

## Facts About Myasthenia Gravis

**Myasthenia Gravis (MG), Lambert-Eaton Myasthenic Syndrome (LES) & Congenital Myasthenic Syndrome (CMS)**

### What is Myasthenia Gravis?

Myasthenia gravis (MG) causes weakness that gets worse with exertion and improves with rest. The disease first appeared in medical reports in 1672, but didn't earn its name, which literally means "grave muscular weakness," until the 1880s.

Physicians in 19th-century Germany, the first to begin systematic studies of the disease, noted that it produces weakness that fluctuates but generally progresses with time. Lacking crucial insights into the properties of nerve and muscle, they weren't able to do much for their patients, many of whom lost strength rapidly and eventually died from respiratory failure. Even in the early 20th century, the mortality rate of MG was around 70 percent.

Fortunately, over the past 100 years, the origins of MG have gradually unfolded, and the outlook for people with the disease has improved dramatically.

MG is an autoimmune disease — a disease that occurs when the immune system attacks the body's own tissues. In MG, that attack interrupts the connection between nerve and muscle — the neuromuscular junction. Muscles that control the eyes, face, neck, and limbs are commonly affected.

Thanks to this understanding of the mechanism behind MG, physicians can now treat it with drugs that suppress the immune system or boost the signals between nerve and muscle. Surgeries and other procedures are also helpful in many cases.

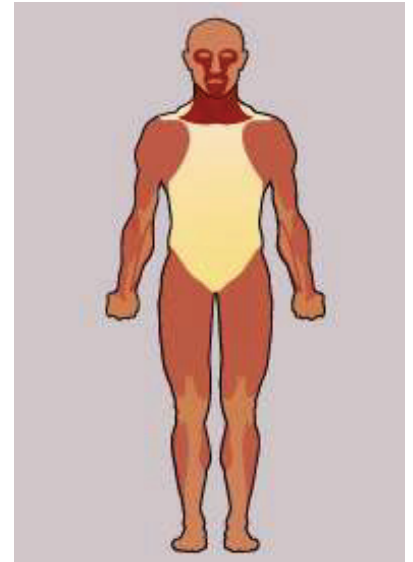
Physicians now estimate, that when MG is properly treated, the mortality rate is near zero. Most people with the disease are able to manage their symptoms and lead active lives, and a few experience remission lasting many years.

This fact sheet provides essential information about MG and two related diseases that affect the neuromuscular junction, Lambert-Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndrome (CMS).

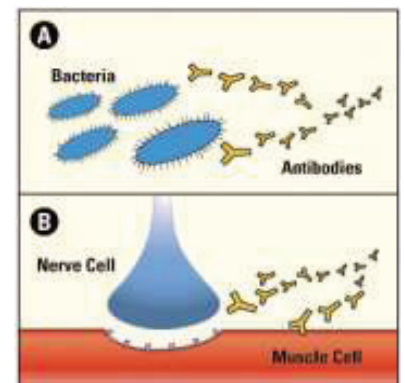
### What causes MG?

The immune system normally defends the body against diseases, but sometimes it can turn against the body, leading to an autoimmune disease. (See diagram on right) MG is just one of many autoimmune diseases, which include arthritis and type I diabetes.

In all of these diseases, an army of immune cells that would normally attack bacteria and disease-causing "germs" mistakenly attacks cells and/or proteins that have essential functions in the body. In most cases of MG, the immune system targets the acetylcholine receptor — a protein on muscle cells that's required for muscle contraction.



In myasthenia gravis, muscle weakness often first appears in the muscles of the face, neck and jaw. The arm and leg muscles are affected later



Normally (A), the immune system releases antibodies to attack foreign invaders, such as bacteria. In autoimmune diseases (B), the antibodies mistakenly attack a person's own tissues. In myasthenia gravis, they attack and damage muscle cells; in Lambert-Eaton myasthenic syndrome, they attack nerve cells that send messages to muscle.

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### Neuromuscular Junction

At the normal neuromuscular junction, a nerve cell tells a muscle cell to contract by releasing the chemical acetylcholine (ACh). ACh attaches to the ACh receptor — a pore or “channel” in the surface of the muscle cell — twisting it open and allowing an inward flux of electrical current that triggers muscle contraction. These contractions enable someone to move a hand, to dial the telephone, walk through a door or complete any other voluntary movement.

About 85 percent of people with MG have antibodies against the ACh receptor in their blood. The antibodies (Yshaped missiles that immune cells called B-cells use to attack bacteria and viruses) target and destroy many of the ACh receptors on muscle. Consequently, the muscle’s response to repeated nerve signals declines with time, and the muscles become weak and tired.

About 15 percent of people with MG are seronegative for antibodies to the ACh receptor, meaning the antibodies aren’t detectable in their blood (serum). Recently, it’s been discovered that a large fraction of these people have antibodies to musclespecific kinase (MuSK), a protein that helps organize ACh receptors on the muscle cell surface.

Scientists don’t know what triggers most autoimmune reactions, but they have a few theories. One possibility is that certain viral or bacterial proteins mimic “self-proteins” in the body (such as the ACh receptor), stimulating the immune system to unwittingly attack the self-protein.

There’s also evidence that an immune system gland called the thymus plays a role in MG. (See illustration below) Located in the chest just below the throat, the thymus is essential to the development of the immune system. From fetal life through childhood, the gland teaches immune cells called T-cells to recognize self from non-self. About 15 percent of people with MG have a thymic tumor, called a thymoma, and another 65 percent have overactive thymic cells, a condition called thymic hyperplasia.

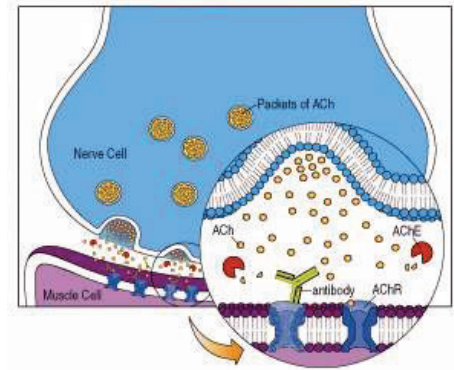
When the thymus doesn’t work properly, the T-cells might lose some of their ability to distinguish self from non-self, making them more likely to attack the body’s own cells.

### Who gets MG?

MG affects two to seven out of every 10,000 people in Western countries. It occurs about one and a half times more often in women than in men. The disease can appear at any age, but the average age of onset in females is 28; in males, it’s 42. In about 10 percent of cases, MG begins in childhood (juvenile onset).

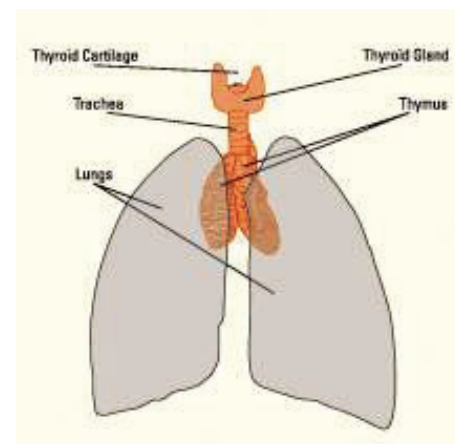
Genetic susceptibility appears to play a role in MG and in other autoimmune diseases. Most studies suggest that if you have a relative with an autoimmune disease, your risk of getting an autoimmune disease is increased — the closer the relative, the higher the risk. Even for identical twins, however, that risk is relatively small. Most studies suggest that when one twin has an autoimmune disease, the other has less than a 50 percent chance of getting the same disease.

Also, people who already have one autoimmune disease have a greater risk of developing another one.



Myasthenia gravis occurs when the immune system makes antibodies that destroy the ACh receptor (AChR), a docking site for the nerve chemical acetylcholine (ACh).

Some treatments block acetylcholinesterase (AChE), an enzyme that breaks down ACh, while others target the immune system.



The thymus, a small gland in the upper chest, seems to play a role in myasthenia gravis.

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It's estimated that 5 percent to 10 percent of people with MG have another autoimmune disease, which appeared before or after the onset of MG.

The most common of these are autoimmune thyroid disease, rheumatoid arthritis and systemic lupus erythematosus (SLE, a disease that affects multiple organs).

### What happens to someone with MG?

#### Weakness and Fatigue

MG weakens and fatigues the body's voluntary muscles (those we can move at will). It doesn't damage the musculature of the heart or the gastrointestinal tract.

Early in its course, MG tends to affect the muscles that control movement of the eyes and eyelids, causing ocular weakness. Consequently, a partial paralysis of eye movements (ophthalmoparesis), double vision (diplopia), and droopy eyelids (ptosis) are usually among the first symptoms of MG.

Weakness and fatigue in the neck and jaw also can occur early in MG. This bulbar weakness — named for the nerves that originate from the bulblike part of the brainstem

— can make it difficult to talk, chew, swallow and hold up the head. Bulbar weakness tends to give speech a slurred, nasal quality. It can also lead to frequent choking spells, and make eating unpleasant and tiresome.

In generalized MG, weakness tends to spread sequentially from the face and neck to the upper limbs, the hands and then the lower limbs. It may become difficult to lift the arms over the head, rise from a sitting position, walk long distances, climb stairs or grip heavy objects.

In severe cases, weakness may spread to muscles in the chest that control breathing.

#### Disease Course

Weakness and fatigue in MG tend to fluctuate from day to day, and even during a single day. People with the disease are often strongest in the morning after a full night's sleep and weakest in the evening.

Over a longer term, the symptoms of MG usually progress, reaching maximum or nearmaximum severity within one to three years of onset in most people. In about 15 percent of people, the disease remains ocular, but in most, it becomes oculobulbar or generalized. If the disease remains ocular for three years, it usually doesn't become generalized.

Weakness serious enough to require a wheelchair is almost unheard of in MG. Most people, when properly treated, find they can remain physically active. Remission, a reversal of some or all symptoms, occurs in about 20 percent of people with MG. Usually, the remissions are temporary, with an average duration of five years, but some people experience more than one remission during their lifetimes. A few people have experienced apparently permanent remissions, lasting over 20 years.

Compared to adult-onset MG, juvenile MG tends to progress more slowly and has a higher incidence of remission. Historically, many children given diagnoses of juvenile MG turned out to have a congenital myasthenic syndrome.



Early in its course, MG affects the muscles that control eye movement, and droopy eyelids are often among the first symptoms.



Juvenile MG progresses more slowly than the adult form, and more often goes into remission.

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### Drugs and Other Concerns

Many prescription drugs can unmask or worsen symptoms of MG. These include:

- muscle relaxants used during surgery
- aminoglycoside and quinolone antibiotics
- cardiac anti-arrhythmics
- local anaesthetics
- magnesium salts (including milk of magnesia)

When taking a new prescription drug for the first time, it's a good idea to consult your doctor about its possible effects on MG. Also, you might want to keep a Medic Alert bracelet or card handy to inform emergency medical personnel that you have MG and that certain drugs can be harmful to you.

Overexertion, emotional stress, infections (from tooth abscesses to the flu), menstruation and pregnancy can also lead to increased weakness in MG. (see below)

### Myasthenic Crisis

Especially in people with bulbar or respiratory symptoms, MG can sometimes worsen to the point of myasthenic crisis, an extreme episode of weakness that culminates in respiratory failure and the need for mechanical ventilation. In some cases, the respiratory muscles themselves give out, and in others, weakness in the throat muscles causes the airway to collapse.

When MG is properly treated, crisis is very rare. And when crisis does occur, it has a good rate of recovery, thanks to the wide range of treatments for MG and the quality of respiratory care at most hospitals.

Sometimes, myasthenic crisis can occur without warning, but it often has an identifiable trigger, such as fever, respiratory infection, traumatic injury, stress, or one of the drug types mentioned. If you have MG, you should have these conditions monitored by a physician, and if you experience labored breathing or unusual weakness, you should seek immediate medical attention.

### Pregnancy

In rare cases, pregnancy appears to trigger the onset of MG. In women who already have MG, pregnancy can cause a worsening of symptoms (usually after birth, but sometimes during the first trimester); an improvement (usually during the first trimester); or no change, with about equal likelihood. These trends aren't consistent from one pregnancy to the next.

Some medications for MG (see "How Is MG Treated?") are safe to use during pregnancy and nursing, but some others aren't recommended. If you're planning to become pregnant, you should consult your physician, and if you're a nursing mother, consult your child's pediatrician.

Between 10 percent and 20 percent of babies born to mothers with MG develop transient neonatal MG, probably because the antibodies that cause MG can pass through the placenta. Symptoms (such as feeble cry, feeding difficulties or respiratory weakness) are often detected within hours to days after birth, and decreased movement may be detected inside the womb.



**Pregnancy can worsen a woman's symptoms of MG, and her child may be born with transient neonatal MG — a temporary condition.**

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As the name implies, transient neonatal MG is only temporary. Most babies require medication and supportive care, but usually recover completely within two months after birth. Permanent weakness or recurrence of MG later in life is extremely rare.

### How is MG treated?

Many drugs and procedures are available for treating MG, each with distinct advantages and disadvantages. Drugs known as cholinesterase inhibitors provide relief from symptoms by blocking the action of acetylcholinesterase and increasing the amount of acetylcholine at the neuromuscular junction.

Immunosuppressant drugs can be used to attack the disease at its source, but they increase susceptibility to infectious diseases and most of them carry other potentially serious side effects.

The benefits and risks of these treatments must be weighed against each other and the needs of the patient. Your doctor or MDA clinic director can help you determine which treatments are appropriate for you.

### Cholinesterase Inhibitors

These drugs, also known as anticholinesterases, have been used against MG since the early 1990s, and can produce relief from symptoms within minutes. The one most commonly used is pyridostigmine (Mestinon).

Cholinesterase inhibitors boost ACh levels not only at the neuromuscular junction, but also in the autonomic nervous system (which controls involuntary bodily functions).

Sometimes the drugs can cause diarrhea, abdominal cramps and/or excessive saliva. To minimize these side effects, your physician might lower the dose of cholinesterase inhibitors or prescribe atropine, which blocks the ACh receptors on nerve cells.

In rare cases, cholinesterase inhibitors prove sufficient for managing MG, but most people also require immunosuppression — treatment that restrains the actions of the immune system.

### Immunosuppressant Drugs

Corticosteroids. These drugs (which include prednisone and prednisolone) reproduce the actions of corticosteroid hormones, which are made by the cortex (outer layer) of the adrenal gland. They have broad anti-immune and anti-inflammatory effects, making them powerful treatments for MG.

They're not as fast-acting as cholinesterase inhibitors, but they're faster than some other immunosuppressants, producing improvement within weeks to months. They're also relatively inexpensive.

A disadvantage of corticosteroids is that they can produce many side effects — some of them potentially serious — including osteoporosis (weakening of bones), mood disturbances, gastrointestinal problems, weight gain, high blood pressure, cataracts and stunted growth (in children). For many people, these side effects can be managed with other therapies; for example, bisphosphonate drugs can be used to prevent osteoporosis.



Various drug treatments are effective in restoring strength in MG, but side effects should be discussed when they're being considered. This woman got good results from cyclophosphamide.

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For others, corticosteroids are used as a first-line defense against MG, then gradually tapered off, and supplemented or replaced with slower-acting immunosuppressants that have fewer side effects. Most of these other drugs were developed to prevent the rejection of transplanted organs, but have since been co-opted for use against MG and other autoimmune diseases.

Azathioprine (Imuran). This was the first non-steroid immunosuppressant to come into widespread use against MG, in the 1970s. It acts more slowly than corticosteroids, producing improvement after three to six months, and usually has few side effects.

Occasionally, however, it can produce serious side effects, including inflammation of the pancreas, liver toxicity, bone marrow suppression and possibly an increased risk of cancer.

Mycophenylate mofetil (CellCept). CellCept is a relatively new immunosuppressant, but so far it's shown promising results against MG in clinical trials. In two small trials completed in 2001, about 65 percent of MG patients experienced gains in strength or a reduced need for prednisone after taking CellCept for several months.

More recent analyses have shown that some people take longer to respond to the drug, but that nearly 75 percent eventually show improvement, with occasional relatively non-serious side effects such as stomach upset, flu-like symptoms, rash and tremor.

Cyclosporine (Neoral, Sandimmune). This is a useful, relatively fast-acting treatment for MG, but it may have side effects including increased blood pressure, abnormal kidney function, unwanted body hair and stomach upset.

Cyclophosphamide (Cytoxan, Neosar). This drug is considered effective against MG, but because it has many potentially serious side effects, it's often reserved for use only when other drugs fail.

### Thymectomy

Thymectomy — surgical removal of the thymus — is recommended for thymoma and for most cases of generalized MG. It's believed to be the only therapy capable of producing long-term, drug-free remission from MG, but most data regarding its use have come from case studies rather than clinical trials.

Thymectomy is estimated to produce remission from MG in about 30 percent of people. It's also known to increase strength or reduce the need for medication in an additional 50 percent. These improvements may take several months to several years after surgery to occur.

Thymectomy usually has the most favorable outcomes in people who are under age 60 and early in the course of the disease. Because the thymus is required for immune system development, most doctors prefer not to perform the surgery on prepubescent children.



Many patients with MG, including television actress Suzanne Rogers, have achieved remission with thymectomy, combined with medication.

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### Plasmapheresis and Intravenous Immunoglobulin

In plasmapheresis, also known as plasma exchange, an intravenous line is used to remove antibodies from the blood. IVIg therapy is essentially an injection of nonspecific antibody (immunoglobulin) that might work by dialing down the immune system's production of its own antibodies, much as warm air tells a thermostat to stop pumping out heat.

These treatments bring about fast, but short-lived relief from MG, and are mostly used until other medications take effect, prior to surgery or for myasthenic crisis. However, some people receive regular plasmapheresis or IVIg as a supplement to immunosuppressant drugs.

### How is MG diagnosed?

Weakness and fatigue are common in the general population, but the degree and pattern of these symptoms — particularly diplopia, ptosis and other signs of weakness in the eye muscles — should alert a neurologist to the possibility of MG.

The neurologist is likely to ask many questions and to conduct a physical exam to determine the extent of weakness. To look for evidence of increased weakness following exertion, he or she might ask the patient to look up without blinking for one or two minutes, hold the arms out for as long as possible or climb up steps.

If the physical exam is consistent with MG, the neurologist usually orders a blood test designed to detect antibodies to the ACh receptor. A blood test for MuSK antibodies can be performed if the ACh receptor antibodies are not detected. A positive test result confirms a diagnosis of MG.

If the blood tests are negative, the next step is usually electrodiagnostic testing, in which electrodes are used to measure the electrical signals in muscle. Surface electrodes (similar to those used in electrocardiograms) deliver small shocks to a nerve in the arm, leg or face, while other surface electrodes record the responses in muscle.

In MG, a muscle's response to repeated nerve stimulation declines rapidly. In addition to or in place of electrodiagnosis, the neurologist might try giving an intravenous injection of edrophonium (Tensilon), a fast-acting cholinesterase inhibitor.

A temporary increase in strength after this "Tensilon test" is consistent with either MG or CMS.

If a diagnosis of MG is confirmed, a CT scan, chest X-rays or magnetic resonance imaging (MRI) will be used to examine the thymus and look for evidence of thymoma.

Additional tests may be used to probe for LEMS or CMS.



Plasmapheresis was developed in the late 1970s to provide relief from MG. The process removes antibodies from the blood and may have to be done repeatedly.



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### What is LEMS?

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease whose symptoms and origins are somewhat similar to those of MG. While MG targets the ACh receptors on muscle cells, LEMS interferes with ACh release from nerve cells. Some 85 percent to 90 percent of people with LEMS test positive for antibodies against the P/Q type voltage-gated calcium channel (VGCC). This protein is a pore that allows calcium entry into nerve cells, which is required for ACh release.

In about 60 percent of cases, LEMS is associated with small-cell lung cancer (and more rarely with other types of cancer), which might be diagnosed at the same time as LEMS or years later. There's evidence that the cancerous cells inappropriately make VGCC, triggering the immune system to make anti-VGCC antibodies. The trigger for LEMS without cancer is unknown.

### What are the symptoms of LEMS?

The first symptoms are usually leg weakness and difficulty walking. Oculobulbar weakness (affecting the muscles of the eyes, face and throat) may occur later, causing ptosis, speech impairment and swallowing problems. Unlike weakness in MG, weakness in LEMS temporarily improves after exertion. (It's thought that, with repeated activity, calcium gradually builds up in the nerve cells, increasing the amount of ACh released.) Because ACh regulates many bodily functions, LEMS sometimes causes autonomic (involuntary) symptoms such as dry mouth, constipation, impotence and bladder urgency.

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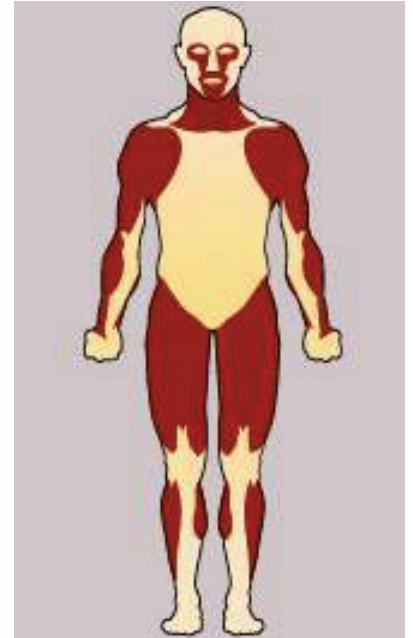
LEMS with cancer has its onset in adulthood, but LEMS without cancer may affect children.

### How is LEMS treated?

Long-term treatment and prognosis of LEMS depend on whether it occurs with or without cancer. Although cancer is life-threatening, it can be treated with radiation, surgery or chemotherapy. When these treatments are successful and the cancer goes into remission, LEMS usually goes into complete or partial remission as well.

Prior to cancer treatment, or in LEMS patients without cancer, immunosuppressant drugs, IVIg and/or plasmapheresis are often helpful.

Symptomatic relief can be achieved with Mestinon and/or 3,4-diaminopyridine (3,4DAP), a drug that prolongs the opening of VGCC in nerve endings and thus enhances ACh release. This drug may be hard to obtain as it's only formulated by a few pharmacies in the United States.



Normally (A), the immune system releases antibodies to attack foreign invaders, such as bacteria. In autoimmune diseases (B), the antibodies mistakenly attack a person's own tissues. In myasthenia gravis, they attack and damage muscle cells; in Lambert-Eaton myasthenic syndrome, they attack nerve cells that send messages to muscle.



Julie Long is an artist who has LEMS.





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### How is LEMS diagnosed?

The autonomic symptoms and predominant leg weakness of LEMS help to distinguish it from MG. Electrodiagnostic testing that shows an increased muscle response to repeated stimulation also favors LEMS rather than MG (in which the response decreases). In most cases, LEMS can be confirmed by detection of anti-VGCC antibodies in the blood.

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### What is Congenital Myasthenic Syndrome (CMS)?

Like MG, CMS produces weakness and fatigue caused by problems at the neuromuscular junction. But while MG is autoimmune, CMS is an inherited disease caused by defective genes. Genes are recipes for making proteins, and the genes defective in CMS are required for making the ACh receptor or other components of the neuromuscular junction.

There are many types of CMS, grouped into three main categories named for the part of the neuromuscular junction that's affected: presynaptic (the nerve cell), postsynaptic (the muscle cell) or synaptic (the space in between).

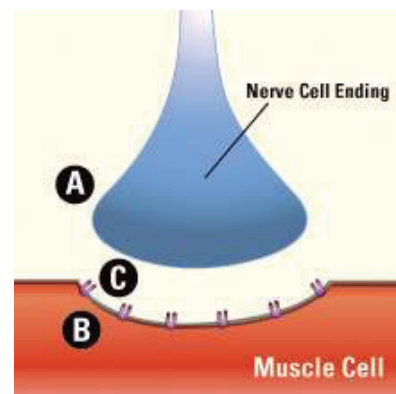
Symptoms and treatment options vary depending on the type of CMS. The cholinesterase inhibitors used to treat MG are helpful in some types of CMS, but may be harmful in others. It's important to realize that since CMS isn't an autoimmune disease, it doesn't respond to immunosuppressant drugs or other treatments aimed at the immune system.

As its name implies, CMS usually has a congenital (at or near birth) onset, but it can manifest in children and even in adults. Later-onset cases tend to be less severe.

### How is CMS inherited?

With the exception of slow-channel CMS, the inheritance pattern for the types of CMS described here is autosomal recessive. This means that it takes two copies of the defective gene — one from each parent — to cause the disease. Slow-channel CMS is inherited in an autosomal dominant manner. This means that one copy of a defective ACh receptor gene is enough to cause the disease, so an affected parent has a 50 percent chance of passing the disease on to a child.

Your neuromuscular clinic physician or genetic counsellor can give you more information about the risks of inheriting or passing on CMS. Also, see MDA's fact sheet, "Genetics and Neuromuscular Diseases."



**CMS results from genetic flaws at the neuromuscular junction — where the nerve cell meets the muscle cell. The type of CMS depends on where the defective gene lies: (A) in the nerve cell — presynaptic CMS; (B) the muscle cell — postsynaptic CMS; or (C) the space in between — synaptic CMS.**

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### What are the types of CMS and how are they treated?!

Presynaptic CMS	
Cause:	Insufficient release of ACh
Symptoms:	Commonly manifests as CMS with episodic apnea (CMS-EA), which has its onset in infancy and causes oculobulbar weakness and episodes of apnea — a temporary cessation of breathing.
Drug treatment:	cholinesterase inhibitors
Postsynaptic CMS (ACh receptor deficiency, Fast-channel CMS)	
Cause:	ACh receptors are missing or don't stay open long enough
Symptoms:	Vary from mild to severe. In infants, may cause severe weakness, feeding and respiratory problems, and delayed motor milestones (sitting, crawling and walking). Childhood and adult-onset cases often cause ptosis and fatigue, but usually don't interfere with daily living.
Drug Treatment:	cholinesterase inhibitors and 3,4-DAP
Postsynaptic CMS	
Cause:	ACh receptors stay open too long.
Symptoms:	Infant-onset cases cause severe weakness, often leading to loss of mobility and respiratory problems in adolescence. Adult-onset cases may not be disabling.
Drug Treatment:	quinidine or fluoxetine (both plug the ACh receptor)
Synaptic CMS	
Cause:	acetylcholinesterase deficiency
Symptoms:	Severe weakness with feeding and respiratory difficulties from birth or early childhood. Weakness also causes delayed motor milestones, and often leads to reduced mobility and scoliosis (curvature of the spine).
Drug Treatment:	None



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### Search for treatments and cures

In the early 1970s, researchers established the autoimmune nature of MG. They showed that people with the disease have a reduced number of ACh receptors and that antibodies to the receptors can induce MG in laboratory animals.

These discoveries led swiftly to the lifesaving use of immunosuppressant drugs to treat the disease.

Scientists began using some of the same drugs for LEMS in the 1980s, when they helped link the disease to an autoimmune attack against the calcium channels in nerve endings. They also began treating LEMS with the drug 3,4-DAP (which increases calcium channel activation) and continue to study calcium channels with an eye toward improved drugs. Researchers are conducting ongoing clinical trials of IVIg, CellCept and thymectomy for MG, and trying to design therapies that would target only the errant immune cells that cause these diseases rather than the entire immune system.

One group is working on a “vaccine” that mimics proteins on T-cells reactive to the ACh receptor, and another group has developed a “guided missile strategy” that involves using the body’s own immune cells to target and destroy the abnormal T-cells involved in the autoimmune response.

Other groups are investigating the difference between MG caused by ACh receptor antibodies and MG caused by MuSK antibodies. They’re finding that certain treatments, such as thymectomy, might have a lower chance of success in MuSK-related MG.

They’re working to improve treatment and to develop a commercial blood test for MuSK-related MG that could be used to distinguish it from other types of MG and from CMS.

In the past, people with CMS were often told they had MG and were subjected to years of pointless immunosuppressive therapy. By identifying the genetic defects that cause CMS, scientists have improved the diagnosis of CMS and discovered drugs that are effective against it. They’re pursuing better drug treatments, and techniques to fix or replace the underlying genetic defects by gene therapy.