

## Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder characterized by muscle weakness. The disease tends to strike women more often than men (by a ratio of about 3:2), usually affecting women between the ages of 20 and 40 (Beers MH 2005). After about age 50, both sexes tend to be equally affected (Phillips LH 1994).

Although the disease is progressive and can affect any muscle groups, people afflicted with myasthenia gravis often have weakness of face, tongue, and neck. This muscle weakness might result in double vision or drooping eyelids, which along with difficulty chewing, swallowing, and talking, are characteristic symptoms of myasthenia gravis.

### WHAT CAUSES MYASTHENIA GRAVIS?

The underlying cause of myasthenia gravis is unknown, although there is probably a genetic component to it, and there is clear evidence that the disease is somehow related to abnormalities in the thymus gland. However, even though an exact cause has not been determined, the disease course is fairly well understood.

Myasthenia gravis affects the neuromuscular junction, or the area where nerve endings communicate with skeletal muscles. At the neuromuscular junction, nerve endings transmit impulses across a tiny space (called a synapse) to the muscle, causing the muscle to contract. When a nerve impulse travels down the nerve, a neurotransmitter called acetylcholine is released from vesicles in the nerve ending into the synapse and bathes acetylcholine receptors located on the muscle side of the synapse, causing the muscle to be stimulated and contract.

The reaction is short-lived; in a very brief time, the acetylcholine in the receptor is metabolized into its components (acetate and choline) by an enzyme called acetylcholinesterase. Any remaining acetylcholine diffuses away from the receptors.

Among people with myasthenia gravis, this normal impulse transmission is disrupted by T-cell-mediated autoantibodies that target the body's own acetylcholine receptors and block them. If enough receptors are blocked by autoantibodies, then the muscle contraction will be weak, causing the principal symptoms of myasthenia gravis.

The disease also affects the synapse in other ways besides blocking the acetylcholine receptors. On the muscle side of the synapse, acetylcholine receptors are normally grouped closely in tight synaptic folds. In myasthenia gravis, however, the autoantibodies work in concert with complement proteins (also part of the immune system) to damage and spread out the receptors and widen the synaptic folds. The result is fewer receptors.

In recent years, several interesting theories have been advanced to explain myasthenia gravis. Up to 90 percent of people with myasthenia gravis suffer from some form of abnormality in the thymus gland. The thymus gland is where T cells—the chief immune cell involved in myasthenia gravis—are produced and “schooled.” About 70 percent of people with myasthenia gravis have an enlarged thymus gland (hyperplasia), and 20 percent have (usually benign) thymic tumors called thymomas (Onodera H 2005). By studying cells from thymomas and tissue from the thymus gland, scientists have begun to develop a unified theory that might one day explain the cause of myasthenia gravis.

According to this theory, the myoid cells in the thymus might be responsible for the autoimmune reaction seen in myasthenia gravis. Myoid cells are musclelike cells within the thymus gland. Recent studies have shown that T cells are first sensitized against myoid cells within the thymus. This has two effects. First, it causes the microscopic thymus changes seen in early-onset myasthenia gravis, which occurs before the age of 40. These changes resemble the changes that will eventually be seen in skeletal muscles. Second, the sensitization of T cell antibodies to myoid cells causes the formation of germinal centers, which are key facilitators in the autoimmune reaction against the body's acetylcholine receptors (Shiono H et al 2003; Roxanis I et al 2002).

Building on this work, researchers have looked more recently at the role of inflammatory cytokines in myasthenia gravis. In several intriguing studies, teams of scientists have discovered that the expression of acetylcholine receptors is modified by inflammatory cytokines such as tumor necrosis factor-alpha. These pro-inflammatory chemicals have been implicated in other autoimmune diseases, such as multiple sclerosis and Lou Gehrig's disease. In one study, researchers found that cytokine activity was enhanced in the myasthenia gravis thymus, possibly influencing acetylcholine-receptor expression and contributing to the initiation of the autoimmune response (Poea-Guyon S et al 2005). While this research is still preliminary, it offers novel therapeutic targets for the future.

## SYMPTOMS OF MYASTHENIA GRAVIS

People with myasthenia gravis generally experience specific muscle weakness, such as in the eye, especially with repeated use of the muscles. This weakness often has a characteristic pattern; muscles of the face and head are involved early in the disease. Drooping eyelids and double vision are the most common early complaints (Kasper DL et al 2005). People afflicted may also have difficulty chewing or facial weakness that affects their smile and might experience a nasal quality to their voice because of weakness in the palate.

The progress of the disease is variable, with periods of remission followed by exacerbations. In about 85 percent of cases, the weakness will progress to a generalized weakness that affects large muscle groups.

At some point in the illness (usually within two to three years after diagnosis), 12 percent to 16 percent of myasthenia gravis patients will experience a crisis episode, in which the weakness becomes so severe that breathing is compromised and respiratory assistance is required (Berrouschot J et al 1997; Cohen MS et al 1981). This eventuality is most likely in people who also have a tongue and mouth weakness or a thymoma (Berrouschot J et al 1997; Cohen MS et al 1981; Thomas CE et al 1997).

The disease myasthenia gravis is distinguishable from congenital myasthenic syndromes. These syndromes are caused by genetic defects in the acetylcholine receptor and other components of the neuromuscular junction. Although they share symptoms, the illnesses respond differently to treatments.

## AGGRAVATING FACTORS FOR MYASTHENIA GRAVIS

Myasthenia gravis is frequently associated with chronic infections of any kind. These infections may cause a myasthenia crisis or exacerbate existing conditions by provoking a T-cell-mediated immune response. Below are other aggravating factors for myasthenia gravis:

- **Hormone fluctuation.** One study documented a relationship between the female menstrual cycle and myasthenia gravis. Of the women studied, 67 percent reported exacerbation of their symptoms two to three days prior to the menstrual period. These exacerbations frequently required therapeutic changes (Leker RR et al 1998). Both progesterone and estrogen levels are lowest at that time of the cycle.
- **Pesticides.** Many pesticides contain organophosphorus chemicals that inhibit the acetylcholinesterase enzyme. Although these agents may produce a cholinergic crisis in anyone who is excessively exposed, myasthenia gravis patients on antiacetylcholinesterase medication are especially susceptible. Halides (like chlorine and fluorine) may pose additional risk for myasthenia gravis patients. In one case report, an individual was exposed to chlorine gas and subsequently developed generalized myasthenia gravis (Foulks CJ 1981). Fluoride is also implicated, and fluoridated water may trigger a myasthenia gravis crisis or contribute to long-term deterioration, with extreme exhaustion and muscle weakness (Waldbott GL 1998).

## DIAGNOSIS

Physicians may suspect myasthenia gravis in anyone with its characteristic weakness. Once myasthenia gravis is suspected, the physician may order various tests to confirm the diagnosis.

**Ice test.** This is a quick test that does not require special equipment and can be performed in the physician's office. After covering the patient's eye with an icepack for a couple of minutes, the physician will look for improvement in eyelid drooping. Any improvement may point toward a myasthenia gravis diagnosis.

**Acetylcholinesterase inhibition.** Because acetylcholine receptors are blocked in myasthenia gravis, drugs that increase the amount of acetylcholine can be used to test for the disease. Edrophonium is a fast-acting acetylcholinesterase inhibitor that, when administered intravenously, will produce immediate and temporary relief of muscle weakness in myasthenia gravis patients by sparing existing acetylcholine. Edrophonium onsets quickly (30 seconds) and lasts for only about five minutes.

**Immunohistochemistry of blood.** Antiacetylcholine receptor antibodies are detectable in the serum of about 85 percent of people with myasthenia gravis. However, they are present in only about 50 percent of people with symptoms that are confined to the eye muscles (Kasper DL et al 2005). More recently, antibodies to muscle-specific kinase (MuSK) have been discovered in about 70 percent of patients who test negative for antiacetylcholine receptor antibodies but suffer from the classic symptoms of myasthenia gravis (Hoch W et al 2001). MuSK is a protein that helps organize acetylcholine receptors on the muscle cell surface, and this test is emerging as a helpful diagnostic tool if no autoantibodies are detected when symptoms of the disease are present.

**Electrophysiological studies.** Nerve conduction studies may be used to detect muscle responses to mild stimuli. Patients with myasthenia gravis will demonstrate progressively smaller or weaker responses. Although this is the most specific nerve test for myasthenia gravis, it is not indicative in all cases and can be done only on certain muscles.

**Thyroid tests and thymic imaging.** A number of tests might be conducted to assess the health of the thyroid and thymus glands. These include a computed tomography chest scan to reveal a thymoma or enlarged thymus gland and thyroid function tests to detect hyperthyroidism.

## CONVENTIONAL TREATMENT

Conventional treatments used in myasthenia gravis take five forms (Drachman DB 1994):

**Acetylcholinesterase inhibitors.** These drugs work by blocking the enzyme that normally destroys acetylcholine in the synapse, which allows the existing acetylcholine more time to interact with the available receptors. The result is stronger and more complete muscle contractions. Excessive use of antiacetylcholinesterase drugs can have fatal side effects. The most commonly used acetylcholinesterase inhibitors in myasthenia gravis are pyridostigmine and neostigmine.

**Thymectomy.** Dozens of studies support the use of thymectomy, or surgical removal of the thymus gland, to treat myasthenia gravis patients (Roberts PF et al 2001). There is some debate, however, over how effective the procedure is among patients who do not have a thymoma: one review suggested an absence of any benefit from thymectomy in myasthenia gravis patients who lacked a thymoma (Gronseth GS et al 2000). Other reports suggest that the procedure is especially valuable in early-onset myasthenia gravis (Onodera H 2005). Following a thymectomy, patients often report that symptoms lessen and, in some cases, disappear completely.

**Immunosuppressants.** Immunosuppressants are often used in myasthenia gravis to blunt the overactive immune response. These drugs might include glucocorticoids such as prednisone, azathioprine, cyclosporine, and others. Although they are effective in many patients, careful management of patients on long-term glucocorticoid therapy is crucial because of the significant side effects associated with these drugs. Glucocorticoid use over the long term is associated with significant metabolic side effects, including central obesity, impairment in insulin sensitivity, and bone loss.

**Plasmapheresis.** Plasmapheresis separates plasma, which contains the autoantibodies, from red blood cells, which are then returned to the body. This treatment improves symptoms temporarily and is especially valuable in preparation for surgical removal of the thymus. Several studies have reported that plasmapheresis is tolerated well in patients. The most common side effects are reversible hypotension (low blood pressure) and mild tremor. Several studies indicate that infection and mortality rates due to plasmapheresis were negligible, and all patients had immediate benefit from the procedure (Carandina-Maffei R et al 2004; Chiu HC et al 2000).

**Intravenous immunoglobulin.** High-dose intravenous human immunoglobulin (IVIg) has emerged as a therapy for various neurologic diseases, including myasthenia gravis. Rather than expunging abnormal antibodies from the blood, the procedure floods the body with gamma globulin antibodies from several donors. In controlled clinical trials, IVIg was effective in treating chronic inflammatory demyelinating polyneuropathy (van Doorn PA et al 1990). IVIg has also produced improvement in some patients with myasthenia gravis (Ronager J et al 2001; Wegner B et al 2002). IVIg therapy generates temporary relief lasting weeks to months. Studies that compared plasmapheresis and IVIg found that although both treatments demonstrated a clinically significant effect in patients with chronic myasthenia gravis, the improvement had a more rapid onset after plasmapheresis than after IVIg (Ronager J et al 2001).

## NUTRITIONAL SUPPORT

Many traditional therapies are somewhat successful in managing myasthenia gravis, but often at a price. Side effects of prescription drugs, especially glucocorticoids, can be serious and even life threatening. Complementary nutrients may offer ways to address myasthenia gravis and to attack it from several standpoints while limiting adverse effects. The following nutrients have been shown to suppress the overactive immune response or enhance the action of acetylcholine:

**Vitamin K.** Vitamin K may have a regulatory effect on myasthenia gravis. This fat-soluble vitamin has been shown to decrease levels of the pro-inflammatory cytokine interleukin-6 (Reddi K et al 1995). This cytokine is involved in myasthenia gravis pathogenesis and correlates with acetylcholine receptor antibody production (Mocchegiani E et al 2000).

**DHEA.** Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal glands that can be converted into estrogen and testosterone. One study sought to detect a possible effect of DHEA in the pathogenesis of experimental myasthenia gravis. DHEA administered to rats resulted in a decrease in antibodies against acetylcholine receptors and an inhibition of the antibody-secreting cells. The authors concluded that these results encourage future study of DHEA treatment in human myasthenia gravis (Duan RS et al 2003).

**Huperzine A.** Huperzine A is an active component of Chinese club moss (*Huperzia serrata*). Huperzine A is a reversible, highly effective, and highly selective inhibitor of the acetylcholinesterase enzyme (Wang R et al 2006). Several experiments have

demonstrated that huperzine A can intensify muscular contractions (Lin JH et al 1997). Research on 128 cases of myasthenia gravis indicated that 99 percent of the clinical symptoms were controlled or improved after treatment with huperzine A (Cheng YS et al 1986).

**Creatine.** Many studies have investigated creatine supplementation to enhance muscle power and strength, both in normal participants and in patients with various neuromuscular diseases. A case study was performed to determine the effects of creatine supplementation in a myasthenia gravis patient who was also taking glucocorticoids. After creatine supplementation (5 g daily) and training, the patient demonstrated increases in body weight, lean muscle mass, and muscle strength. The authors concluded that resistance exercise plus creatine supplementation may promote gains in strength and lean muscle mass in myasthenia gravis patients (Stout JR et al 2001).

**Choline and lecithin.** Choline is critical to normal membrane structure and function. Lecithin (phosphatidylcholine) is abundant in nerve cell membranes and is required for nerve growth and function. Lecithin is a safer means of dietary choline supplementation than is choline itself. Additionally, it is fully compatible with pharmaceuticals and with other nutrients. The bioavailability of lecithin is high: about 90 percent of the administered amount is absorbed over 24 hours. Also, lecithin is an excellent emulsifier that enhances the bioavailability of coadministered nutrients.

Choline is a precursor of the biosynthesis of acetylcholine. Consumption of supplemental choline has been shown experimentally to increase acetylcholine release and enhance cholinergic function (Wurtman RJ et al 1978). A subsequent trial of oral choline ameliorated symptoms in patients with tardive dyskinesia, a disease associated cholinergic dysfunction. The authors suggested a role for dietary precursors in treating diseases associated with neurotransmitter abnormality (Wurtman RJ et al 1978). Another study of choline supplementation of five patients with tardive dyskinesia produced similar results. Both choline and lecithin increased blood choline levels and improved abnormal movements in all patients. Lecithin had fewer adverse effects than choline (Gelenberg AJ et al 1979). Choline and lecithin supplementation may be an effective means of increasing the levels of acetylcholine in myasthenia gravis patients and thus relieving symptoms or preventing myasthenic episodes.

**Considering all the options.** Besides the supplements mentioned above, there are many nutrients that have a profound impact on muscle function or can moderate the production of inflammatory cytokines, which have been implicated in myasthenia gravis. Although these supplements haven't yet been studied in the context of myasthenia gravis, there may nevertheless be justification to experiment with them and see if beneficial results are obtained, provided there is no contraindication. As always, a supplement program should be launched in conjunction with a qualified physician who is familiar with your particular condition. Supplements that might help with muscle function or reduce inflammation include branch chain amino acids, coenzyme Q10, fish oil, NADH, vitamin E, and minerals such as calcium and potassium. The B vitamin complex is also highly involved in cellular function and acetylcholine production and may help boost acetylcholine levels.

Similarly, many people report that dietary modification helped their myasthenia gravis. While these claims aren't supported in peer-reviewed studies, some patients with myasthenia gravis advocate a raw food or gluten-free diet. As long as adequate nutrition is maintained (a multivitamin is probably a good idea), these diets can be attempted under the supervision of a physician.

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

People with myasthenia gravis should keep regular physician appointments to monitor their disease. It is also recommended that they reduce stress as much as possible and avoid infection because both are associated with flare-ups of the disease. In addition, a program of muscle-boosting and anti-inflammatory supplements might be considered, including the following:

- **Life Extension Mix**—as directed on label of this broad-spectrum, multinutrient formula containing the B complex vitamins; vitamins A, C, D, and E; grape seed extract; citrus bioflavonoids; and more
- **Huperzine A**—50 micrograms (mcg) daily
- **Vitamin K**—10 milligrams (mg) daily
- **DHEA**—15 to 75 mg daily to start, followed by blood testing in three to six weeks to make sure that optimal levels of this hormone are maintained
- **Creatine**— taken in two phases (in conjunction with weight training): the loading phase (higher dosage) and the maintenance phase (Doses of 5 grams (g) daily have been studied in myasthenia gravis.)
- **Lecithin granules**—1 heaping tablespoon daily, with meals
- **Freeze-dried thymus capsules**—as directed on label (only for people whose thymus gland has been removed)
- **Coenzyme Q10**—100 mg daily with food
- **Fish oil**—1400 mg EPA and 1000 mg DHA daily
- **Calcium**—1200 mg daily
- **Potassium**—99 mg daily
- **NADH**—5 mg daily
- **Branch Chain Amino Acids**—as directed on the label

## MYASENTHIA GRAVIS SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### Calcium

- Do not take calcium if you have hypercalcemia.
- Do not take calcium if you form calcium-containing kidney stones.
- Ingesting calcium without food can increase the risk of kidney stones in women and possibly men.
- Calcium can cause gastrointestinal symptoms such as constipation, bloating, gas, and flatulence.
- Large doses of calcium carbonate (12 grams or more daily or 5 grams or more of elemental calcium daily) can cause milk-alkali syndrome, nephrocalcinosis, or renal insufficiency.

### Coenzyme Q10

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

### Creatine

- Do not take creatine if you have diabetes, kidney failure, a kidney disorder such as nephrotic syndrome, or are otherwise at risk of having a kidney disorder.
- If you take creatine, have your serum creatinine level monitored frequently.
- Creatine can cause muscle cramping, muscle strains, and gastrointestinal symptoms such as nausea and diarrhea.

### DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

### EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

### Huperzine A

- Do not take huperzine A if you have a seizure disorder, cardiac arrhythmias, asthma, irritable bowel syndrome, inflammatory bowel disease, or malabsorption syndrome.
- Huperzine A can cause excessive perspiration, blurred vision, fasciculations (involuntary muscle twitching), dizziness, bronchospasm, bradycardia, arrhythmias, seizures, urinary incontinence, increased urination, excessive salivation, and gastrointestinal symptoms such as nausea, abdominal cramps, diarrhea, and vomiting.

### Lecithin

- Lecithin may cause gastrointestinal symptoms such as stomach pain, loose stools, and diarrhea.

### Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

### NADH (Nicotinamide Adenine Dinucleotide)

- NADH can cause gastrointestinal symptoms such as nausea and loss of appetite.

## Potassium

- Do not take potassium if you have hyperkalemia (a greater-than-normal concentration of potassium in the blood).
- Consult your doctor before taking potassium for potassium deficiency.
- Potassium can cause rash and gastrointestinal symptoms such as nausea, vomiting, and diarrhea.

## Vitamin K

- Do not take vitamin K if you are taking warfarin sodium unless, the vitamin K is specifically prescribed by your physician.

For more information see the Safety Appendix

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