Myasthenia Gravis

Myasthenia gravis interferes with messages your nerves send to your muscles. Myasthenia gravis often affects muscles in your head. Common symptoms are trouble with eye and eyelid movement, facial expression and swallowing. If you have myasthenia gravis, it is important to follow your treatment plan. If you do, you can expect your life to be normal or close to it.

Myasthenia gravis is caused by a problem in the transmission of nerve signals to your muscles. Normally, nerve endings release a substance that attaches to receptors on your muscles. That tells your muscles to contract. If you have myasthenia gravis, your body's own immune system makes antibodies to block that signal.

Medicine can help improve nerve-to-muscle messages and make muscles stronger. Other medicines can keep your body from making so many abnormal antibodies. Sometimes surgery to take out the thymus gland helps.

Myasthenia gravis is a chronic disorder characterized by weakness and rapid fatigue of any of the muscles under your voluntary control. The cause of myasthenia gravis is a breakdown in the normal communication between nerves and muscles.

The disorder affects only the function of your muscles, and the muscle weakness you experience improves when you rest. Myasthenia gravis may cause double vision, drooping eyelids, difficulties with speech, chewing, swallowing and breathing, as well as weakness of your limbs.

Myasthenia gravis can affect people of any age, but it's more common in women younger than 40 or older than 70, and in men older than 50. There's no cure for myasthenia gravis, but treatments are available to help control the signs and symptoms of the condition.

**Signs and symptoms**

Myasthenia gravis can affect any of the muscles that you control voluntarily. It most commonly affects certain muscles, including those of your face, eyes, arms and legs, and those muscles involved in chewing, swallowing and talking. Muscles that control breathing and the movement of your head, arms and legs also can be involved.

Signs and symptoms may include:

- Facial muscle weakness, including drooping eyelids
- Double vision

www.healthoracle.org
• Difficulty in breathing, talking, chewing or swallowing
• Muscle weakness in your arms or legs
• Fatigue brought on by repetitive motions

The more often a muscle action is repeated, the worse the weakness becomes. In myasthenia gravis, good days may alternate with bad days. Temporary remissions may occur. In rare cases, breathing or swallowing problems worsen markedly, requiring emergency medical care.

**Causes**

When your neuromuscular system functions normally, the chemical acetylcholine transmits nerve impulses to your muscles. At specialized areas of your muscles, called neuromuscular junctions, receptor sites receive nerve impulses and signal your muscles to contract, such as when you raise a spoon to your mouth.

In myasthenia gravis, there's a breakdown in communication between your nerves and your muscles. The culprit is your immune system. For unknown reasons, myasthenia gravis causes your immune system to produce antibodies that block or destroy many of the receptor sites for acetylcholine in your muscles. With fewer receptor sites available, your muscles receive fewer nerve signals, resulting in weakness.

It's believed that the thymus gland, a part of your immune system located in the upper chest beneath the breastbone, may trigger or maintain the production of these antibodies. Large in infancy, the thymus is small in healthy adults. But, in some adults with myasthenia gravis, the thymus is abnormally large. Some people also have tumors.
of the thymus. Usually, thymus gland tumors are non cancerous (benign).

Some factors can make myasthenia gravis worse, including fatigue, illness, stress, extreme heat, and some medications, such as beta blockers, calcium channel blockers, quinine and some antibiotics. Check with your doctor before taking any new medications, even over-the-counter drugs.

**When to seek medical advice**

If you experience muscle weakness or have difficulty controlling the muscles of your eyes, face and mouth, have trouble breathing or experience fluctuating weakness in your arms and legs, see your doctor. These signs and symptoms could be indications of myasthenia gravis.

Although there's no cure for myasthenia gravis, the outlook for managing its signs and symptoms is good. The earlier you see your doctor, the sooner treatments can be initiated to help you improve your muscle strength, and the sooner you can learn about strategies to help you use your energy in the most efficient ways.

**Screening and diagnosis**

The key sign that points to the possibility of myasthenia gravis is muscle weakness that improves with rest. Tests to confirm the diagnosis may include:

- **Neurological examination.** This may include testing of your reflexes, muscle strength, muscle tone, senses of touch and sight, gait, posture, coordination, balance and mental skills.

- **Blood analysis.** A blood test may reveal the presence of abnormal antibodies that disrupt the receptor sites where nerve impulses signal your muscles to move.
- **Edrophonium test.** Injection of the chemical edrophonium (Tensilon) may result in a sudden, although temporary, improvement in your muscle strength, an indication that you may have myasthenia gravis. Edrophonium acts to block an enzyme that breaks down acetylcholine, the chemical that transmits signals from your nerve endings to your muscle receptor sites.

- **Nerve conduction studies and single-fiber electromyography.** During the first part of this test, a small electrical impulse is applied to your skin, stimulating your nerves in order to test the strength of your muscle contraction. In the second part, a thin-needle electrode inserted into one of your muscles helps measure patterns of electrical activity in your muscle at rest and with slight muscle contraction.

**Treatment**

Doctors use a variety of treatments, alone or in combination, to relieve symptoms of myasthenia gravis:

- **Medications.** Drugs called cholinesterase inhibitors, such as pyridostigmine (Mestinon) and neostigmine (Prostigmin), enhance communication between nerves and muscles. These drugs don't treat the underlying problem, but they do improve muscle contraction and muscle strength.

Corticosteroids inhibit the immune system, limiting antibody production. Prolonged use of corticosteroids, however, can lead to serious side effects, such as bone thinning, weight gain, diabetes, increased risk of some infections and a redistribution of body fat.

Your doctor may also prescribe other medications that alter your immune system, such as azathioprine (Imuran), mycophenolate mofetil (CellCept), cyclophosphamide (Cytoxan) or cyclosporine (Sandimmune, Neoral).
• **Surgery.** It's generally been believed that removal of the thymus gland (thymectomy) brings relief to the majority of people with myasthenia gravis. But only about 25 percent of those who have the surgery go into remission within a year, and significant improvement is often delayed for years. The surgery has generally been recommended for people younger than 60.

Recent analysis has cast some doubt on the benefit of thymectomy in people who have myasthenia gravis but do not have thymomas (tumors in the thymus). A large international trial is being conducted to assess whether thymectomy should be routinely recommended in that group.

• **Plasmapheresis (plaz-muh-fuh-RE-sis).** This procedure can remedy life-threatening stages of myasthenia gravis. Plasmapheresis involves removal of antibodies from your blood that block transmission of signals from your nerve endings to your muscles' receptor sites. Blood is taken from your body, passed through a filter that removes antibodies and then returned to your body.

This approach is expensive and time-consuming. Also, other forms of therapy are necessary for long-term restoration of muscle strength. Otherwise, the immune system soon makes new antibodies to replace those that have been removed.

• **Intravenous immune globulin.** This therapy provides your body with normal antibodies, which alters your immune system response. It has a lower risk of side effects than do plasmapheresis and immune-suppressing therapy, but it can take a week or two to start working and lasts only several weeks to months.

This therapy is expensive, and it's not clear that intravenous immune globulin offers clear advantages over other available therapies. For those reasons, it's often reserved for people who are severely ill.
As part of your treatment, your doctor may suggest physical therapy and occupational therapy to help you adjust to tasks you need to do around the house and in your job.

Be sure not to take any medications without checking with your doctor. Some medications, such as some heart medications and botulinum toxin, can worsen myasthenia gravis.

**Coping skills**

Supplementing your medical care with these approaches may help you make the most of your energy and cope with the symptoms of myasthenia gravis:

- **Adjust your eating routine.** Try to eat when you have good muscle strength. A good time is after taking a cholinesterase inhibitor, such as pyridostigmine (Mestinon) and neostigmine (Prostigmin). Also, take your time eating and rest between bites. More frequent, smaller meals may be easier to handle. Also, try soft foods and avoid sticky foods that require lots of chewing.

- **Use safety precautions at home.** Install grab bars or railings in places where you may need support, such as next to the bathtub. Keep the floors and halls in your house clear of clutter, cords and loose rugs. Outside your home, keep the steps, sidewalk and path to your car clear.

- **Use electric appliances and power tools.** Save your energy in the bathroom, in the kitchen or at the workbench by using electric appliances, such as toothbrushes, can openers and screwdrivers.

- **Wear an eye patch.** If you have double vision, using an eye patch can help relieve this problem. Wear the patch while you read or watch television. To avoid eyestrain, periodically switch the patch from one eye to the other.
• **Plan.** If you have a chore to do around the house, shopping to do or an errand to run, plan the activity to coincide with the time at which your medication provides your peak energy level. If you're working on a project at home, gather everything you need for the job at one time, to eliminate extra trips that may drain your energy.

• **Ask for help.** Depending on your energy level, you may not be able to do everything you have planned around the house or run every errand that you need to. Ask family members and friends to lend a hand.

• **Manage stress.** Because emotional stress can make myasthenia gravis worse, look for ways to reduce stress. These may include relaxation techniques such as biofeedback and meditation.

**Pathophysiology**

Myasthenia gravis is an autoimmune disease; it features antibodies directed against the body's own proteins. While in various similar diseases the disease has been linked to a cross-reaction with an infective agent, there is no known causative pathogen that could account for myasthenia. There is a slight genetic predisposition: particular HLA types seem to predispose for MG (B8 and DR3 with DR1 more specific for ocular myasthenia). Up to 25% have a concurrent thymoma, a tumor (either benign or malignant) of the thymus, and other abnormalities are frequently found. The disease process generally remains stationary after thymectomy (removal of the thymus).

In MG, the autoantibodies are directed most commonly against the acetylcholine receptor (nicotinic type), the receptor in the motor end plate for the neurotransmitter acetylcholine that stimulates muscular contraction. Some forms of the antibody impair the ability of acetylcholine to bind to receptors. Others lead to the destruction of receptors, either by complement fixation or by inducing the muscle cell to eliminate the receptors through endocytosis.

The antibodies are produced by plasma cells, that have been derived from B cells. These plasma cells are activated by T-helper cells, which in turn are activated by binding to acetylcholine receptor antigenic peptide sequences (epitopes) that rest within the histocompatibility antigens of antigen presenting cells. The thymus plays an important role in the development of T-cells, which is why myasthenia gravis is associated with thymoma. The exact mechanisms are however not convincingly clarified.
In normal muscle contraction, cumulative activation of the ACh receptor leads to influx of sodium and calcium. Only when the levels of these electrolytes inside the muscle cell is high enough will it contract. Decreased numbers of functioning receptors therefore impairs muscular contraction.

It has recently been realized that a second category of gravis is due to auto-antibodies against the MuSK protein (muscle specific kinase), a tyrosine kinase receptor which is required for the formation of the neuromuscular junction. Antibodies against MuSK inhibit the signaling of MuSK normally induced by its nerve-derived ligand, agrin. The result is a decrease in patency of the neuromuscular junction, and the consequent symptoms of MG.

People treated with penicillamine can develop MG symptoms. Their antibody titer is usually similar to that of MG, but both the symptoms and the titer disappear when drug administration is discontinued.

MG is more common in families with other autoimmune diseases. A familial predisposition is found in 5% of the cases. This is associated with certain genetic variations such as an increased frequency of HLA-B8 and DR3. People with MG suffer from co-existing autoimmune diseases at a higher frequency than members of the general population. Of particular mention is co-existing thyroid disease where episodes of hypothyroidism may precipitate a severe exacerbation.

**Diagnosis**

Myasthenia can be a difficult diagnosis, as the symptoms can be subtle and hard to distinguish from both normal variants and other neurological disorders. A thorough physical examination can reveal easy fatiguability, with the weakness improving after rest and worsening again on repeat of the exertion testing. Applying ice to weak muscle groups characteristically leads to improvement in strength of those muscles. Additional tests are often performed, as mentioned below. Furthermore, a good response to medication can also be considered a sign of autoimmune pathology.

**Physical examination**

Muscle fatigability can be tested for many muscles. A thorough investigation includes:

- looking upward and sidewards for 30 seconds: ptosis and diplopia.
- looking at the feet while lying on the back for 60 seconds
- keeping the arms stretched forward for 60 seconds
- 10 deep knee bends
- walking 30 steps on both the toes and the heels
- 5 situps, lying down and sitting up completely

**Blood tests**
If the diagnosis is suspected, **serology** can be performed in a **blood test** to identify antibodies against the **acetylcholine receptor**. The test has a reasonable **sensitivity** of 80–96%, but in MG limited to the eye muscles (ocular myasthenia) the test may be negative in up to 50% of the cases. About half of the patients without antibodies against the acetylcholine receptor have antibodies against the **MuSK protein**. In specific situations (decreased reflexes which increase on facilitation, co-existing autonomic features, suspected presence of neoplasm, presence of increment or facilitation on repetitive EMG testing) testing is performed for **Lambert-Eaton syndrome**, in which other antibodies (against a voltage-gated **calcium channel**) can be found.

**Neurophysiology**

Muscle fibers of patients with MG are easily fatigued, and thus do not respond as well as muscles in healthy individuals to repeated stimulation. By repeatedly stimulating a muscle with electrical impulses, the fatiguability of the muscle can be measured. This is called the repetitive nerve stimulation test. In single fiber **electromyography**, which is considered to be the most sensitive (although not the most specific) test for MG, a thin needle electrode is inserted into a muscle to record the electric potentials of individual muscle fibers. By finding two muscle fibers belonging to the same motor unit and measuring the temporal variability in their firing patterns (i.e. their 'jitter'), the diagnosis can be made.

**Edrophonium test**

The "edrophonium test" is infrequently performed to identify MG; its application is limited to the situation when other investigations do not yield a conclusive diagnosis. This test requires the **intravenous** administration of **edrophonium chloride** (Tensilon®, Reversol®), a drug that blocks the breakdown of acetylcholine by **cholinesterase** and temporarily increases the levels of acetylcholine at the **neuromuscular junction**. In people with myasthenia gravis involving the eye muscles, edrophonium chloride will briefly relieve weakness.

**Imaging**

A **chest X-ray** is frequently performed; it may point towards alternative diagnoses (e.g. Lambert-Eaton due to a lung tumor) and comorbidity. It may also identify widening of the **mediastinum** suggestive of **thymoma**, but **computed tomography** (CT) or **magnetic resonance imaging** (MRI) are more sensitive ways to identify thymomas, and are generally done for this reason.

**Pulmonary function test**

**Spirometry** (lung function testing) may be performed to assess respiratory function if there are concerns about a patient's ability to breathe adequately. The FEV1 (forced expired volume in one second) or the PEFR (peak expiratory flow rate) may be monitored at intervals in order not to miss a gradual worsening of muscular weakness.
Severe myasthenia may cause respiratory failure due to exhaustion of the respiratory muscles.

**Pathological findings**

*Immunofluorescence* shows IgG antibodies on the neuromuscular junction. (Note that it is not the antibody which causes myasthenia gravis that fluoresces, but rather a secondary antibody directed against it.) Muscle electron microscopy shows receptor infolding and loss of the tips of the folds, together with widening of the synaptic clefts. Both these techniques are currently used for research rather than diagnostically.

**What is myasthenia gravis?**

Myasthenia gravis is a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal (voluntary) muscles of the body. The name myasthenia gravis, which is Latin and Greek in origin, literally means "grave muscle weakness." With current therapies, however, most cases of myasthenia gravis are not as "grave" as the name implies. In fact, for the majority of individuals with myasthenia gravis, life expectancy is not lessened by the disorder.

The hallmark of myasthenia gravis is muscle weakness that increases during periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often, but not always, involved in the disorder. The muscles that control breathing and neck and limb movements may also be affected.

**What causes myasthenia gravis?**

Myasthenia gravis is caused by a defect in the transmission of nerve impulses to muscles. It occurs when normal communication between the nerve and muscle is interrupted at the neuromuscular junction - the place where nerve cells connect with the muscles they control. Normally when impulses travel down the nerve, the nerve endings release a neurotransmitter substance called acetylcholine. Acetylcholine travels through the neuromuscular junction and binds to acetylcholine receptors which are activated and generate a muscle contraction.

In myasthenia gravis, antibodies block, alter, or destroy the receptors for acetylcholine at the neuromuscular junction which prevents the muscle contraction from occurring. These antibodies are produced by the body's own immune system. Thus, myasthenia gravis is an autoimmune disease because the immune system - which normally protects the body from foreign organisms - mistakenly attacks itself.

**What is the role of the thymus gland in myasthenia gravis?**

The thymus gland, which lies in the upper chest area beneath the breastbone, plays an important role in the development of the immune system in early life. Its cells form a part of the body's normal immune system. The gland is somewhat large in infants, grows gradually until puberty, and then gets smaller and is replaced by fat with age. In adults with myasthenia gravis, the thymus gland is abnormal. It contains certain clusters of immune cells indicative of lymphoid hyperplasia - a condition usually found only in the spleen and lymph nodes during an active immune response. Some individuals with myasthenia gravis develop thymomas or tumors of the thymus gland. Generally thymomas are benign, but they can become malignant.
The relationship between the thymus gland and myasthenia gravis is not yet fully understood. Scientists believe the thymus gland may give incorrect instructions to developing immune cells, ultimately resulting in autoimmunity and the production of the acetylcholine receptor antibodies, thereby setting the stage for the attack on neuromuscular transmission.

What are the symptoms of myasthenia gravis?

Although myasthenia gravis may affect any voluntary muscle, muscles that control eye and eyelid movement, facial expression, and swallowing are most frequently affected. The onset of the disorder may be sudden. Symptoms often are not immediately recognized as myasthenia gravis.

In most cases, the first noticeable symptom is weakness of the eye muscles. In others, difficulty in swallowing and slurred speech may be the first signs. The degree of muscle weakness involved in myasthenia gravis varies greatly among patients, ranging from a localized form, limited to eye muscles (ocular myasthenia), to a severe or generalized form in which many muscles - sometimes including those that control breathing - are affected. Symptoms, which vary in type and severity, may include a drooping of one or both eyelids (ptosis), blurred or double vision (diplopia) due to weakness of the muscles that control eye movements, unstable or waddling gait, weakness in arms, hands, fingers, legs, and neck, a change in facial expression, difficulty in swallowing and shortness of breath, and impaired speech (dysarthria).

Who gets myasthenia gravis?

Myasthenia gravis occurs in all ethnic groups and both genders. It most commonly affects young adult women (under 40) and older men (over 60), but it can occur at any age.

In neonatal myasthenia, the fetus may acquire immune proteins (antibodies) from a mother affected with myasthenia gravis. Generally, cases of neonatal myasthenia gravis are transient (temporary) and the child's symptoms usually disappear within 2-3 months after birth. Other children develop myasthenia gravis indistinguishable from adults. Myasthenia gravis in juveniles is common.

Myasthenia gravis is not directly inherited nor is it contagious. Occasionally, the disease may occur in more than one member of the same family.

Rarely, children may show signs of congenital myasthenia or congenital myasthenic syndrome. These are not autoimmune disorders, but are caused by defective genes that produce proteins in the acetylcholine receptor or in acetylcholinesterase.

How is myasthenia gravis diagnosed?

Unfortunately, a delay in diagnosis of one or two years is not unusual in cases of myasthenia gravis. Because weakness is a common symptom of many other disorders, the diagnosis is often missed in people who experience mild weakness or in those individuals whose weakness is restricted to only a few muscles.

The first steps of diagnosing myasthenia gravis include a review of the individual's medical history, and physical and neurological examinations. The signs a physician must look for are impairment of eye movements or muscle weakness without any changes in the individual's ability to feel things. If the doctor suspects myasthenia gravis, several tests are available to confirm the diagnosis.
A special blood test can detect the presence of immune molecules or acetylcholine receptor antibodies. Most patients with myasthenia gravis have abnormally elevated levels of these antibodies. However, antibodies may not be detected in patients with only ocular forms of the disease.

Another test is called the edrophonium test. This approach requires the intravenous administration of edrophonium chloride or Tensilon(r), a drug that blocks the degradation (breakdown) of acetylcholine and temporarily increases the levels of acetylcholine at the neuromuscular junction. In people with myasthenia gravis involving the eye muscles, edrophonium chloride will briefly relieve weakness. Other methods to confirm the diagnosis include a version of nerve conduction study which tests for specific muscle “fatigue” by repetitive nerve stimulation. This test records weakening muscle responses when the nerves are repetitively stimulated. Repetitive stimulation of a nerve during a nerve conduction study may demonstrate decrements of the muscle action potential due to impaired nerve-to-muscle transmission.

A different test called single fiber electromyography (EMG), in which single muscle fibers are stimulated by electrical impulses, can also detect impaired nerve-to-muscle transmission. EMG measures the electrical potential of muscle cells. Muscle fibers in myasthenia gravis, as well as other neuromuscular disorders, do not respond as well to repeated electrical stimulation compared to muscles from normal individuals. Computed tomography (CT) may be used to identify an abnormal thymus gland or the presence of a thymoma.

A special examination called pulmonary function testing - which measures breathing strength - helps to predict whether respiration may fail and lead to a myasthenic crisis.

**How is myasthenia gravis treated?**

Today, myasthenia gravis can be controlled. There are several therapies available to help reduce and improve muscle weakness. Medications used to treat the disorder include anticholinesterase agents such as neostigmine and pyridostigmine, which help improve neuromuscular transmission and increase muscle strength. Immunosuppressive drugs such as prednisone, cyclosporine, and azathioprine may also be used. These medications improve muscle strength by suppressing the production of abnormal antibodies. They must be used with careful medical followup because they may cause major side effects.

Thymectomy, the surgical removal of the thymus gland (which often is abnormal in myasthenia gravis patients), reduces symptoms in more than 70 percent of patients without thymoma and may cure some individuals, possibly by re-balancing the immune system. Other therapies used to treat myasthenia gravis include plasmapheresis, a procedure in which abnormal antibodies are removed from the blood, and high-dose intravenous immune globulin, which temporarily modifies the immune system and provides the body with normal antibodies from donated blood. These therapies may be used to help individuals during especially difficult periods of weakness. A neurologist will determine which treatment option is best for each individual depending on the severity of the weakness, which muscles are affected, and the individual's age and other associated medical problems.

**What are myasthenic crises?**

A myasthenic crisis occurs when the muscles that control breathing weaken to the point that ventilation is inadequate, creating a medical emergency and requiring a respirator for assisted ventilation. In patients whose respiratory muscles are weak, crises - which generally call for immediate medical attention - may be triggered by infection, fever, or an adverse reaction to medication.

**What is the prognosis?**
With treatment, the outlook for most patients with myasthenia gravis is bright: they will have significant improvement of their muscle weakness and they can expect to lead normal or nearly normal lives. Some cases of myasthenia gravis may go into remission temporarily and muscle weakness may disappear completely so that medications can be discontinued. Stable, long-lasting complete remissions are the goal of thymectomy. In a few cases, the severe weakness of myasthenia gravis may cause a crisis (respiratory failure), which requires immediate emergency medical care. (see above).

**What research is being done?**

Within the Federal Government, the National Institute of Neurological Disorders and Stroke (NINDS), one of the Federal Government's National Institutes of Health (NIH), has primary responsibility for conducting and supporting research on myasthenia gravis.

Much has been learned about myasthenia gravis in recent years. Technological advances have led to more timely and accurate diagnosis, and new and enhanced therapies have improved management of the disorder. Much knowledge has been gained about the structure and function of the neuromuscular junction, the fundamental aspects of the thymus gland and of autoimmunity, and the disorder itself. Despite these advances, however, there is still much to learn. The ultimate goal of myasthenia gravis research is to increase scientific understanding of the disorder. Researchers are seeking to learn what causes the autoimmune response in myasthenia gravis, and to better define the relationship between the thymus gland and myasthenia gravis.

Today's myasthenia gravis research includes a broad spectrum of studies conducted and supported by NINDS. NINDS scientists are evaluating new and improving current treatments for the disorder. One such study is testing the efficacy of intravenous immune globlin in patients with myasthenia gravis. The goal of the study is to determine whether this treatment safely improves muscle strength. Another study seeks further understanding of the molecular basis of synaptic transmission in the nervous system. The objective of this study is to expand current knowledge of the function of receptors and to apply this knowledge to the treatment of myasthenia gravis.