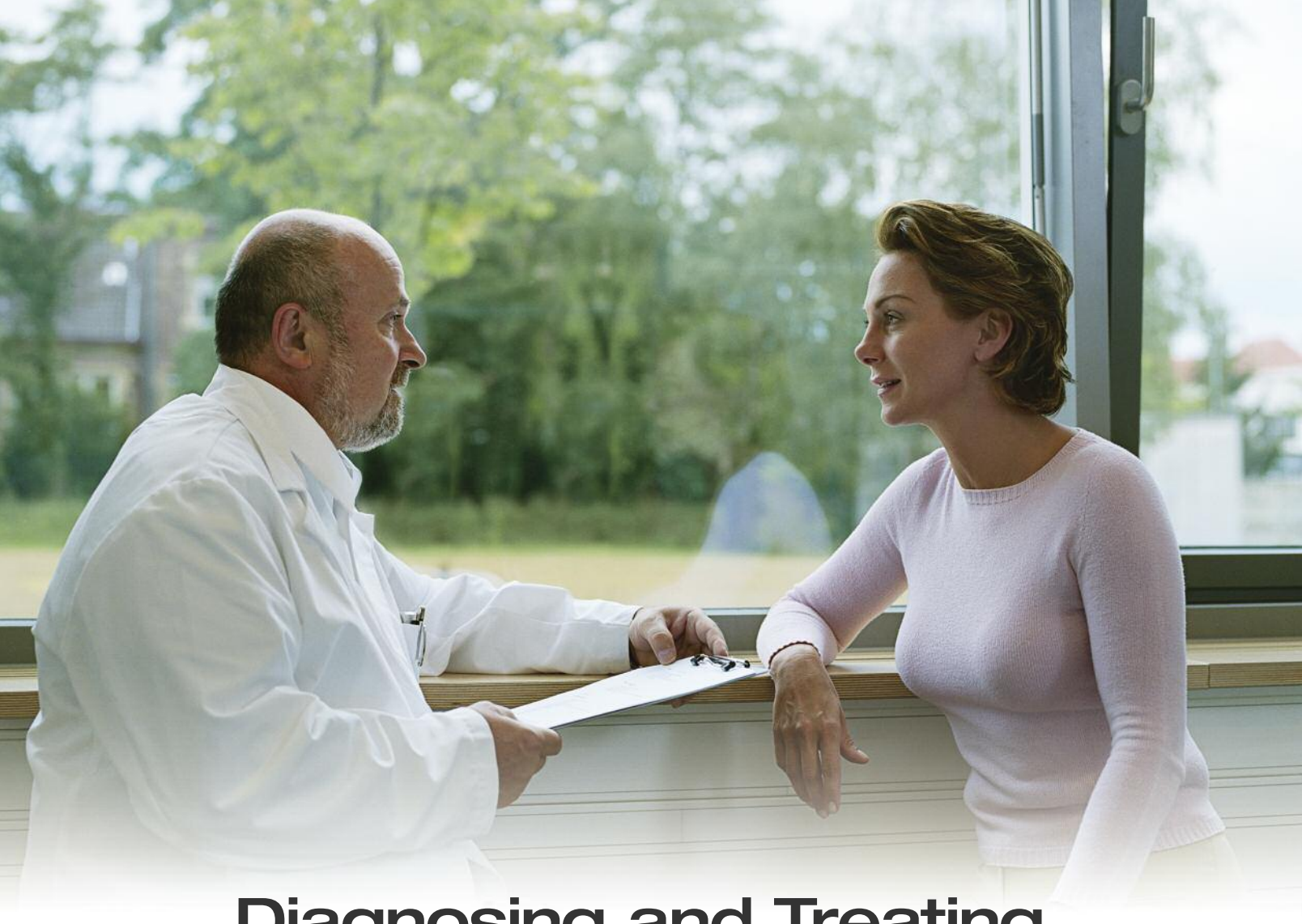

Diagnosing and Treating Myasthenia Gravis

By Ronale Tucker Rhodes, MS

This rare disease, which has been around since the 17th century, has grown in prevalence, but because it is now thoroughly understood, myasthenics are living a longer and better quality of life due to improved treatments.

Myasthenia gravis (MG) patients, referred to as myasthenics, often describe their disease as nothing working but their brain. It is a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal (voluntary) muscles of the body, which is caused by a defect in the transmission of nerve impulses to muscles.[1] The defect occurs when circulating antibodies cause weakness by blocking acetylcholine receptors (AChRs) at the post-synaptic neuromuscular junction. These anti-AChR antibodies inhibit the stimulative effect of the neurotransmitter acetylcholine.[2] In short, normal communication between the nerve and muscle is interrupted at the neuromuscular junction where the nerve cells connect with the muscles they control.[1]

In the more than 50 years since studies of the epidemiology of MG have been conducted, there has been an increase in the reported prevalence of MG (also known as Goldflam disease).[3] Today, the Myasthenia Gravis

Foundation of America (MGFA) estimates that MG is diagnosed in 20 out of every 100,000 people in the U.S. Therefore, with an estimated 314 million people in the U.S., approximately 63,000 of them are myasthenics.[4] And, it is a sporadic disease, meaning it strikes at random and it does not run in families. In those who present with MG at less than 40 years old, 75 percent are women. In those older than 40, 60 percent are men. However, in patients who have MG as a consequence of having a thymoma (an uncommon tumor associated with MG), there is no age or sex predominance.[5]

While the first described case of MG occurred in 1672, the disease remained a mystery until 1960 when it was proposed that MG was caused by antibodies attacking neurotransmitters. Then, in 1973, MG was demonstrated to be autoimmune in origin. Today, MG is one of the most thoroughly understood neurological disorders, which has led to treatments that vastly improve the length and quality of life of myasthenics.[5]

Types and Causes of MG

Most cases of MG are the adult-onset type; however, there are two other types that occur in adults, including drug-related MG and viral/bacterial MG. There have been many instances in which patients have experienced an onset of MG during penicillamine treatment for diseases such as rheumatoid arthritis. The onset of MG may be caused by an alteration of the immune system that allows for the production of anti-AChR antibodies due to the effects of the drug. Several other drugs also can heighten the symptoms of MG in patients who already have the disease. MG also can be brought on by a bacterial or viral infection. Researchers believe this occurs when the protein amino acid sequence of the foreign invader is similar to the same sequence in the body, which causes the immune system to recognize both the foreign and the new self molecule as foreign. In the case of MG, the herpes simplex virus is similar enough to initiate such an immune response against protein components of AChRs.[6]

In rare cases (approximately 10 percent of MG patients), children are diagnosed with juvenile MG. Typically, juvenile MG develops in female adolescents, especially white females, and it is a lifelong condition that may go in and out of remission. But children also can develop two other types of MG, including congenital MG and transient neonatal MG. Congenital MG is a very rare, nonimmune form of MG that is inherited as an autosomal recessive disease that affects both males and females equally, usually occurs in the baby's first year of life and is lifelong. For a baby to have congenital MG, two copies of the gene, one inherited from each parent, are necessary. Between 12 and 20 percent of babies born to mothers with MG may have a temporary form of MG known as transient neonatal MG caused by antibodies common in MG crossing the placenta to the developing fetus. However, symptoms of congenital MG usually last only a few weeks, and babies are not at greater risk for developing MG later in life.[4]

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Symptoms of MG

The muscle weakness caused by MG is experienced differently among patients, and it can lead to a variety of symptoms, which is why myasthenics think that the only thing working is their brain. The symptoms most often experienced include breathing difficulty because of weakness of the chest wall muscles; chewing or swallowing difficulty that can cause gagging, choking or drooling; difficulty climbing stairs, lifting objects or rising from a seated position; difficulty talking; a drooping head; facial paralysis or weakness of the facial muscles; fatigue; hoarseness or a changing voice; double vision; difficulty maintaining a steady gaze; and eyelid drooping. Fortunately, while muscle weakness worsens with activity, it improves with rest.[7]

Diagnosing MG

Testing for MG starts with a complete medical and neurological evaluation. If MG is suspected, physicians will normally test to see if muscle weakness changes during periods of activity and rest. For instance, clinicians may have patients look upward to see if their eyelids start to droop (clinically referred to as ptosis) when open for several minutes. They may then have patients lie down with their eyes closed for several minutes and retest to see if function improves.

To confirm a diagnosis of MG, five different tests can be conducted. A blood test can detect abnormal AChR antibodies. Approximately 85 percent of myasthenics have this antibody, which makes the detection of the antibody strongly indicative of MG. For the remaining 15 percent of myasthenics who test negative for AChR antibodies, a blood test will detect seronegative MG (SNMG). About

40 percent to 70 percent of patients with SNMG test positive for the anti-MuSK antibody. The remaining have unidentified antibodies causing their MG.

An electromyography (EMG) study and single fiber EMG studies can support the diagnosis of MG when characteristic patterns are present. And, finally, office tests such as the sleep, ice pack and edrophonium tests can be performed by specialists to evaluate an improvement in strength that may be consistent with MG.[8]

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The ice pack test is one reliable bedside test that can differentiate MG from other conditions. It consists of the application of ice to the eyes for two to five minutes, ensuring that the ice is covered to prevent ice burns. If positive, the patient no longer has the characteristic ptosis of MG. However, it's important for the ice pack to not be left for too long, because the test becomes uncomfortable for the patient and the reduction of muscle fiber temperature below 72 degrees Fahrenheit will reduce the contractile force of the muscle itself and create a false-negative result. In a recent study of myasthenic diplopia, the sensitivity of this test was 76.9 percent, and the specificity was 98.3 percent with no false-positives reported.[9]

Treating MG

While MG is not curable, the disease can be managed with medications and other treatments. Common medicines prescribed include pyridostigmine, which increases the amount of acetylcholine available to stimulate the receptors, and prednisone and other immunosuppressant drugs such as azathioprine, cyclosporine or cyclophosphamide to slow down the production of anti-AChR antibodies.[10]

In severe cases of MG, patients may need to undergo plasmapheresis, which involves having the blood sent through a machine that removes antibody-containing plasma and replaces it with antibody-free plasma. And, they may need intravenous immune globulin (IVIG) therapy.[10] Both plasmapheresis and IVIG may be given once as an acute therapy to act as a rapidly acting but short-lasting treatment for a flare of the disease, or given intermittently as chronic therapy. Historically, IVIG has been used as an acute therapy for MG, and it has been an alternate therapy to plasmapheresis, which is similar in efficacy. Recently, there has been increased interest in using IVIG to chronically treat MG due to its decreased side effects compared with plasmapheresis and prednisone. Plasmapheresis requires the placement of an intravenous catheter that is prone to clot or become a site of infection. And, prednisone decreases resistance to infection more than IVIG, as well as suppresses many of the symptoms of infection such as fever and swelling.[11]

Myasthenics who have thymoma will need to have their thymus removed. A doctor may even recommend a thymectomy even if no tumor is present because removal of the thymus often improves symptoms in patients.[10]

Scientists are currently evaluating new treatments and improving current ones. Different drugs are being tested either alone or in combination with existing therapies to see if they are effective. For instance, one study seeks to understand the molecular basis of synaptic transmission in the nervous system.[12] Thymectomy is being studied in individuals who do not have thymoma to assess the long-term benefit that surgery may have over medical therapy alone. And, autologous hematopoietic stem cell transplantation is being examined for its safety and efficacy to treat refractory and severe MG.[7]

Living with MG

Most myasthenics with treatment can significantly improve muscle weakness and, in some, the disease goes into temporary remission. However, there are cases in which myasthenics may experience exacerbations of the disease.

In some, the severe weakness of MG may cause respiratory failure, which results in a myasthenic crisis. During a myasthenic crisis, patients may be unable to breathe, cough or protect their airway, and they may need mechanical breathing assistance in a hospital until their strength improves.[13] The most common cause of a myasthenic crisis is infection. However, many other factors influence a crisis, including drugs, temperature and emotional state.

More than 30 medications have been reported to have an effect on neuromuscular transmission. But because these exacerbations have been published mainly in case reports, the true incidence is difficult to determine. The drugs to be used with caution can be remembered by referring to them as the "13 As." They include: ACTH and

steroids; analgesics; anesthetics (local: cocaine, procaine); antacids or laxatives containing magnesium; antiarrhythmics (quinidine, lidocaine, procainamide); antibiotics (aminoglycosides, quinolones, ampicillin, imipenem); anticonvulsants (phenytoin); antihypertensives (beta-blockers, calcium channel blockers); antimanics (lithium salts); antipsychotics (chlorpromazine); antirheumatics (chloroquine); arthritis (penicillamine-induced MG); and all neuromuscular blocking agents.[14]

Other factors that can cause a myasthenic crisis include fatigue or insufficient sleep, stress or anxiety, illness, overexertion or repetitive motion, pain, hot foods or beverages, sudden fear or extreme anger, depression, extreme temperatures (hot or cold weather, hot showers or baths, sunbathing, saunas and hot tubs), humidity, sunlight or bright lights that affect the eyes, alcoholic beverages, quinine or tonic water, low potassium or low thyroid levels, exposure to some chemicals (household cleaners, insecticides and pet flea sprays) and chemical lawn treatments.[13]

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Pregnancy also can exacerbate or cause remission of MG. Generally during pregnancy, one-third of patients experience an exacerbation, whereas the other two-thirds remain clinically unchanged, and complete remission occurs in some patients. In a study conducted between 1996 and 2003, 18 pregnant women (11 percent) with MG had an improvement in the clinical symptoms of MG, seven (39 percent) had clinical worsening of the condition, and nine others (50 percent) remained clinically unchanged. Only one infant presented with transient neonatal MG.[15]

An Evolving Disease

Since the 17th century when MG was first discovered, the disease has evolved from one that could not be explained to one that is now the most understood neurological disorder. With this increased understanding has come expanded methods of diagnosis, new and improved treatments and a drastically enhanced outlook for patients. In 1958, the mortality rate for myasthenics was 30 percent. Today, with optimal care, the mortality rate is close to zero.[16]

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