REFRACTORY GENERALIZED MYASTHENIA GRAVIS (gMG)

DISEASE OVERVIEW

Refractory generalized myasthenia gravis (gMG) is an ultra-rare segment of the broader MG population in which patients experience severe disease-related morbidities despite currently available therapies.[1-3]

MG is a debilitating, complement-mediated neuromuscular disease.[4,5] It can occur at any age but most commonly affects women under the age of 40 and men over the age of 60.[6] The disease typically begins with weakness in the ocular muscles and often progresses to the more severe and generalized form, known as gMG, to include weakness of the head, neck, trunk, limbs, and respiratory muscles.[7]

While most patients with gMG are managed with conventional therapies, 10 to 15 percent are considered refractory—meaning they have largely exhausted conventional therapy and continue to suffer profound muscle weakness throughout the body.[5,8]

SYMPTOMS

Patients with refractory gMG can experience severe and debilitating symptoms, including slurred speech; difficulty chewing and swallowing food, leading to choking; drooping of one or both eyelids, double vision or blurred vision; upper and lower extremity weakness; disabling fatigue; shortness of breath due to respiratory muscle weakness; and episodes of respiratory failure.[5,6,9,10] Up to 20 percent of patients will experience a myasthenic crisis, defined as severe weakness requiring respiratory support, which frequently results in hospitalization, often involving stays in the intensive care unit.[5]

CAUSES

In patients with MG, the immune system mistakenly produces antibodies that block, alter, or destroy receptors at the neuromuscular junction (NMJ), the area where nerve cells connect with the muscles they control.[6] The disruption of communication between the nerve and muscle prevents normal muscle contraction from occurring, resulting in debilitating muscle weakness.[5,6]

Most gMG patients—approximately 80 to 90 percent—produce anti-acetylcholine receptor (AChR) antibodies that bind, modulate or block AChR receptors at the NMJ and disrupt normal neuromuscular transmission.[11,12] Complement activation plays a major role in the underlying disease pathophysiology in patients with gMG.[11] Antibody binding to the AChR activates the complement cascade, leading to the destruction of AChR and AChR-related proteins.[12,13]

A smaller group of gMG patients—approximately 8 to 10 percent—have antibodies that target muscle-specific kinase (MuSK), and in approximately 5 to 10 percent of patients, no specific antibody is detected (referred to as "double seronegative MG").[14,15,16]

DIAGNOSIS

MG is typically diagnosed with a physical examination to evaluate distinct symptoms of fatigable muscle weakness, such as impaired eye movement, droopy eyelids, inability to hold the head straight, speech disturbances, and limb weakness.[6,17] Blood tests to check for anti-AChR antibodies or anti-MuSK antibodies are also used in diagnosis.[17] Other diagnostic tests include nerve and muscle stimulation and body imaging studies (chest computed tomography or magnetic resonance imaging).[17]

CURRENT TREATMENT LANDSCAPE

Many patients with gMG are managed with conventional therapy, including acetylcholinesterase inhibitors and immunosuppressive therapies such as corticosteroids.[8] Short-term "rescue therapy" with plasma exchange and intravenous immunoglobulin (IVIG), which involves removal of the abnormal antibodies from the blood and the infusion of antibodies from donated blood, may be used to treat acute, severe disease exacerbations.[6,8,14] Thymectomy, the surgical removal of the thymus gland, which is often abnormal in patients with MG, is recommended for patients who develop thymomas (tumors of the thymus gland).[6]

Despite the availability of these treatments, a subset of gMG patients remains refractory to conventional therapies, characterized by continued suffering from severe symptoms despite otherwise adequate doses and duration of treatment, poor tolerability of conventional therapy, or repeated rescue treatments.[8,18] Many of these refractory gMG patients have tried and failed treatment with multiple immunosuppressive agents and continue to have a high degree of disease severity, including persistent muscle weakness that severely impairs their ability to engage in simple daily activities such as talking, chewing, swallowing, and even breathing normally.[5,6,8,17]

Today, there are no therapies that are effective for this ultra-rare segment of patients with refractory gMG.[1-3,8]

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

US/UNB-gMG/16/0005

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