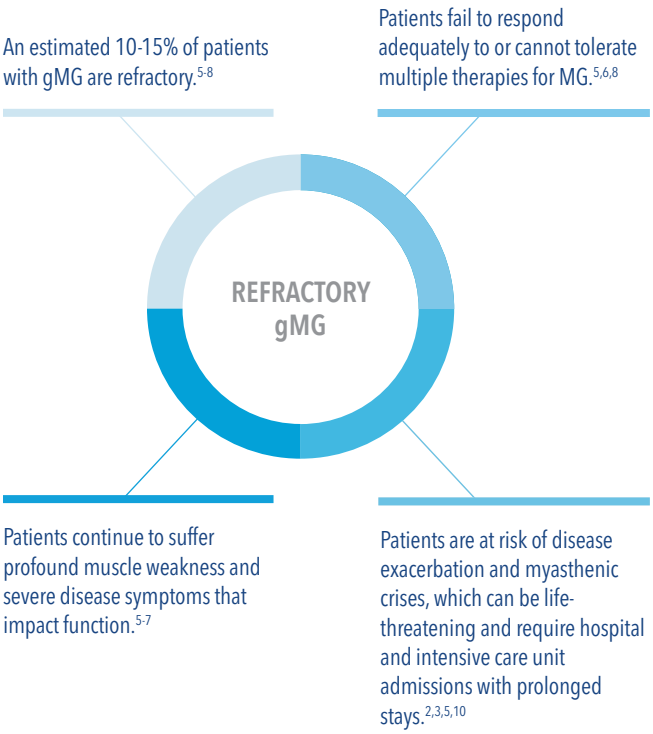
REFRACTORY GENERALIZED MYASTHENIA GRAVIS (gMG)

OVERVIEW

Myasthenia gravis (MG) is a debilitating, chronic and progressive autoimmune neuromuscular disease that can occur at any age, but most commonly begins for women before the age of 40 and men after the age of 60.[1-4] It typically begins with weakness in the muscles that control the movements of the eyes and eyelids, and often progresses to the more severe and generalized form, known as generalized myasthenia gravis (gMG), with weakness of the head, neck, trunk, limb and respiratory muscles.[4]

While most patients with gMG can be managed with therapies for MG, 10–15% of patients are considered refractory—meaning they fail to respond adequately to or cannot tolerate multiple therapies for MG and continue to suffer profound muscle weakness and severe disease symptoms that limit function.[5-7]

In 53–75% of patients with refractory gMG, the immune system turns on itself to produce antibodies against the acetylcholine receptor (AChR) that plays an important role in the communication between nerves and muscles.[8-10] Patients with refractory gMG who are anti-AChR antibody-positive represent an ultra-rare portion of patients with MG (an estimated 5–10% of patients with MG).[5,6,8,11]



SYMPTOMS AND COMPLICATIONS

Patients with refractory gMG can suffer from slurred speech; choking; impaired swallowing; double or blurred vision; disabling fatigue; immobility requiring assistance; shortness of breath; and episodes of respiratory failure. Complications, exacerbations and myasthenic crises can require hospital and intensive care unit admissions with prolonged stays, and can be life-threatening.[2,3,10]

CAUSES

In MG, an autoimmune response leads to progressive inflammation and damage at the neuromuscular junction (NMJ), the area where nerve cells reach the muscles they control. This damage impairs the communication between nerve and muscle, which in turn leads to a loss of normal muscle function.[2,3]

In patients with refractory gMG who are anti-AChR antibody-positive, these antibodies bind to the AChR, a receptor located on muscle cells in the NMJ and used by nerve cells to communicate with the muscle. The binding of these antibodies to the AChR activates the complement cascade, another component of the immune system that results in the localized destruction of the muscle membrane at the NMJ.[12-14]

DIAGNOSIS AND MANAGEMENT

MG is typically diagnosed with a physical examination to evaluate distinct symptoms of muscle weakness, such as impaired eye movement, droopy eyelids, inability to hold the head straight, speech disturbances, and limb weakness. Blood tests for anti-AChR or other antibodies are also used, as well as nerve and muscle stimulation, and chest computed tomography or magnetic resonance imaging.[3,15]

Therapies for gMG include acetylcholinesterase inhibitors, corticosteroids and other immunosuppressive therapies.[3,6] Plasma exchange and intravenous administration of immunoglobulin to remove or neutralize abnormal antibodies from the blood, and the infusion of antibodies from donated blood, may be used as "rescue therapy" for severe disease exacerbations.[6] The surgical removal of the thymus gland, which is often abnormal in patients with MG, is recommended for patients who develop tumors of the thymus gland (thynoma) and some patients without thynoma.[3]

For more information on MG, visit the Myasthenia Gravis Foundation of America website at myasthenia.org.

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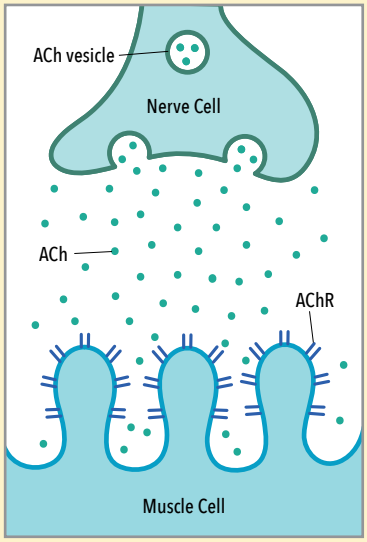
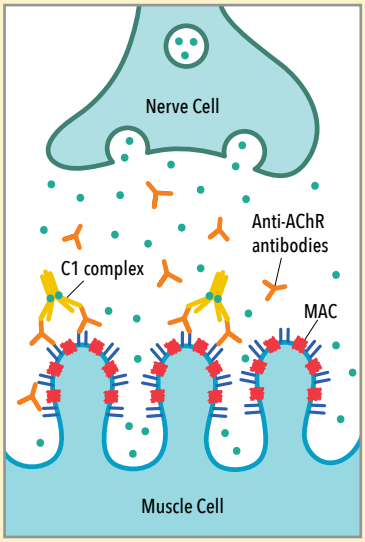
ANTI-ACHR ANTIBODY-POSITIVE MG [4,9,14,16]

1 HEALTHY NMJ



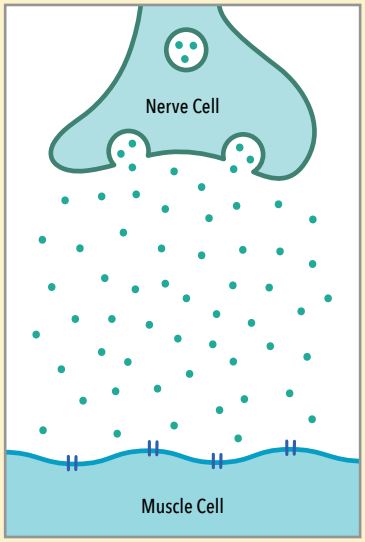
ACh released by nerve cells binds to AChR on muscle cells, resulting in muscle activation.

2 COMPLEMENT BINDING AND ACTIVATION AT THE NMJ



Anti-AChR antibodies bind to AChRs, which can directly interfere with signaling and trigger the activation of the complement cascade (C1 complex). The complement cascade produces the MAC that damages the muscle cell membrane, resulting in loss of AChRs.

3 COMPLEMENT-MEDIATED DAMAGE TO THE MUSCLE MEMBRANE AT THE NMJ



The localized destruction of the NMJ impairs the communication between nerve and muscle, which in turn leads to a loss of normal muscle function.

Acetylcholine (ACh), Neuromuscular Junction (NMJ), Acetylcholine Receptor (AChR), Membrane Attack Complex (MAC)

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