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A MODERN VIEW ON THE PATHOGENESIS OF MYASTHENIA IN THE ELDERLY

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Abstract

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder whose incidence has increased substantially among elderly individuals over the past two decades. Since 2020, accumulating evidence indicates that late-onset myasthenia gravis (LOMG) and very-late-onset MG represent distinct clinical and immunological entities rather than delayed forms of early-onset disease. Aging-related immune dysregulation, residual thymic activity, diverse autoantibody profiles, and drug-related triggers—particularly statins—contribute to disease onset and progression in older adults. This review summarizes contemporary evidence (2020–2025) on epidemiology, immunopathogenesis, thymic involvement, clinical presentation, diagnostic challenges, and therapeutic considerations of MG in the elderly.

Keywords

myasthenia gravis; late-onset; elderly; immunosenescence; thymus; statins

Introduction

Late-onset myasthenia gravis (LOMG), typically defined as disease onset after 50–60 years of age, now accounts for a growing proportion of newly diagnosed MG cases worldwide. Very-late-onset MG (≥65 years) has become increasingly recognized due to population aging and improved diagnostic sensitivity. Recent studies emphasize that LOMG differs from early-onset MG in epidemiology, immune mechanisms, thymic pathology, and clinical outcomes, necessitating age-specific diagnostic and therapeutic approaches.

Epidemiology of Late-Onset MG (2020–2025)

Population-based studies published since 2020 consistently demonstrate a rising incidence and prevalence of MG among individuals older than 60 years. European and Asian cohorts report prevalence peaks in the seventh and eighth decades of life, with incidence rates continuing to increase over time. Unlike early-onset MG, which predominantly affects women, LOMG shows a clear male predominance. These trends likely reflect both demographic aging and advances in antibody detection, although a true increase in disease occurrence is also suggested.

Comorbid Conditions in Late-Onset Myasthenia Gravis

A characteristic feature of myasthenia gravis in elderly patients is the high prevalence of comorbid somatic and autoimmune diseases, which significantly influence the clinical presentation, diagnostic process, and therapeutic decision-making. The presence of comorbid conditions often complicates early diagnosis, as the manifestations of myasthenia gravis may be masked by symptoms of coexisting disorders.

Cardiovascular diseases are among the most common comorbidities in elderly patients, including arterial hypertension, ischemic heart disease, cardiac arrhythmias, and chronic heart

failure. Reduced cardiorespiratory reserve in this patient population increases the risk of myasthenic crisis and limits the use of intensive immunosuppressive therapy.

Metabolic disorders, such as type 2 diabetes mellitus, obesity, and dyslipidemia, are widely prevalent among elderly patients with myasthenia gravis. The use of glucocorticosteroids may exacerbate these conditions, leading to deterioration of glycemic control and an increased cardiovascular risk, which necessitates individualized dose selection and careful monitoring.

Respiratory diseases, including chronic obstructive pulmonary disease and bronchial asthma, are of particular clinical importance, as even moderate weakness of the respiratory muscles in myasthenia gravis may result in respiratory failure. This highlights the need for early assessment of pulmonary function in patients with late-onset disease.

Myasthenia gravis is frequently associated with other autoimmune disorders, such as autoimmune thyroid diseases, rheumatoid arthritis, and pernicious anemia, supporting the role of shared immunopathogenetic mechanisms in the development of the disease in elderly individuals.

An additional clinically relevant factor is polypharmacy, which is common in this age group. Several medications frequently prescribed to elderly patients, including beta-blockers, certain antibacterial agents, and statins, may impair neuromuscular transmission and provoke the onset or exacerbation of myasthenia gravis.

Thus, the high prevalence of comorbid conditions in patients with late-onset myasthenia gravis necessitates a comprehensive and individualized approach to diagnosis and management, as well as close multidisciplinary collaboration.

Immunosenescence and Pathogenesis

Aging is accompanied by immunosenescence and chronic low-grade inflammation ("inflammaging"). Recent immunological studies confirm that thymic involution, reduced naive T-cell output, impaired regulatory T-cell function, and altered cytokine profiles contribute to loss of immune tolerance in elderly individuals. Concurrently, age-related B-cell dysregulation favors autoantibody production. Together, these mechanisms increase susceptibility to autoimmune diseases, including LOMG, and may influence disease severity and treatment response.

Autoantibody Profiles in Elderly MG

While antibodies against the acetylcholine receptor (AChR) remain the most common in LOMG, contemporary cell-based assays have revealed higher frequencies of additional autoantibodies, including titin, ryanodine receptor (RyR), MuSK, and LRP4 antibodies. Titin antibody positivity has been associated with more severe generalized disease, higher risk of bulbar and respiratory involvement, and poorer short-term outcomes in elderly patients. Improved antibody detection has also reduced the proportion of truly seronegative MG cases.

Thymic Involvement and Aging

Thymic hyperplasia is uncommon in late-onset MG, and thymoma occurs less frequently than in early-onset disease. Nevertheless, recent histological and molecular studies demonstrate persistent thymopoiesis even in advanced age, as evidenced by detectable T-cell receptor excision circles. Residual thymic activity may still contribute to autoreactive T-cell selection and

autoimmunity in elderly MG patients. Despite this, thymectomy is generally not recommended in LOMG patients without thymoma due to limited benefit and increased surgical risk.

Clinical Presentation in the Elderly

LOMG often presents with bulbar symptoms, including dysarthria and dysphagia, as well as neck and limb weakness. Ocular symptoms may be less prominent than in younger patients.

Very-late-onset MG is associated with an increased risk of respiratory muscle involvement and myasthenic crisis, largely due to reduced physiological reserve and coexisting cardiopulmonary disease. Comorbidities such as stroke, diabetes, and neurodegenerative disorders frequently complicate clinical assessment.

Diagnostic Challenges

Diagnosis of MG in elderly patients is often delayed due to symptom overlap with other age-related neuromuscular and neurological conditions. Standard serological assays may fail to detect low-titer antibodies, making cell-based assays particularly valuable. Electrophysiological testing may be less specific in older individuals because of concomitant peripheral neuropathy or myopathy. Early recognition is critical to prevent severe complications, especially respiratory failure.

Drug-Induced and Statin-Associated MG

Since 2020, pharmacovigilance studies and case series have strengthened the association between statin therapy and MG onset or exacerbation. Statins may promote a Th2-biased immune response and enhance B-cell–mediated autoantibody production, thereby unmasking subclinical MG or worsening established disease. Given the widespread use of statins in elderly populations, clinicians should maintain a high index of suspicion when new fatigable weakness develops. Discontinuation of the offending drug often leads to clinical improvement.

Therapeutic Considerations

Acetylcholinesterase inhibitors remain first-line symptomatic therapy and are generally well tolerated in elderly patients. Immunosuppressive treatments, including corticosteroids and steroid-sparing agents, are effective but require cautious use due to increased risks of infection, osteoporosis, metabolic complications, and cardiovascular events. Recent studies support early initiation of low-dose immunotherapy with close monitoring to balance efficacy and safety. Thymectomy is typically reserved for patients with thymoma.

Future Directions

There is a critical need for prospective, multicenter studies focusing specifically on very-late-onset MG. Future research should aim to clarify age-specific immunopathogenic mechanisms, optimize treatment regimens for elderly patients, and identify biomarkers predictive of prognosis and therapeutic response. Inclusion of older adults in clinical trials is essential to improve evidence-based care.

Conclusion

Late-onset myasthenia gravis is an increasingly prevalent autoimmune disorder with distinct epidemiological, immunological, and clinical characteristics. Evidence published since 2020

highlights the roles of immunosenescence, residual thymic function, and drug-related triggers such as statins in disease pathogenesis. Early diagnosis and individualized management strategies are essential to improve outcomes and quality of life in elderly MG patients.

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