ORIGINAL RESEARCH

Myasthenia Gravis: A Contemporary Review in 2023

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ABSTRACT:
Myasthenia gravis (MG) stands as an autoimmune neurological disorder characterized by impaired transmission at the neuromuscular junction. The incidence of MG ranges from 5.1 to 30 cases per million person-years, with a prevalence rate falling between 150 and 200 cases per million. MG serves as a classic illustration of antibody-mediated autoimmune disease, with a majority of patients exhibiting autoantibodies against acetylcholine receptors (Ach Rs). Other, less frequently observed autoantibodies target muscle-specific kinase (Mu SK), low-density lipoprotein receptor-related protein 4 (Lrp4), and agrin. These autoantibodies interfere with cholinergic transmission between nerve terminals and muscle fibers, leading to downregulation, destruction, functional blocking of Ach Rs, or disruption of AC hR clustering in the postsynaptic membrane. The primary clinical manifestation of MG is fatigable muscle weakness, impacting ocular, bulbar, respiratory, and limb muscles. The specific clinical presentation varies based on the type of autoantibody and the presence of a thymoma.
Keywords:myasthenia gravis; acetylcholine receptor; autoantibodies; cytokines; B cells; T cells

INTRODUCTION:

Myasthenia gravis (MG) emerges as the predominant autoimmune disorder impacting the neuromuscular junction. Although MG is generally manageable, it carries the potential for substantial morbidity and, in severe cases, mortality. Timely diagnosis and the application of suitable treatments are pivotal in averting adverse outcomes. MG displays heterogeneity in both phenotype and pathogenesis, presenting a spectrum of symptoms that spans from a purely ocular manifestation to pronounced weakness affecting limb, bulbar, and respiratory muscles.[1] Onset age varies widely, occurring from childhood to late adulthood, with peaks in incidence observed among younger adult women and older men.Myasthenia gravis (MG) stands out as a classic exemplar of an autoimmune disorder mediated by antibodies, showcasing a class II hypersensitivity reaction. In this intricate immunological process, IgG autoantibodies engage with intra or extracellular antigens, instigating consequential damage to end organs. The prevailing majority of individuals grappling with MG possess autoantibodies targeting acetylcholine receptors (AChRs), while a distinct subset exhibits antibodies against muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (Lrp4), or agrin. These antibodies not only serve as fundamental markers for categorizing disease subgroups but also contribute to the delineation of distinctive phenotypic variants.Within a specific subgroup of MG patients, striational antibodies have been identified, encompassing those directed against titin, ryanodine receptor, and the alpha subunit of the voltage-gated K+ channel (Kv1.4). These antibodies play a pivotal role as biomarkers, offering insights into the severity of the disease. They are frequently detected in individuals experiencing late-onset MG or those concurrently diagnosed with thymoma. Moreover,

some of these individuals may present with concomitant myositis and/or myocarditis.Although MG is predominantly characterized by the presence of autoantibodies, it is imperative to recognize the intricate involvement of diverse T cell subtypes and their associated cytokines in the pathogenesis of the disease.[2] This comprehensive review delves into the epidemiological landscape, clinical manifestations, and genetic predisposing factors associated with adult MG. Following this, it offers an insightful overview of pediatric MG and concludes with an up-to-date exploration of the intricate pathophysiological mechanisms underlying MG.

EPIDEMIOLOGY

Myasthenia gravis (MG) is a rare neurological disorder, and the occurrence of pediatric MG is even more infrequent. Geographical variations significantly influence both the incidence and prevalence of MG. Over the past seven decades, there has been a global increase in MG incidence, with rates varying across different regions.[3] In the period from 1915 to 1934, the estimated prevalence was 1 in 300,000, but it surged to 1 per 30,000 after the introduction of anticholinesterase drugs in 1934. The discovery of AC hR antibodies in 1969 further elevated the prevalence to 1 per 18,000 population. Presently, prevalence rates range from 100 to 200 cases per million, reflecting a steady rise over the past 60 years. This increase is attributed, at least in part, to advancements in the recognition, diagnosis, and treatment of MG, as well as an overall improvement in life expectancy. Recent European studies indicate incidence rates ranging from 4.1 to 30 cases per million person-years. In North America and Japan, the annual rates are lower, ranging from 3 to 9.1 cases per million. Studies from China report even lower incidence and prevalence rates, with estimates at 0.155–0.366 per million and 2.19–11.07 per 100,000, respectively. In Korea, prevalence rates increased from 9.67–10.42 per 100,000 in 2010 to 12.99 per 100,000 in 2014. Conversely, a smaller study in Argentina reported an incidence of MG at 38.8 per 1,000,000 person-years, showcasing the significant variability in rates attributed to differing methodologies, diagnostic criteria, and potential sources of bias.Incidence rates exhibit a bimodal distribution in women, with peaks around ages 30 and 50. In men, the incidence rises steadily with age, reaching its highest rates between ages 60 and 89. Women are more commonly affected before age 40, with a female-to-male ratio of 3:1 for early-onset MG. In the fifth decade, both genders are equally affected, but men have a higher proportion after age 50, resulting in a male-to-female ratio of 3:2.[4] Approximately 10% of MG cases are pediatric, defined as onset before age 18. MG affects individuals of all races and ethnic backgrounds, with a slightly higher prevalence in patients of African ancestry. The phenotype of MG may also vary based on ethnic background, as observed in studies from South Africa, the United States, and elsewhere. These variations underscore the complexity of MG and emphasize the need for comprehensive studies considering demographic, ethnic, and regional factors.

Subtypes of MG and Their Clinical Manifestations: The nicotinic acetylcholine receptor (AChR) is a heteropentamer composed of two α-subunits, along with one each of β-, δ-subunit, and γ-subunit (embryonic type) or ε-subunit (adult type), organized around a central pore. In MG patients, approximately 80% exhibit antibodies against the A ChR. Notably, at least half of these Ach R autoantibodies are specifically directed at the Ach R α-subunits. The pathogenicity of these α-subunit antibodies is believed to surpass those directed against the beta subunit, likely due to the alpha subunit's more exposed location within the receptor and its role in modulating receptor sensitivity to acetylcholine (ACh) binding. Additionally, the presence of two alpha subunits per receptor increases the likelihood of antibody binding.AChR antibodies are primarily of the IgG1 and IgG3 subclasses, with IgG2 and IgG4 subclasses identified in fewer cases.[5] The diverse pathogenic mechanisms and functional spectrum of Ach R antibodies include binding, blocking, or modulating the receptor activity. The predominant mechanism involves antibody binding and subsequent activation of the complement cascade, culminating in the formation of the membrane attack complex (MAC). This MAC formation leads to damage to the postsynaptic membrane and the destruction of synaptic folds, which house Ach Rs and associated proteins, including voltage-gated sodium channels.Other mechanisms contributing to pathogenicity include antigenic modulation, where Ach Rs undergo increased endocytosis and degradation due to antibody binding and crosslinking. Additionally, Ach R function can be impaired by either blocking ACh binding to the receptor or preventing channel opening. While most blocking antibodies are associated with binding antibodies, the unique presence of blocking antibodies is considered rare, and its clinical implications remain unclear. Notably, the administration of blocking antibodies has been shown to induce acute and severe weakness in rodent models. These intricate mechanisms underscore the complexity of the immune response in MG and its impact on neuromuscular transmission.

Clinical manifestations: The primary clinical hallmark of myasthenia gravis (MG) is characterized by fatigable muscle weakness, exacerbated by exertion and alleviated by rest. Ocular symptoms, notably double vision and ptosis, are frequently the initial and most common presenting manifestations. A substantial proportion of patients, up to 80% with ocular onset, progress to develop generalized symptoms, typically within the first two years of disease onset.[6,7] A recent population-based study by

the Mayo Clinic revealed that 51% of patients presented initially with ocular symptoms, and 55% of these subsequently developed generalized symptoms.Bulbar muscles are commonly affected, leading to manifestations such as flaccid dysarthria, dysphagia, and weakness in the facial and jaw muscles. Axial weakness may also be present, with neck flexion weakness more prevalent than weakness in neck extension. Approximately 10% of MG patients, as indicated by a retrospective study, experienced head-drop during the course of their disease, with associations noted for age over 60 and male gender. Limb muscle weakness tends to be symmetric and proximal, with patients frequently reporting difficulties in activities such as climbing stairs, rising from chairs, and raising their arms above their head.[8,9] In certain cases, distal muscles may be predominantly affected, either symmetrically or asymmetrically. Examples include weakness in finger and wrist extension and flexion, as well as foot drop.Respiratory weakness, necessitating mechanical ventilation and termed MG crisis, can develop in 15–20% of patients with AChR-MG. Spontaneous remissions, lasting varying lengths of time, may occur during the course of adult-onset MG. In an earlier study conducted before widespread use of steroids and other immunosuppressants, around one fourth of patients experienced complete or near-complete spontaneous remission, with an average duration of 4.6 years and up to 17 years.[10] Half of these remissions occurred within the first year after onset. Another study by Oosterhuis et al. reported a 22% spontaneous remission rate in patients treated solely with anticholinesterase medications. These findings underscore the dynamic and diverse clinical course of MG, highlighting the potential for both spontaneous improvements and variations in symptom presentation over time.

AChR MG Subtypes

Ocular MG: The trajectory of myasthenia gravis (MG) often involves progression from ocular symptoms at onset to generalized forms of the disease, typically within the initial two years. Among those who do not progress to generalization, about 90% will continue to exhibit ocular manifestations exclusively.[11,12] This defines ocular MG, characterized by isolated extra-ocular involvement persisting for a minimum of two years. More than half of individuals falling into this category possess antibodies against acetylcholine receptors (Ach Rs).Several factors contribute to the preferential involvement of extraocular muscles (EOMs) in MG. EOMs are prone to fatigue due to their requirement for tonic contractions to sustain gaze in specific directions. Additionally, the fibers in EOMs exhibit a high frequency of synaptic firing and quicker tension development.[13,14] Moreover, EOMs have a lower density of Ach R, making them more susceptible to symptoms. Theorized explanations also include the possibility of differing epitope expression in EOMs, contributing to their distinct vulnerability in the context of MG.

Generalized AChR Ab Positive MG (AChR-MG): Early vs. Late Onset Early-onset myasthenia gravis (EOMG) is characterized by symptom onset before the age of 50, and it is notably more prevalent in females, with a female-to-male ratio of 3:1.[15,16] Individuals in this category often exhibit thymic hyperplasia, and studies have demonstrated the effectiveness of thymectomy in improving clinical outcomes and reducing the need for immunotherapy.Late-onset myasthenia gravis (LOMG), defined by onset after the age of 50, does not display the female predominance seen in EOMG. In fact, there may be a slightly higher prevalence among men, especially after the age of 60. Thymic hyperplasia is rare in this group, and the response to thymectomy tends to be less favorable. There is a notable familial predisposition to autoimmune diseases in both EOMG and LOMG.[17] A strong correlation exists with certain human leukocyte antigen (HLA) haplotypes, particularly HLA-DR and HLA-B8. Early-onset MG is frequently associated with the A1-B8-DR3 haplotype. In non-thymomatousAChR antibody-positive LOMG individuals of Italian ancestry, positive associations were found with HLA-DRB1*07 and HLA-DQB1*02, while HLA-DRB1*02, HLA-DRB1*03, HLA-DRB1*11, and HLA-DQB1*03 were identified as protective alleles.Studies conducted in various populations have highlighted different HLA associations. For instance, research in a Turkish cohort found a strong association of class I HLA-B/MICA in EOMG patients, specifically HLA-B*08:01. In contrast, LOMG showed no association with HLA class I but demonstrated a correlation with HLA-DQA1 and HLA-DRB1. Another study on Norwegian MG patients older than 60 revealed a significant association with HLA-DRB1*15:01. These findings underscore the complex genetic underpinnings of MG, emphasizing the importance of HLA haplotypes in influencing disease susceptibility and presentation across different age groups.

Thymoma-Associated MG: Myasthenia gravis (MG) stands out as the most prevalent paraneoplastic disorder linked to thymoma. Thymoma-related disorders with lower association rates include myositis, Morvan syndrome, and pure red aplasia. Interestingly, about 50% of individuals diagnosed with a thymoma develop positive acetylcholine receptor (AChR) antibodies without presenting clinical manifestations, and approximately 30% of them will eventually develop MG. Conversely, 10–20% of MG patients are found to have thymomas.[18]The response to thymectomy in thymoma-associated MG varies, generally tending to be less favorable compared to patients with early-

onset MG. Despite extensive research, studies on human leukocyte antigen (HLA) alleles have not consistently demonstrated a clear association between HLA and thymomatous MG. This underlines the complexity of the relationship between thymoma and MG, as well as the intricate interplay between genetic and environmental factors in the development of these conditions.

Pathophysiology: The neuromuscular junction serves as the crucial site for impulse transmission between nerve terminals and muscle fibers, orchestrating the complex process of muscle contraction.[19] This intricate sequence involves the presynaptic release of acetylcholine (ACh), which then binds to postsynaptic ACh receptors. The release of ACh from synaptic vesicles is triggered by an action potential that activates voltage-gated calcium channels, permitting calcium influx into the nerve terminal. ACh, upon release, has a brief diffusion time across the synaptic cleft and is subject to modulation by the enzyme acetylcholinesterase (AC hE), which facilitates ACh degradation.The spontaneous release of synaptic vesicles results in miniature end plate potentials (MEPPs).[20] In contrast, nerve fiber stimulation leads to synchronous release of multiple synaptic vesicles, causing significant depolarization of the end plate membrane and generating evoked endplate potentials. This depolarization triggers an action potential in the myofiber, ultimately culminating in muscle contraction. The quantity of ACh released exceeds the minimum required for action potential generation, ensuring reliable transmission.The binding of ACh to its receptors in the postsynaptic membrane initiates the opening of ACh cation-specific channels, inducing localized depolarization and activating adjacent voltage-gated sodium channels. This translates the chemical reaction into an electric signal, constituting the muscle fiber action potential. The role of Ach E in the hydrolyzation of A Ch is pivotal, preventing a single ACh molecule from repetitively activating A Ch receptors. Several factors contribute to the effectiveness of neuromuscular junction transmission, including the amount of ACh released, the density of ACh receptors in the postsynaptic membrane, and the density of voltage-gated sodium channels at the endplate.[21] The presence of folds in the postsynaptic membrane determines the latter, influencing the density of voltage-gated sodium channels and enhancing the efficient coupling of localized endplate potentials to myofiber action potentials. This intricate interplay underscores the precision and complexity of neuromuscular transmission.

Immune Dysregulation in MG

Defective B Cell Tolerance:B cell tolerance, a crucial aspect of the immune system, is primarily maintained through mechanisms such as clonal deletion or receptor editing in newly generated B cell clones within the bone marrow, particularly at the stage of immature B cells. Another critical checkpoint occurs as new emigrant or transitional B cells navigate their way into the mature naïve B cell compartment. Research by Lee et al. has revealed that in both acetylcholine receptor myasthenia gravis (AChR-MG) and muscle-specific kinase myasthenia gravis (MuSK-MG), there is a higher frequency of new emigrant/transitional B cells and mature B cells expressing polyreactive and autoreactive B cell receptors (BCRs).[22,23] This observation supports the idea that individuals with MG exhibit defects in both central and peripheral B cell tolerance.As a consequence of these tolerance breakdowns, individuals with MG are at an increased risk of developing other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and thyroiditis. This breach in tolerance is further supported by data derived from deep sequencing of BCR repertoires, revealing distinct biases in gene segment usage within both the variable heavy (VH) and variable light (VL) sequences. These biases are evident in both the naïve and memory B cell compartments in AChR-MG and Mu SK-MG. This data underscores the complexity of the immune dysregulation observed in MG, implicating both central and peripheral mechanisms in the breakdown of B cell tolerance and the potential development of autoimmune comorbidities.

Role of Thymus in MG: The involvement of autoreactive T cells is a significant factor in the development of myasthenia gravis (MG). The process of T cell selection crucially occurs in the thymus, primarily within the thymic medulla, where negative selection for self-antigens takes place. Thymic epithelial cells present self-antigens to developing T cells, either directly or through antigen-presenting cells. T cells that strongly bind to these self-antigens undergo mechanisms for removal, including clonal deletion, induction of anergy, or clonal diversion/ transformation into regulatory T cells (Tregs).[24] Thymic myoid and epithelial cells express various muscle proteins, such as acetylcholine receptors (AChRs), ryanodine, and titin. The autoimmune regulator (AIRE) transcription factor plays a crucial role in T cell autoimmunity, inducing tolerance over autoimmunity by aiding in the expression of self-antigens in thymic cells. The activity of AIRE is modulated by estrogen, providing a potential explanation for the early female predominance observed in the disease.MG is distinctively associated with thymus hyperplasia and thymoma. The presence of ectopic germinal centers is linked to early-onset Ach R-MG but not Mu SK-associated MG. Thymic hyperplasia and thymoma may impair the T cell selection process. Thymomas can exhibit defective AIRE expression and lack thymic medulla, which is crucial for the negative selection of T cells. These abnormalities contribute to the release of autoreactive

CD4+ and CD8+ T cells, exacerbating the autoimmune response in MG.

Role of T Cells and Cytokines in the Development of MG: While myasthenia gravis (MG) is primarily considered a B cell-mediated disease, CD4+ T cells and their associated cytokines contribute significantly to its development.[25] Animal studies have demonstrated that mice with depleted CD4+ T cells or lacking class II major histocompatibility complex (MHC II) did not develop experimental autoimmune MG after sensitization to acetylcholine receptors (AChRs), affirming the pivotal role of CD4+ T cells.Patients with MG exhibit autoreactive Th1 and Th2 cells, but the specific role of these T cell subsets in autoantibody production is not entirely clear. Conflicting results often arise from cytokine measurements in sera, but it is generally acknowledged that both Th1 and Th2 responses play roles in MG immunopathogenesis.[26] Th2 cytokines, such as interleukin-4 (IL-4), are known to induce B cell activation, suggesting a direct role in the development of the disease. Conversely, Th1 cells, characterized by interferon-gamma (IFN-γ) secretion, are implicated in promoting autoantibody production by inducing MHC II and costimulatory molecule expression in adjacent tissues.Th17 T cells, associated with autoimmune inflammatory disorders, are also implicated in MG pathogenesis. These cells release interleukin-17 (IL-17) and other cytokines, indirectly promoting immunoglobulin production and influencing the cytokine profile of Th1 and Th2 cells. Studies have shown elevated levels of Th17 cells and IL-17 in MG patients, correlating with disease severity and antibody titers. The intricate interplay between these T cell subsets and their cytokines underscores the complexity of MG immunopathology, contributing to our understanding of the disease's multifaceted nature.

Regulatory T Cells (Tregs), Regulatory B Cells (Bregs), and B Cell-Activating Factor (BAFF) Signaling in MG: Autoimmune diseases like myasthenia gravis (MG) arise from an altered balance between autoreactive T and B cells and regulatory cell types that normally suppress their activity.[27] Regulatory cell types, including regulatory T cells (Tregs) and regulatory B cells (Bregs), play a crucial role in maintaining immune homeostasis. Tregs, identified by the expression of forkhead box protein 3 (FoxP3), suppress the function of other effector T cells and antigen-presenting cells through the release of anti-inflammatory cytokines like IL-10 and transforming growth factor beta (TGF-ß). Imbalances in the ratio of Th17 (pro-inflammatory T helper 17) cells to Tregs have been reported in MG patients, particularly those with generalized forms and thymomatous MG.[28,29] While the number of CD4+ Tregs may remain unchanged, their suppressive function is often impaired.In the realm of Bregs, subsets of B cells capable of producing IL-10 and suppressing pro-inflammatory responses have been identified, but consensus in the field has been elusive due to the lack of a unique transcription factor. MG patients tend to exhibit a decrease in the frequency of specific Breg subsets and IL-10-producing B cells within those subsets. Restoring the expansion or function of Tregs and Bregs represents a potential therapeutic avenue for MG.Conversely, there is evidence of enhanced B-cell activating factor (BAFF) signaling in MG. BAFF, a member of the tumor necrosis factor family, is crucial for B cell survival, maturation, and development into plasmablasts and plasma cells. Circulating BAFF levels, secreted by myeloid cells, are increased in MG patients, along with an elevation in BAFF-R+ B cells. These findings suggest a role for dysregulated BAFF signaling in MG pathogenesis, offering potential targets for therapeutic interventions.

CONCLUSION:

Myasthenia gravis (MG) exhibits a diverse demographic impact, affecting individuals across all age groups. Peaks in its occurrence are o bserved in younger women and older men. Geographical and regional variations in MG rates are substantial, with overall incidence and prevalence rates on the rise, partly attributed to heightened awareness and advancements in diagnostic practices. Juvenile MG is more prevalent among individuals of Asian and African descent.A subset of MG cases associated with acetylcholine receptor antibodies (AChR-MG) is linked to thymoma or thymic hyperplasia. The remaining AChR-MG cases, along with those involving muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (Lrp4), and seronegative-MG, are predominantly of autoimmune origin. These autoimmune forms are influenced by a combination of genetic background and environmental factors, although the complete understanding of these factors is still evolving.While MG is primarily considered an antibody-mediated disorder, various T and B cell subsets, including Th2, Th1, Th17, Tfh, Treg, and Breg, along with their associated cytokines, play pivotal roles in its pathogenesis. The intricate interplay of these immune components contributes to the complex immunopathology of MG. A deeper understanding of MG subgroups and their unique immunopathogenic mechanisms holds the promise of identifying therapeutic targets and developing more precisely targeted treatment strategies for this autoimmune disorder.

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