Generalized Myasthenia Gravis

Classification, Clinical Presentation, Natural History, and Epidemiology

Michael K. Hehir, MD[a,*], Nicholas J. Silvestri, MD[b]

KEYWORDS

• Myasthenia gravis • Acetylcholine receptor • Antimuscle-specific kinase • Ocular

KEY POINTS

- Myasthenia gravis (MG) is a rare disease.
- A common yet nonspecific feature of MG is the fluctuating nature of weakness that patients experience, a phenomenon referred to as fatigability.
- The majority of patients with MG first present with ocular symptoms.
- Most patients with MG will experience at least 1 exacerbation of symptoms throughout the course of their illness.

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction. It is the prototypic autoimmune disease most commonly caused by antibodies to the acetylcholine receptor (AChR) leading to characteristic fatigable weakness of the ocular, bulbar, respiratory, axial, and limb muscles. This article will cover the epidemiology, clinical presentation, classification, and natural history of MG.

EPIDEMIOLOGY

MG is a rare disease. Wide variability in reported incidence rates (IRs) and prevalence rates (PRs) are based on several epidemiologic studies performed primarily in Europe and the United States over the past 70 years.[1–3] In general, both IR and PR are increasing in nonlinear fashion over time. The biggest increase occurred around 1980. These increases are attributed to greater awareness of the disease and improvements in diagnostic antibody testing, epidemiologic methodology, and treatment of the disease leading to better survival. Meta-analyses estimate the IR between

[a] Department of Neurosciences, Larner College of Medicine at the University of Vermont, University of Vermont, 1 South Prospect Street, Burlington, VT 05401, USA; [b] Department of Neurology, University at Buffalo Jacobs School of Medicine & Biomedical Sciences, 1010 Main Street, Buffalo, New York 14202, USA
* Corresponding author.
E-mail address: Michael.hehir@uvmhealth.org

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5 to 30 cases per million person years.[2,3] Prevalence is estimated between 10 to 20 cases per 100,000 population; this rate is predicted to increase over time due to improved treatment and survival.[1]

There is a bimodal age distribution in the incidence of MG, with a peak around the age of 30 years and again at the age of 50 years, with a steady rise in incidence thereafter.[4,5] There is a higher frequency of females in the younger age group, which is typical of autoimmune disorders and a slightly higher frequency seen in men in the older age group.[6] Juvenile MG is defined as disease with onset before the age of 18 years and accounts for roughly 10% of all cases of MG.[1] It is more commonly reported in East Asia with a high frequency of ocular disease.[7] There is otherwise a relatively equal geographic distribution in the incidence and prevalence of MG in both adults and children. Although all ethnicities are affected by MG, there is a slightly higher prevalence among people of African descent, especially in antimuscle-specific kinase (MuSK) antibody-positive disease.[8,9] MuSK antibody-positive disease also appears to be more common in geographic locations closer to the equator.[10]

CLINICAL PRESENTATION

A common yet nonspecific feature of MG is the fluctuating nature of weakness that patients experience, a phenomenon referred to as fatigability. Patients will typically report worsening of symptoms with exercise or as the day goes on, indicative of a reduced safety factor in neuromuscular transmission due to the loss of functioning AChRs.

Patients with MG also have a distinctive pattern of weakness due to the selective vulnerability of certain muscle groups in this disorder. Most patients-roughly two-thirds-initially present with ocular symptoms: ptosis and/or diplopia without pupillary abnormalities.[11] Weakness of the eye muscles is often asymmetrical and variable. Whereas lesions of cranial nerves III, IV, or VI lead to reliable patterns of diplopia, patients with MG will often experience a combination of horizontal, vertical, or diagonal diplopia. Similarly, the degree of ptosis and eye involved can change dramatically over time. Multiple bedside maneuvers can be performed to confirm fatigable ocular weakness including sustained horizontal and vertical gaze, evaluation for Cogan lid twitch, and evaluation for a curtain sign.[12]

About 75% of patients will develop generalized weakness, typically within the first 2 to 3 years following presentation; generalization may be more rapid in anti-MuSK MG.[6,13,14] When disease becomes generalized, there is a predilection for bulbar, neck, and proximal limb muscle involvement.[11,15,16] Approximately 10% to 15% of patients can present with bulbar dysfunction.[11] Patients may develop difficulty chewing due to jaw fatigue as a meal progresses. Similarly, swallowing may be affected because of weakness of pharyngeal or tongue muscles, with dysphagia for liquids occurring more commonly than for solids. Because of a predilection for soft palate involvement, some patients describe nasal regurgitation of fluid or coughing fits after eating or drinking, the latter due to aspiration. Dysarthria is manifest by fatigable nasal, lingual, guttural, and/or labial dysarthria, or dysphonia, in contrast to the spastic dysarthria of amyotrophic lateral sclerosis. Fatigability of speech can be assessed in the clinic by asking a patient to count out loud to 50 or 100. Bifacial weakness can result in expressionless facial expression, trouble smiling, trouble whistling, and inability to fully close the eyelids.[12] Lack of facial expression can be a source of social distress for patients. Neck flexion weakness predominates in MG.[12] Rare patients can present with head drop due to neck extensor weakness; this presentation is more common in anti-MuSK MG.[13,15] When limb weakness occurs, there is preferential