Understanding MG

An incurable but generally treatable autoimmune neuromuscular disease that leads to muscle weakness and fatigue, MG is often misdiagnosed due to symptoms similar to other conditions.

By Jim Trageser

WITH NO TYPICAL case — and with the most common symptoms mimicking those of amyotrophic lateral sclerosis (Lou Gehrig's disease), velopharyngeal incompetence[1] or even a stroke[2] — myasthenia gravis (MG) can be difficult to diagnose. And yet, because it leads to the weakness and extreme fatigue of the voluntary muscles, MG can be life-threatening in many patients, making an early diagnosis and beginning treatment all the more critical.

What Is MG?

MG is an autoimmune neuromuscular disease that occurs when the nervous system has difficulty communicating with the voluntary muscles, resulting in weakness and rapid fatigue.[3] The condition generally affects only a select group of muscles in any particular patient at onset, with the most frequent initial symptoms occurring in the facial and ocular muscles.[4] However, MG typically grows more severe, with up to 90 percent of patients experiencing a generalized spread throughout their body within a year of onset.[5]

When the muscles used for breathing are affected, it can prove fatal.[4] Weakness in the mouth or throat can lead to aspiration pneumonia if drooling or difficulty swallowing allows food into the lungs.[5] Patients with MG will experience heightened symptoms following physical activity, and will show marked improvement after resting.[4]

MG was first described in 1672 by English doctor Thomas Willis. In 1877, Samuel Wilks, a London physician, provided the first modern definition of the disease.[6] However, it wasn't until the 20th century and the discovery of the chemical acetylcholine and its role in neurotransmission that knowledge of MG progressed further. In 1973, a study by J. Patrick and J. Lindstrom established a link between blocked acetylcholine

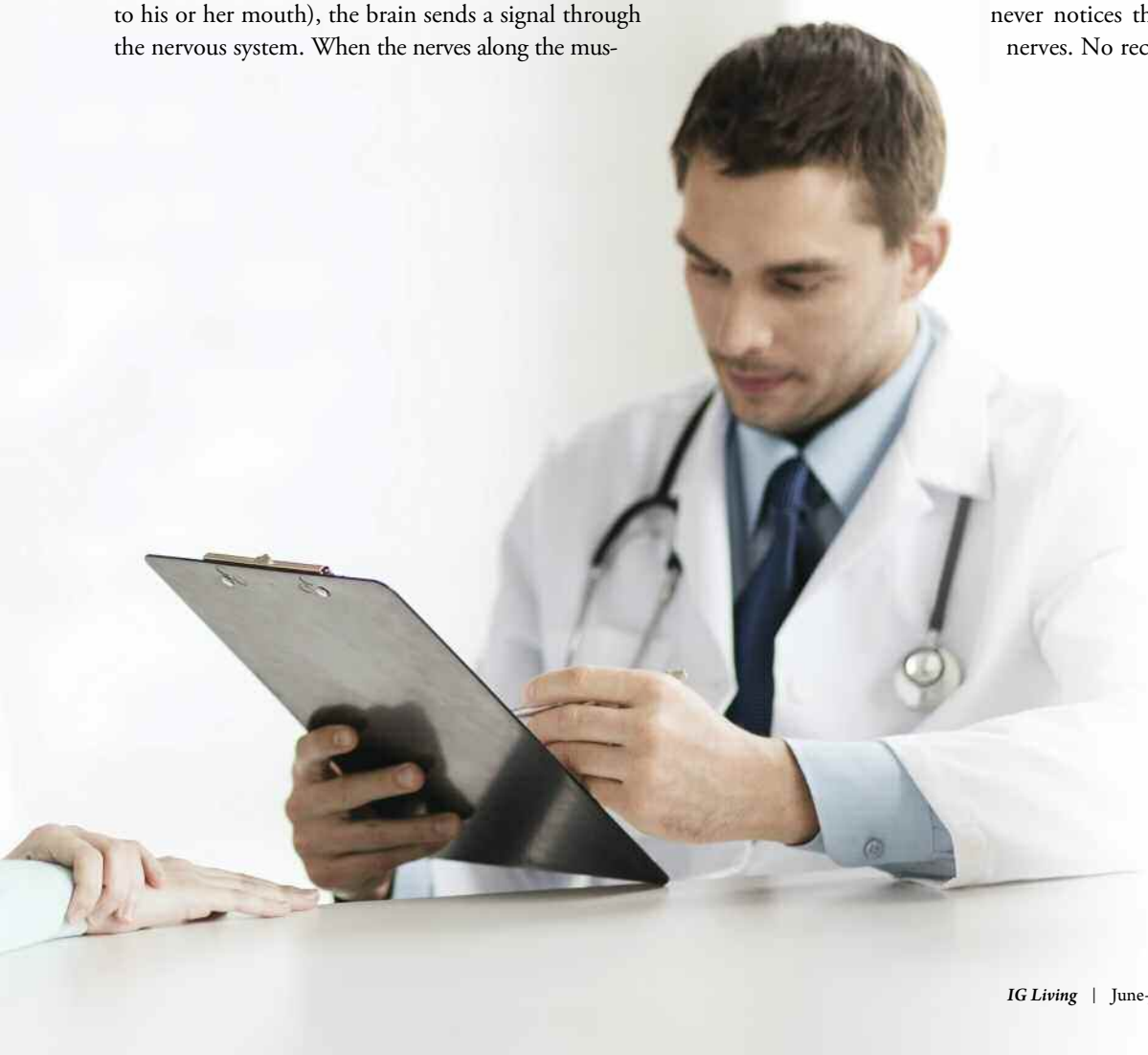
Myasthenia Gravis

receptors and antibodies,[7] giving us our first full understanding of the disease. Subsequent discoveries in molecular biology have further revealed how the disease works at the cellular level.[8]

What Causes MG?

MG is caused by antibodies produced by the patient's own body interfering with the normal communication between nerves and muscles. When a healthy person wants to move a muscle (for instance, bring a spoonful of breakfast cereal to his or her mouth), the brain sends a signal through the nervous system. When the nerves along the muscles of the arms and hands get the signal, they release acetylcholine, which then travels the very short distance to special neuroreceptors on the muscle (a special protein that reacts to acetylcholine), causing the muscle to contract. When everything goes smoothly, the muscles contract in proper order, and the person delivers a spoonful of raisin bran to his or her mouth.

In patients with MG, however, the body produces rogue antibodies that attack and/or block the neuroreceptors on the muscle tissue so that the muscle never notices the acetylcholine sent by the nerves. No reception, no contraction.[4]



As with many autoimmune diseases, the root cause of the production of these antibodies is not fully understood. MG does not appear to be hereditary. Some cases of MG appear to be tied to abnormalities in the thymus gland — oftentimes a tumor. Scientists suspect that many cases of MG — perhaps most — are triggered by an earlier infection that confuses the body into attacking the neuroreceptor proteins on the muscles.[9]

Some cases of MG do not involve the acetylcholine receptors. This is a variant of the disease known as antibody-negative MG. Researchers believe this type of MG involves antibodies attacking another protein known as lipoprotein-related protein 4.[10]

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Symptoms of Progression of MG

Initial symptoms of MG vary widely, ranging from double vision or droopy eyelids (more than half of all cases[11]) to difficulty swallowing. Less-common initial symptoms include unstable walking, slurred speech, shallow breathing or general weakness in the limbs.[4]

Onset of symptoms is generally rapid, and most patients will see a continuing, significant worsening of their condition — with almost 90 percent experiencing a widespread, general condition within a year of the first symptom.[5] A small number of patients will regress to the point that they suffer a myasthenic crisis, in which the muscles used for breathing are too compromised to provide adequate ventilation. Respiratory assistance is used to stabilize them while treatment is begun to restore muscle strength.

Women under 40 (typically in their 30s) and men over 60 are most likely to develop MG, although it affects all ages and nationalities. Juvenile MG is relatively rare, however.[4]

Spontaneous remission is also rare, except in neonatal cases where the baby contracts it from the mother during pregnancy; these cases usually clear up within a few months of birth.[4]

Diagnosing MG

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When patients exhibit any of these symptoms, physicians may examine the eyes for weakness and conduct other standard neurological tests: reflexes, muscle tone, coordination, etc.[12] If MG is suspected, a blood test for the antibodies can confirm most cases (except for antibody-negative MG). About a third of patients with antibody-negative MG will test positive for the anti-MuSK antibody on a blood test, further enhancing doctors' ability to provide a definitive diagnosis.[4]

For patients who exhibit symptoms but do not display the antibodies on either blood test, doctors may administer the edrophonium test, which involves an intravenous dosage of edrophonium chloride. If symptoms are relieved, this is further evidence of MG. Another test used in determining a diagnosis is single fiber electromyography, which uses mild electrical pulses to test muscle reaction. Further, if the thymus is suspected of being the cause of MG, a chest MRI or CT scan may be ordered.[4]

Treating MG

There is currently no cure for MG, nor a method to prevent it. However, most patients will respond to one of the treatment methods currently available — and be able to lead normal lives.[4]

Depending on the symptoms, the patient's history and the specific diagnosis, a doctor may prescribe anticholinesterase drugs, such as neostigmine and pyridostigmine. These help block the rogue antibodies, allowing the nerve to once again communicate effectively with the muscles. Other immunosuppressive drugs may be used to limit production of antibodies, including azathioprine, mycophenolate mofetil, cyclosporine or tacrolimus. However, extended use of immunosuppressants can increase the chance of infection, and cause liver or kidney damage.

Another treatment option is plasmapheresis, which is a blood-filtering process similar to dialysis. For MG, it is used to remove the antibodies causing the disease.

If a tumor on the thymus is suspected of being the cause, surgery to remove the thymus may be scheduled. About half of patients who receive this treatment recover completely. In some cases, even those patients without a tumor or thymus abnormality may benefit from removal of the thymus and elect to undergo the procedure.

One of the more recent treatment options is the use of intravenous immune globulin (IVIG), which provides the body with

normal antibodies that don't block the muscle receptors, thus providing relief to many patients.[13] IVIG also is less likely to provoke side effects than immunosuppressants or plasmapheresis, although it can take as much as a week before patients begin to show improvement.

IVIG provides the greatest relief to patients with the most severe symptoms,[14] but its effectiveness wanes in some patients after a period of three weeks to six weeks.[13] Thus, it is often used to bring improvement to seriously ill patients until other treatment options can be explored[15] (although some patients will continue on a long-term regimen of IVIG if they continue to show improvement[16]).

MG Research

Important advances are already being made in treating the symptoms of MG. There are more than four dozen ongoing studies involving MG listed on the National Institutes of Health's clinicaltrials.gov website. Among them is a study looking at whether the lymphoma-leukemia drug Rituximab can help control MG. There is also a study investigating whether 3,4-diaminopyridine — used in other countries to treat another autoimmune neuromuscular disease, Lambert-Eaton myasthenic syndrome — might also help the symptoms of MG.[17]

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One study from St. Louis University planned to explore whether a subcutaneous (SC) administration of IG would be more effective than IVIG in treating MG. While it was recently terminated due to a lack of test subjects, it is possible it will be restarted.[18] Another study by University Health Network in Toronto, Canada, looked at whether plasma exchange rather than IV was a more effective way to administer IG in MG patients. This study has been completed, but the results have not yet been published.[19]

Additional studies are researching whether self-administered SCIG can be effective in treating MG, whether IVIG is effective in treating advanced (generalized) MG, whether IVIG can be used to ease patients off of long-term corticosteroid treatment, and whether IVIG might help treat MG patients with certain exacerbations.[17]

As researchers gain additional insight into how the neurological system interacts with the muscular system, studies based on that new discovery are likely to yield improved treatment options in the decades to come.

MG Outlook

Since there is no cure, nor any preventive treatment, the prognosis for those diagnosed with MG varies according to the severity of each case. Fortunately, most MG patients respond positively to current treatment options and are able to lead full, productive lives. ■

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References

1. Wheeler, SD. Misdiagnosis of Myasthenia Gravis. *Journal of the National Medical Association*, 1987 Apr; 79(4): 425–429. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC2625490.
2. Kleiner-Fisman, G, and Kott, HS. Myasthenia Gravis Mimicking Stroke in Elderly Patient. *Mayo Clinic Proceedings*, 1998 Nov;73(11):1077-8. Accessed at www.ncbi.nlm.nih.gov/pubmed/9818042.
3. Mayo Clinic. Diseases and Conditions: Myasthenia Gravis. Accessed at www.mayoclinic.org/diseases-conditions/myasthenia-gravis/basics/definition/con-20027124.
4. National Institute of Neurological Disorders and Stroke. Myasthenia Gravis Fact Sheet. Accessed at www.ninds.nih.gov/disorders/myasthenia_gravis/detail_myasthenia_gravis.htm#3153_1.
5. Patient.info. Myasthenia Gravis. Accessed at patient.info/doctor/myasthenia-gravis-pro.
6. Hughes, T. The Early History of Myasthenia Gravis. *Neuromuscular Disorders*, vol. 15, issue 12, pages 878–886. Accessed at www.sciencedirect.com/science/article/pii/S0960896605002567.
7. Patrick, J, and Lindstrom, J. Autoimmune Response to Acetylcholine Receptor. *Science*, 1973 May 25;180(4088): 871-2. Accessed at www.ncbi.nlm.nih.gov/pubmed/4706680.
8. Fujioka, T. Myasthenia Gravis and Acetylcholine. *Brain Nerve*, 2014 May;66(5):517-25. Accessed at www.ncbi.nlm.nih.gov/pubmed/24807368.
9. Muscular Dystrophy Association. Myasthenia Gravis Causes/Inheritance. Accessed at www.mda.org/disease/myasthenia-gravis/causes-inheritance.
10. Mayo Clinic. Myasthenia Gravis Causes. Accessed at www.mayoclinic.org/diseases-conditions/myasthenia-gravis/basics/causes/con-20027124.
11. Mayo Clinic. Myasthenia Gravis Symptoms. Accessed at www.mayoclinic.org/diseases-conditions/myasthenia-gravis/basics/symptoms/con-20027124.
12. Mayo Clinic. Myasthenia Gravis Tests and Diagnosis. Accessed at www.mayoclinic.org/diseases-conditions/myasthenia-gravis/basics/tests-diagnosis/con-20027124.
13. Mayo Clinic. Myasthenia Gravis Treatments and Drugs. Accessed at www.mayoclinic.org/diseases-conditions/myasthenia-gravis/basics/treatment/con-20027124.
14. Zinman, L, and Bril, V. IVIG Treatment for Myasthenia Gravis: Effectiveness, Limitations, and Novel Therapeutic Strategies. *Annals of the New York Academy of Sciences*, 2008;1132:264-70. doi: 10.1196/annals.1405.038. Accessed at www.ncbi.nlm.nih.gov/pubmed/18567877 http://www.ncbi.nlm.nih.gov/pubmed/18567877.
15. National Health Service (U.K.) Myasthenia Gravis Treatment. Accessed at www.nhs.uk/Conditions/Myasthenia-gravis/Pages/Treatment.aspx.
16. Wegner, B, and Ahmed, I. Intravenous Immunoglobulin Monotherapy in Long-Term Treatment of Myasthenia Gravis. *Clinical Neurology and Neurosurgery*, 2002 Dec;105(1):3-8. Accessed at www.pptaglobal.org/plasma-products-databases/immunoglobulin/neurology/760-intravenous-immunoglobulin-monotherapy-in-long-term-treatment-of-myasthenia-gravis.
17. ClinicalTrials.gov. Myasthenia Gravis. Accessed at clinicaltrials.gov/ct2/results?term=Myasthenia+Gravis&pg=1.
18. ClinicalTrials.gov. Subcutaneous Ig Maintenance Therapy for Myasthenia Gravis (SIMM). Accessed at clinicaltrials.gov/ct2/show/NCT01828294?term=Myasthenia+Gravis&rank=8.
19. ClinicalTrials.gov. Intravenous Immunoglobulin and Plasma Exchange in Myasthenia Gravis. Accessed at clinicaltrials.gov/ct2/show/NCT01179893?term=Myasthenia+Gravis&rank=22.