps, and diarrhea. Increased bronchial and oral secretions are a serious problem in patients with swallowing or respiratory insufficiency. Symptoms of muscarinic overdosage may indicate that nicotinic overdosage (weakness) is also occurring. Excessive nicotinic receptor overdosage results in Myasthenic Crisis characterized by severe generalized weakness and respiratory failure.

**Thymectomy**

Thymectomy is recommended by many physicians for most patients with myasthenia gravis. Most reports do not correlate the severity of weakness before surgery and the timing or degree of improvement after thymectomy. The maximal favorable response generally occurs 2 to 5 years after surgery. However, the response is relatively unpredictable and significant impairment may continue for months or years after surgery. Sometimes, improvement is only appreciated in retrospect. The best responses to thymectomy are in young people early in the course of their disease, but improvement can occur even after 30 years of symptoms. Patients with disease onset after the age of 60 rarely show substantial improvement from thymectomy. Patients with thymomas do not respond as well to thymectomy as do patients without thymoma. A large, international multi-center clinical trial began in 2006 to determine the role of thymectomy in steroid-treated patients.

**Corticosteroids**

Marked improvement or complete relief of symptoms occurs in more than 75% of patients treated with prednisone, and some improvement occurs in most of the rest. Much of the improvement occurs in the first 6 to 8 weeks, but strength may increase to total remission in the months that follow. The best responses occur in patients with recent onset of symptoms, but patients with chronic disease may also respond. The severity of disease does not predict the ultimate improvement. Patients with thymoma have an excellent response to prednisone before or after removal of the tumor. The most predictable response to prednisone occurs when treatment begins with a daily dose of 1.5 to 2 mg/kg/day. About one-third of patients become weaker temporarily after starting prednisone, usually within the first 7 to 10 days, and lasting for up to 6 days. Treatment can be started at low dose to minimize exacerbations; the dose is then slowly increased until improvement occurs. Exacerbations may also occur with this approach and the response is less predictable. The major disadvantages of chronic corticosteroid therapy are the side effects.

**Immunosuppressant Drugs**

Azathioprine reverses symptoms in most patients but the effect is delayed by 4 to 8 months. Once improvement begins, it is maintained for as long as the drug is given, but symptoms recur 2 to 3 months after the drug is discontinued or the dose is reduced below therapeutic levels. Patients who fail corticosteroids may respond to azathioprine and the reverse is also true. Some respond better to treatment with both drugs than to either alone. Because the response to azathioprine is delayed, both drugs may be started simultaneously with the intent of rapidly tapering prednisone when azathioprine becomes effective. Approximately one-third of patients have mild dose-dependent side effects that may require dose reductions but do not require stopping treatment.

Cyclosporine inhibits predominantly T-lymphocyte-dependent immune responses and is sometimes beneficial in treating myasthenia gravis. Most patients with myasthenia gravis improve 1 to 2 months after starting cyclosporine and improvement is maintained as long as therapeutic doses are given. Maximum improvement is achieved 6 months or longer after starting treatment. After achieving the maximal response, the dose is gradually reduced to the minimum that maintains improvement. Renal toxicity and hypertension, the important adverse reactions of cyclosporine. Many drugs interfere with cyclosporine metabolism and should be avoided or used with caution.

Cyclophosphamide has been used intravenously and orally for the treatment of myasthenia gravis. More than half of patients become asymptomatic after one year. Side effects are common. Life-threatening infections are an important risk in immunosuppressed patients, but in our experience, this risk is limited to patients with invasive thymoma. The long-term risk of malignancy is not established, but there are no reports of an increased incidence of malignancy in patients with myasthenia gravis receiving immunosuppression. Mycophenolate mofetil (MMF) selectively inhibits the proliferation of activated B and T lymphocytes. It also suppresses the formation of antibodies active in complement-dependent lysis and antibody-dependent, cell-mediated cytotoxicity, a necessary feature to promote many autoimmune diseases. While case reports, pilot studies and retrospective series have demonstrated a potential role for MMF as a corticosteroid-sparing agent and as adjunctive or primary therapy in refractory MG, a large clinical trial did not show superiority of MMF as a corticosteroid-sparing agent. Similar findings were found for methotrexate (MTX). Others are using both as a preferred treatment because of their faster onset of action when compared to azathioprine. Both the MMF and MTX trials have been criticized for study design failings and the fact that prednisone was a much better drug than anyone thought it was. Despite these failings the majority of experts continue to use MMF as a primary and secondary treatment for MG.  Eculizumab, a humanized monoclonal antibody to the fifth component of complement (C5), was shown to be successful in improving strength in patients with refractory (failing at least 2 immunotherapies for at least 1 year) generalized myasthenia gravis. This first-in-kind therapy is currently in Phase 3 trials.

**Plasma Exchange**

Plasma exchange is used as a short-term intervention for patients with sudden worsening of myasthenic symptoms for any reason, to rapidly improve strength before surgery, and as a chronic intermittent treatment for patients who are refractory to all other treatments. The need for plasma exchange, and its frequency of use is determined by the clinical response in the individual patient. Almost all patients with acquired myasthenia gravis improve temporarily following plasma exchange. Maximum improvement may be reached as early as after 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 respond to the first plasma exchange will respond again to subsequent courses. Repeated exchanges do not have a cumulative benefit.

**Intravenous Immune Globulin (IVIG)**

Several groups have reported a favorable response to high-dose (2 grams/kg infused over 2 to 5 days) IVIG. Possible mechanisms of action include down-regulation of antibodies directed against AChR and the introduction of anti-idiotypic antibodies. Improvement occurs in 50 to 100% of patients, usually beginning within 1 week and lasting for several weeks or months. The common adverse effects of IVIG are related to the rate of infusion. The mechanism of action is not known but is probably non-specific down regulation of antibody production. Most recently a subcutaneous form of the preparation is available and may be used as an alternative treatment option, especially in patients with limited intravenous access.

**The Future**

The future of Myasthenia Gravis lies in the continued elucidation of the molecular immunology of the multi-faceted immunological response with the goal of developing a rational treatment paradigms for the illness that will control and perhaps cure the abnormality in the immune system. The last decade has seen us rapidly broaden our understanding of the intertwining of immune function. It is no longer sufficient to target simply one arm of the immune system as we suggested a decade ago. While important work will continue in this realm, e.g. understanding T-regulatory cell function, targeting antigen specific CD4+ T-cells  and co-stimulatory responses, Phase 2 clinical trials are underway to target antigen specific B-cells with Rituximab. Phase 3 clinical trials are in progress to confirm pilot data on the role of complement inhibition as a first-in-kind therapeutic strategy to treat refractory MG. Pre-clinical studies inducing nasal tolerance or anergy of the CD4+ T-cell to the autoantigen or the CD4+ epitopes appears successful and will lead to Phase 2 clinical trial in the near future. Similarly, immunization with cytoplasmic domains to multiple AChR epitopes prevented the induction or reversed the severity of weakness of experimental Myasthenia Gravis. Exploration of the role of the FcRn receptor is gaining interest as inhibition may improve autoimmune disease. The research landscape looks bright. It has brought many advances over the last decade of which some are being actively translated into new therapies.