EDUCATIONAL COMMENTARY – AUTOIMMUNE MYASTHENIA GRAVIS

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Learning Outcomes
On completion of this exercise, the participant should be able to

- describe the role of autoantibodies in myasthenia gravis (MG);
- discuss the thymus in relation to MG;
- list the symptoms of MG;
- discuss the diagnosis of MG; and
- list treatments for MG.

Introduction
Myasthenia gravis (MG) is a rare neuromuscular disease characterized by muscle weakness and muscle fatigue in the absence of other neurologic involvement. The name *myasthenia gravis* is a combination of Greek and Latin for “grave muscle weakness.” As more and more has been learned about the disease, the gravity of the diagnosis has lessened. Treatments have greatly improved, and most individuals with MG have a normal life expectancy.1 According to the Myasthenia Gravis Foundation of America, “MG is the most common primary disorder of neuromuscular transmission.”2 The disease is usually autoimmune in nature, but there are cases caused by genetic abnormalities that affect the neuromuscular junction.

In a healthy individual, skeletal muscles contract after nerve endings produce acetylcholine, a neurotransmitter, in the neuromuscular junction. The acetylcholine attaches to acetylcholine receptors located on the muscle end-plate membrane. The acetylcholine receptors are activated, an electrical current is produced, and the muscle contracts. In MG, a dysfunction of the immune system leads to the production of autoantibodies directed against acetylcholine receptors. These autoantibodies block or alter the acetylcholine receptors on the muscle end-plate membrane, interrupting the transmission of nerve impulses across the neuromuscular junction. The ability of the nerves to transmit signals to the muscles is reduced, resulting in a reduction in muscle contraction. Muscle strength declines as the individual’s activity level increases, and improves after periods of rest. As a result, persons with MG are stronger in the morning and experience increasing muscle weakness as the day progresses.

Thymus Involvement
Although approximately 75% of persons with MG have abnormalities of the thymus, the role of the thymus in the disease remains uncertain.2,3 In most cases of MG, thymic hyperplasia exists. The function of the thymus in the immune system is to develop self-tolerance. When the immune system does not recognize tissues as self, it produces autoantibodies. Research indicates that certain cells in the thymus have
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muscle-like characteristics and stimulate the production of autoantibodies against acetylcholine receptors on the muscle end-plates.\textsuperscript{3} Thymic tumors (thymomas) may develop in persons with MG. In most cases, the tumors are benign and well encapsulated and are removed surgically. Patients with thymomas tend to have more severe disease, higher antibody levels, and more severe electromyographic abnormalities. Of persons diagnosed with MG between the ages of 30 and 60 years, 20\% have thymomas. Persons diagnosed over the age of 60 years are less likely to have thymomas.\textsuperscript{2}

Prevalence
There are 36,000 to 60,000 cases of MG in the United States, a prevalence of 14 to 20 cases per 100,000 population.\textsuperscript{2} It appears that the incidence of MG has increased over the past several decades.\textsuperscript{3} As in most autoimmune diseases, MG is often underdiagnosed. Symptoms are vague, fluctuate, and resemble those of many other conditions. When a mild weakness occurs in only a few muscles, misdiagnosis is common. Early studies showed that women were more likely to be diagnosed as having MG overall, but as the population ages, the predominance of cases are identified in men. Women are usually diagnosed in their 20s or 30s; men are more likely to be diagnosed in their 70s or 80s.\textsuperscript{2}

Symptoms
Patients usually present with specific muscle weakness rather than overall fatigue. Although any voluntary muscle can be affected, early symptoms in two-thirds of diagnosed persons include ptosis (drooping eyelids) and diplopia (double vision) caused by weakness of the eye muscles. Other complaints involve weakness of the muscles that control facial expression, swallowing, and speech. The degree of weakness varies greatly from individual to individual, but in most cases it is progressive. Cases range from those in which only the eye muscles are affected (ocular MG) to widespread muscle weakness that involves many muscle groups (generalized MG). In approximately 10\% of patients, the muscles required for breathing are affected, which may lead to respiratory failure,\textsuperscript{1,3} known as myasthenic crisis. Myasthenic crisis may be triggered by respiratory infection, stress, surgery, or an abrupt change in corticosteroid dosage.\textsuperscript{3} Muscle atrophy of the face or tongue may occur in patients who produce an antibody directed against the muscle-specific receptor tyrosine kinase (anti-MuSK).

A transient form of MG may occur in newborns of mothers with MG, caused by the transplacental transfer of antibodies from mother to fetus. The neonate displays low muscle tone, muscle weakness, a weak cry, or little spontaneous movement. Symptoms disappear within days to weeks.\textsuperscript{3}

Diagnosis
Diagnosis begins with the patient’s medical history, symptoms, and physical and neurologic examinations. The patient usually displays muscle weakness that presents as impaired eye movement. This weakness does not result in numbness or lack of sensation. Difficulty in properly diagnosing MG is a
result of the wide variety of muscles that may be affected, the waxing and waning of symptoms, and the similarity of these symptoms with those of many other diseases.

Laboratory testing confirms the diagnosis. Anti-acetylcholine receptor antibodies may be detected in up to 90% of affected individuals with generalized disease and up to 50% of those with the ocular form. The concentration of serum antibodies does not correlate with the severity of disease. The diagnosis of MG is not ruled out in a patient who has the clinical symptoms of MG but is seronegative for anti-acetylcholine receptor antibodies. Antibodies may not be measurable at the onset of symptoms but may be detectable later. Anti-MuSK is positive in 30% to 40% of MG patients who do not have detectable anti-acetylcholine receptor antibodies. There remain some cases of MG, approximately 10%, in which neither antibody is detectable. Usually these are cases in which only ocular muscles are affected.

Nonlaboratory evaluations may be performed, including nerve conduction studies, single-fiber electromyography (EMG) and the edrophonium chloride test. Intravenous administration of edrophonium chloride improves weakness caused by abnormal neuromuscular transmission in MG patients. Diagnostic imaging of the chest is used to detect the presence of a thymoma, and pulmonary function testing is performed to evaluate breathing strength and predict the extent of respiratory failure that occurs in myasthenic crisis.

Treatment
Mild cases of MG may not require treatment. Before corticosteroid therapy became available, approximately one-third of patients improved spontaneously, one-third became worse, and one-third died. Today there are many therapies that are commonly used to reduce muscle weakness and fatigue, such as anticholinesterase agents and immunosuppressive medications. Because of the risk for opportunistic infections and cancer, patients taking immunosuppressive drugs must be carefully monitored.

Thymectomy is recommended for patients with thymomas. The surgery may also reduce muscle weakness in those without thymomas and is often performed on younger patients with generalized disease. Sometimes, the surgery leads to a drug-free remission.

Therapeutic plasma exchange is also used to decrease the concentration of autoimmune antibodies circulating in the blood. In this process, blood is removed from the patient, the plasma is separated from the blood cells, and only the cells and a replacement fluid are reinfused to the patient.

Conclusion
Myasthenia gravis is a rare disease that can manifest in forms that range from mild to critical. It is, in most cases, an autoimmune disease in which the antibodies produced interfere with the conduction of nerve impulses to the muscles. The result is a reduction in muscle contraction, which leads to muscle
weakness and muscle fatigue. After periods of rest, persons with MG regain some strength. Therapies are available that reduce or alleviate the symptoms and, in some cases, lead to long-term remission.

References

