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MYASTHENIA GRAVIS: CURRENT INSIGHTS INTO PATHOPHYSIOLOGY, DIAGNOSIS, AND TREATMENT APPROACHES

Rupali Pawar*, Prem Pokale, Yash Chavhan, Shailesh Pawar, Anand Kamble, Dr. Rahul Bijwar

Jagadambha Institute of Pharmacy and Research, Kalamb, Yavatmal, Maharashtra, India-445401.

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***Corresponding Author**

Rupali Pawar

Jagadambha Institute of Pharmacy and Research Kalamb.

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ABSTRACT

Skeletal muscle weakness and fatigability fluctuate in myasthenia gravis (MG), an acquired autoimmune neuromuscular condition. The condition is mostly caused by autoantibodies that impede neuromuscular transmission; these antibodies are typically directed against muscle-specific kinase (MuSK) and the acetylcholine receptor (AChR). Clinically, MG manifests as involvement of the eyes, brain, limbs, and respiratory system; the degree of involvement depends on the antibody subtype and immunogenetic background. In terms of pathophysiology, MG is a model autoimmune illness that exhibits postsynaptic membrane injury at the neuromuscular junction, complement activation, and antigenic modulation. Improved serological testing for AChR, MuSK, and LRP4 antibodies, as well as clinical assessment scales and electrophysiological methods like repetitive nerve stimulation and single-fiber electromyography, have all contributed to increased precision in diagnosis. Imaging is essential for identifying thymic disease, especially CT/MRI of the mediastinum. Pulmonary involvement, with immunogenetic background and antibody subtype influencing severity. Beyond traditional immunosuppression and symptomatic cholinesterase inhibitors, therapeutic approaches now include targeted biological medicines such neonatal Fc-receptor (FcRn) blockers and complement inhibitors (eculizumab). For certain people, thymectomy is still a recognized

treatment option. Unmet needs still exist despite significant advancements, particularly in the areas of seronegative MG, therapy response variability, biologics access, and long-term illness monitoring. Personalized immunotherapy, biomarker-guided stratification, and enhanced outcome prediction are key areas for future research. All things considered, MG research keeps moving in the direction of safer, more individualized, and more focused management approaches.

KEYWORDS: Myasthenia Gravis (MG), Autoimmune disorder, Neuromuscular junction, Immunotherapy, Complement inhibitors.

1. INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disease that affects the connection between nerves and muscles, known as the neuromuscular junction. It causes muscle weakness that becomes worse with activity and improves with rest. The immune system mistakenly produces antibodies that attack the receptors or proteins involved in muscle activation, such as acetylcholine receptors (AChR), musclespecific kinase (Musk), and lipoprotein receptor-related protein 4 (LRP4). This reduces the communication between nerves and muscles, leading to weakness. The muscle weakness in MG can affect specific parts of the body or be more widespread. Common symptoms include drooping eyelids or double vision due to eye muscle weakness, difficulty speaking, chewing, or swallowing from bulbar muscle weakness, and weakness in the arms and legs. A severe complication called myasthenia crisis occurs in about 15% of patients and can cause breathing problems or respiratory failure.[1-3]

This is more likely in people whose bulbar or breathing muscles are involved. Treatment for MG focuses on improving muscle strength and controlling the immune response. Common treatments include acetylcholinesterase (Ache) inhibitors, which help increase the amount of acetylcholine available at the neuromuscular junction; immunosuppressive drugs that reduce the immune system's attack; monoclonal antibody therapies; and intravenous treatments. In some patients, especially those with AChR antibodies, surgical removal of the thymus gland (Thymectomy) can also help improve symptoms. Administering general anesthesia in patients with MG requires special care because of their sensitivity to muscle relaxants.[4-6]

These patients are usually resistant to depolarizing muscle relaxants like succinylcholine but are very sensitive to non-depolarizing agents such as rocuronium and vecuronium. Therefore, anesthesiologists must use lower doses and carefully monitor the patient's response during

surgery to avoid complications related to muscle relaxation and breathing Traditionally, drugs called acetylcholinesterase inhibitors, such as neostigmine, have been used to reverse the effects of muscle relaxants after surgery.[7-8]

However, these drugs can sometimes cause problems, including muscle weakness after surgery or a condition called cholinergic crisis, which leads to excessive muscle stimulation and symptoms like wheezing and increased secretions. A newer drug, Sugammadex, offers a safer option. It works by directly binding to and neutralizing muscle relaxants like rocuronium without affecting acetylcholine, allowing faster and safer recovery from anesthesia in MG patients.[9-10]

EPIDEMIOLOGY

2 Epidemiology of Myasthenia Gravis

2.1 Prevalence and Incidence

Estimated prevalence: 50–200 per million people globally.Incidence: Approximately 4–12 per million per year. Higher prevalence in developed countries due to better diagnosis and longer survival.[11-12]

2.2 Age Distribution

MG has a bimodal age distribution: Early-onset MG: Usually in women aged 20–40 years. Late-onset MG: More common in men aged 50–70 years.[13-14]

2.3 Gender Distribution

Early-onset MG: Female predominance (3:1). Late-onset MG: Male predominance (2:1).[15-16]

2.4 Geographic and Ethnic Variations

Some differences exist in antibody subtypes among ethnic groups:Anti-MuSK antibodies are more common in certain Asian populations. Thymoma-associated MG shows higher incidence in older adults.[17-18]

2.5 Risk Factors

Autoimmune predisposition (family history of autoimmune diseases). Presence of Thymic abnormalities (hyperplasia or Thymoma).Genetic factors influencing immune response (HLA associations, e.g., HLA-B8, HLA-DR3).[19]

2.6 Clinical Features of Myasthenia Gravis

MG is characterized by fluctuating skeletal muscle weakness that worsens with activity and improves with rest.

1. **General Characteristics**

Weakness is fatigable—worsens during the day or with repetitive muscle use. Often asymmetric. Does not typically affect sensory function, reflexes, or bowel/bladder control.

2. **Muscle Groups Commonly Affected**

a. Ocular Muscles (Most Common Initial Presentation): Ptosis: Drooping of one or both eyelids. Diplopia: Double vision due to extra ocular muscle weakness. Present in ~50–60% of patients initially.

b. Bulbar Muscles: Dysarthria (slurred speech). Dysphagia (difficulty swallowing). Weakness in facial expression, chewing. More common in older adults.

c. Limb Muscles: Proximal > distal weakness (shoulders, hips).Difficulty climbing stairs, lifting objects, or rising from a chair.

d. Respiratory Muscles: Severe weakness can lead to myasthenia crisis (respiratory failure). Requires immediate medical attention and often ventilator support.

3. **Pattern of Weakness:** Worsens with exertion and improves with rest. May fluctuate day-to-day or even within the same day. Remissions and exacerbations are common.

4. **Associated Conditions:** Thymic abnormalities (Thymoma or Thymic hyperplasia).Other autoimmune diseases (thyroid disease, rheumatoid arthritis.[20]

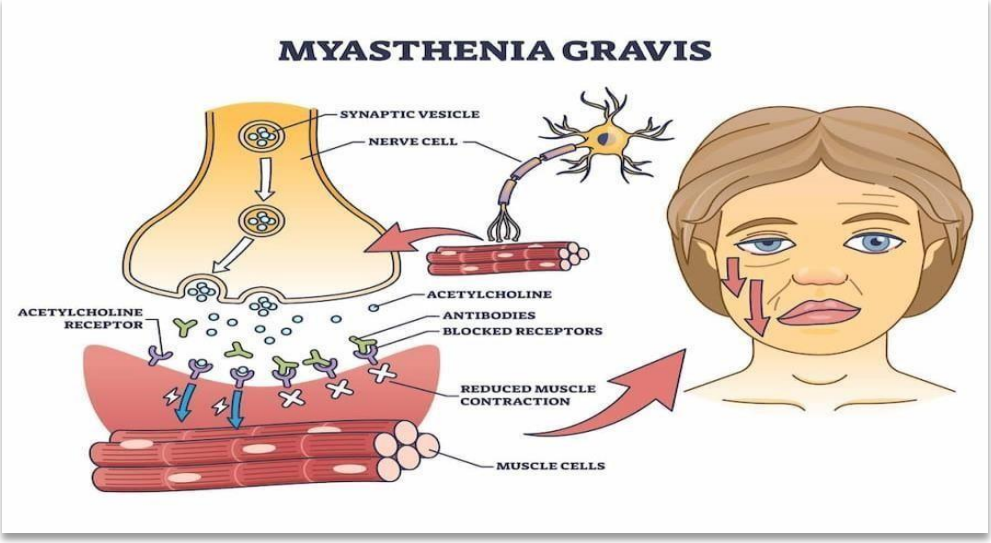

Figure no. 1: Myasthenia Gravis.

3. PATHOPHYSIOLOGY OF MYASTHENIA GRAVIS

3.1 Normal Neuromuscular Transmission

In healthy individuals: A nerve impulse reaches the presynaptic terminal. Acetylcholine (Ach) is released into the synaptic cleft. Ach binds to acetylcholine receptors (ACHRS) on the postsynaptic muscle membrane. This triggers muscle contraction. Acetylcholinesterase breaks down Ach to end the signal.[21]

3.2 Autoimmune Mechanism in MG

In MG, the body produces autoantibodies that attack components of the NMJ. The most common targets: ACHR (Acetylcholine Receptor) — about 80–85% of cases. MUSK (Muscle-Specific Kinase) — about 5–8%.LRP4 (Lipoprotein-related Protein 4) — rare.[22]

3.3 Effect of Autoantibodies

Anti-ACHR antibodies cause: Blockage of Ach binding sites. Internalization and degradation of receptors. Complement-mediated destruction of the postsynaptic membrane.[23]

3.4 Role of the Thymus

The thymus gland plays a central role in the pathogenesis of myasthenia gravis, acting as the site of autoimmune sensitization against the acetylcholine receptor (AChR). The thymus gland is often abnormal in MG patients: Thymic hyperplasia (enlargement) in most cases. Thymoma (tumor) in about 10–15% of patients.[24]

3.5 Consequences on Muscle Function

Because fewer receptors are available: Nerve impulses fail to trigger normal muscle contraction. Muscle fibers fatigue easily. Weakness worsens with activity and improves with rest. Myasthenia gravis causes defective neuromuscular transmission, leading to weakness and fatigability of skeletal muscles. The underlying defect is autoimmune destruction or blockade of acetylcholine receptors (AChR) at the postsynaptic membrane of the neuromuscular junction (NMJ).[25]

3.6 Clinical Correlation: The defective transmission leads to: Ptosis (drooping eyelids) Diplopia (double vision. Difficulty swallowing, speaking, or breathing. Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction characterized by fluctuating weakness and fatigability of voluntary muscles. The clinical picture correlates closely with

the underlying pathophysiological defect — the reduction in functional acetylcholine receptors (AChR) due to autoantibody-mediated destruction.[26-28]

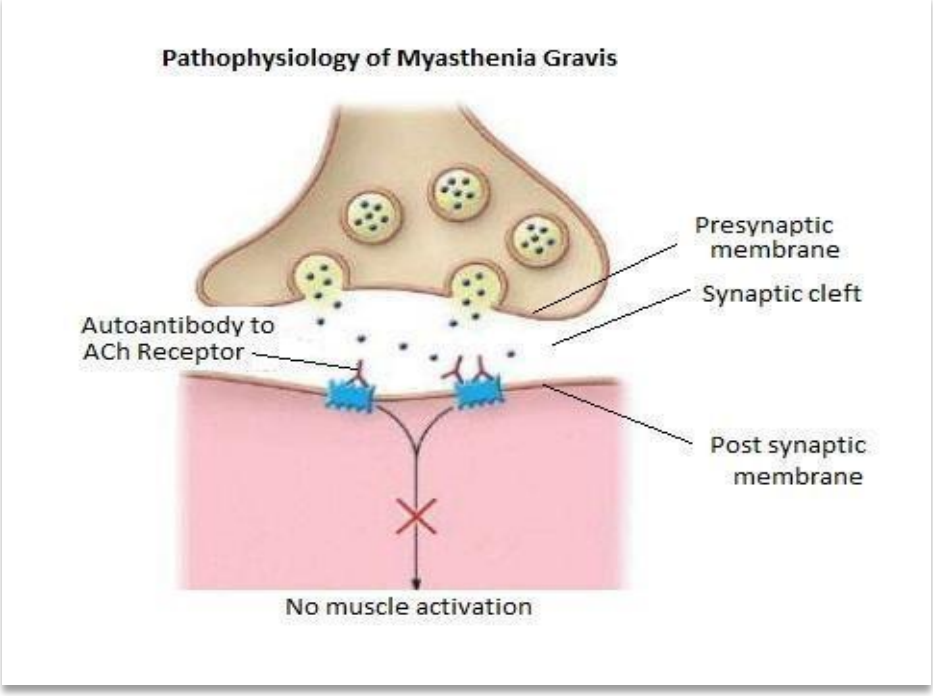

Figure no. 2: Pathophysiology of Myasthenia Gravis.

4. ADVANCE IN DIAGNOSIS OF MYASTHENIA GRAVIS

4.1 Clinical Assessment

Traditional Approach: Focused on history-taking (fatigable muscle weakness, ptosis, diplopia) and bedside tests like the ice pack test or edrophonium test.

Advances: Standardized scoring systems: e.g., Myasthenia Gravis Composite (MGC) score, Quantitative Myasthenia Gravis (QMG) score for consistent disease severity assessment. Digital tools: Wearable devices and apps to monitor muscle strength and daily activity levels for early detection of fluctuations. Remote assessment: Telemedicine evaluations allow repetitive observation of fatigable weakness over time.[29-30]

4.2 Electrophysiological Tests

Traditional Tests: Repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG).

Advances: High-resolution EMG: Improves sensitivity in detecting neuromuscular junction dysfunction. Automated SFEMG: Reduces operator dependency, allowing more reproducible results. Combined modalities: Integration of EMG with nerve conduction studies for more

accurate localization and subtype differentiation. On-invasive wearable EMG sensors: Continuous monitoring in real-life settings.[31-33]

4.3 Serological Biomarkers

Traditional Biomarkers: Detection of anti-AChR, anti-Musk, or anti-LRP4 antibodies.

Advances: Cell-based assays (CBA): Higher sensitivity and specificity compared to older radioimmunoassay, especially for seronegative MG. Novel biomarkers: Emerging antibodies like again, colQ, or cortactin autoantibodies help detect atypical or seronegative cases. Cytokine and proteomic profiling: Potential to monitor disease activity and treatment responsible.[34-35]

4.4 Imaging Techniques

Traditional: Chest CT or MRI to detect Thymoma in MG patients.

Advances: High-resolution CT and MRI: Detect small Thymic hyperplasia or microthymomas. PET/CT imaging: Useful for metabolic characterization of Thymic lesions and systemic involvement. Muscle MRI: Detects fatty infiltration or edema in affected muscles, helpful for differential diagnosis in atypical presentations. Advanced ultrasonography: Real-time evaluation of muscles and neuromuscular junctions.[36-38]

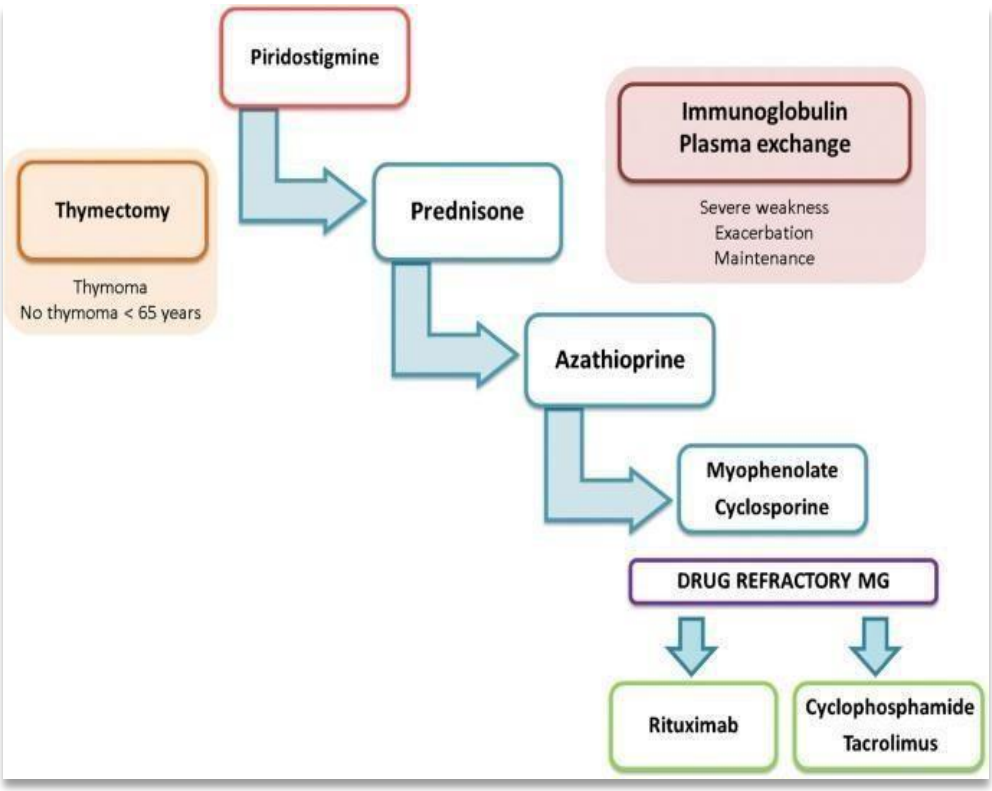

Figure no. 3: Flowchart for the Treatment of Myasthenia Gravis.

5. CURRENT TREATMENT APPROACH IN MYASTHENIA GRAVIS

5.1 Symptomatic Therapies: Cholinesterase inhibitors (e.g., pyridostigmine)Improve communication between nerves and muscles by increasing acetylcholine levels at the neuromuscular junction. Provide rapid but temporary relief of muscle weakness.[39,40]

a)Supportive care: Physical therapy and occupational therapy to maintain muscle function. Respiratory support in severe cases (e.g., ventilator assistance during myasthenia crisis).[41]

5.2 Immunosuppressive Strategies:- Corticosteroids (e.g., prednisone. Reduce autoimmune activity and decrease antibody production. Steroid-sparing immunosuppressant's. Azathioprine, mycophenolate mofetil, cyclosporine, etc., for long-term management to reduce steroid side effects.[42]

5.3 Biologic and Targeted Therapies:- Monoclonal antibodiesEculizumab: inhibits complement-mediated damage to the neuromuscular junction. Rituximab: targets B-cells to reduce antibody production (mainly for MuSK-positive MG). Other emerging therapiesFcRn inhibitors: reduce circulating pathogenic antibodies.[43]

5.4 Surgical Interventions:- Thymectomy. Removal of the thymus gland, especially in patients with Thymoma or generalized AChR-positive MG. Can improve symptoms and reduce dependence on immunosuppressive drugs. Minimally invasive approaches Video-assisted thoracoscopic surgery (VATS) or robotic-assisted Thymectomy for faster recovery.[44]

6. DRUG USED IN MYASTHENIA GRAVIS

Table No. 1.

Classes	MOA	Example of Drug	Common site
Anticholinesterase	Inhibition acetylcholinesterase. At neuromuscular junction improve transmission	- neostigmine - pyridostigmine - Ambenonium	Abdominal diarrhea bradycardia, fasciculation cramps, salivation muscle
Corticosteroid	Suppress immune response and reduce autoantibody production	Prednisolone	Weight Hyperglycemia osteoporosis, Hypertension change gain mode
Immunosuppressant	Inhibit-T and B-cell proliferation decrease antibodies production	.Azathioprine mycophenolate, cyclosporine, cyclophosphamide,	Bone suppression, Hepatotoxicity increased infection risk marrow

Rapid immunomodulators	Neutralize or remove circulating auto antibodies	IUIG Plasmapheresis	Headache, thrombosis IUIG, hypothesis bleeding risk
Biology (rare advance cases	Inhibit compliment activation or specific immune pathway	Ecalizumab	Risk of meaning coccal infections headache

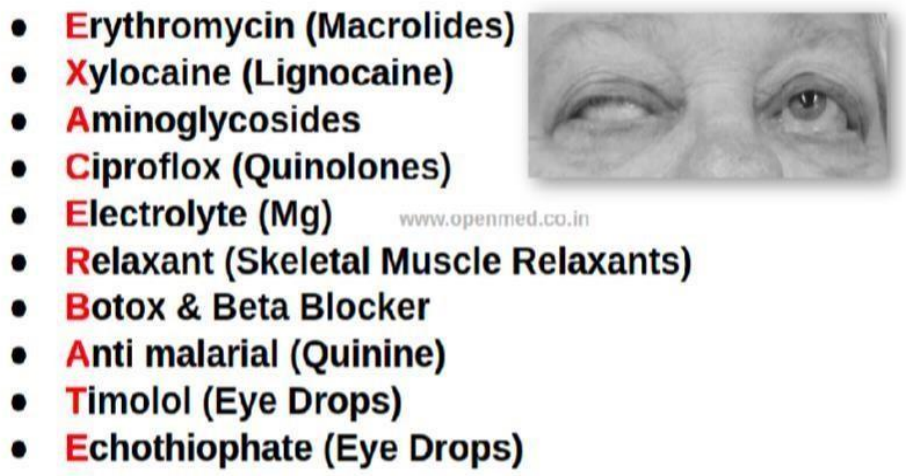

Figure No. 4: Drug used in Myastheni Gravis.

7. CHALLENGES AND UNMET NEEDS IN MYASTHENIA GRAVIS

7.1 Challenges

Myasthenia Gravis (MG) poses significant challenges due to its unpredictable course and diverse symptoms. Patients often experience fluctuating muscle weakness, particularly in the eyes, face, throat, and limbs, which can interfere with speech, swallowing, and breathing.[45] The variability of symptoms from day to day makes disease management difficult for both patients and healthcare providers. Misdiagnosis or delayed diagnosis is common, as MG can resemble other neurological or muscular disorders, leading to treatment delays and potential worsening of symptoms.[46-47]

Managing MG is complicated by the limitations of conventional therapies. While medications such as corticosteroids and immunosuppressant's can be effective, they carry risks of serious side effects including weight gain, diabetes, infections, and bone loss. Clinicians must carefully balance the need to control symptoms against the potential for adverse effects, requiring close monitoring.[48-50] In some cases, patients develop treatment-resistant MG, where standard therapies fail, prompting consideration of newer or experimental interventions that may not be widely available.[51-52]

Living with MG also brings considerable emotional and social challenges. Chronic fatigue, anxiety, and depression are common, particularly when physical limitations disrupt work, relationships, and daily routines.[53-54] The unpredictability of symptom flare-ups, combined with a general lack of public awareness, can contribute to social isolation and diminished quality of life. Access to comprehensive care—including mental health support, physiotherapy, and patient education—is critical but not always attainable.[55-58]

Another pressing issue is equitable access to advanced therapies. Newer treatments, such as complement inhibitors, FcRn blockers, and experimental cell-based therapies, are highly effective but expensive and often limited to specialized centers. Patients in low-resource regions may face financial barriers or lack healthcare infrastructure to receive these treatments. Addressing these challenges through healthcare reform, improved global accessibility to medications, and continued research is essential for enhancing outcomes and quality of life for all individuals living with Myasthenia Gravis.[59-63]

8. EMERGING THERAPIES AND FUTURE DIRECTIONS

Recent research in myasthenia gravis (MG) is transforming how the disease is diagnosed and treated, moving from broad immunosuppression to precise, long-lasting, and personalized therapies. Advances in immunology and biotechnology have led to safer treatments that improve both muscle function and patients' quality of life. Complement inhibitors like zilucoplan and ravulizumab protect the nerve-muscle connection by blocking part of the immune system that causes damage, leading to better strength and endurance. These therapies are convenient— zilucoplan can be self-injected at home, while ravulizumab requires fewer hospital visits due to its long-lasting effect.[64-66] New drugs called FcRn inhibitors, such as efgartigimod and rozanolixizumab, quickly lower levels of harmful antibodies, often improving symptoms within weeks. They are well-suited for repeated short treatment cycles and are being studied in children and pregnant women because they selectively act on antibodies and have reversible effects.[67-69]

Meanwhile, B-cell– and T-cell–targeted drugs including rituximab and inebilizumab show strong results in severe or MuSK-positive MG cases, reducing dependency on steroids and controlling symptoms more effectively. Revolutionary cell-based approaches like CAR-T therapies (e.g., Descartes-08, KYV-101, CABA-201) are being explored as potential long-term cures. These therapies reprogram a patient's immune cells to target and eliminate the specific cells that cause MG. Initial results show sustained muscle improvement and reduced

relapses, raising hopes for functional remission.[70-73] Researchers are working to make these treatments safer and more affordable so they can move beyond specialized centers into routine clinical use. Other promising approaches include small-molecule drugs like NMD670, which act directly on skeletal muscle to enhance neuromuscular signaling without suppressing the immune system.[74-76]

Combined with improvements in thymectomy—now performed using minimally invasive and robotic methods—patients benefit from quicker recovery and potentially longer-lasting remission. Research also emphasizes managing non-motor symptoms such as fatigue, pain, and anxiety, integrating psychological and physical therapies as essential parts of MG care. Looking ahead, personalized and combination therapy is becoming the cornerstone of MG management. Biomarker tests and immune profiling will soon help doctors select the most effective and safest drugs for each patient. Combining FcRn inhibitors for quick relief, complement blockers for stability, and B- or T-cell therapies for long-term control may optimize outcomes. With innovations in early diagnosis, AI-based testing, and accessible drug formulations, the next decade could bring not just better disease control but the possibility of lasting remission—or even a functional cure—for MG patients.[77-80]

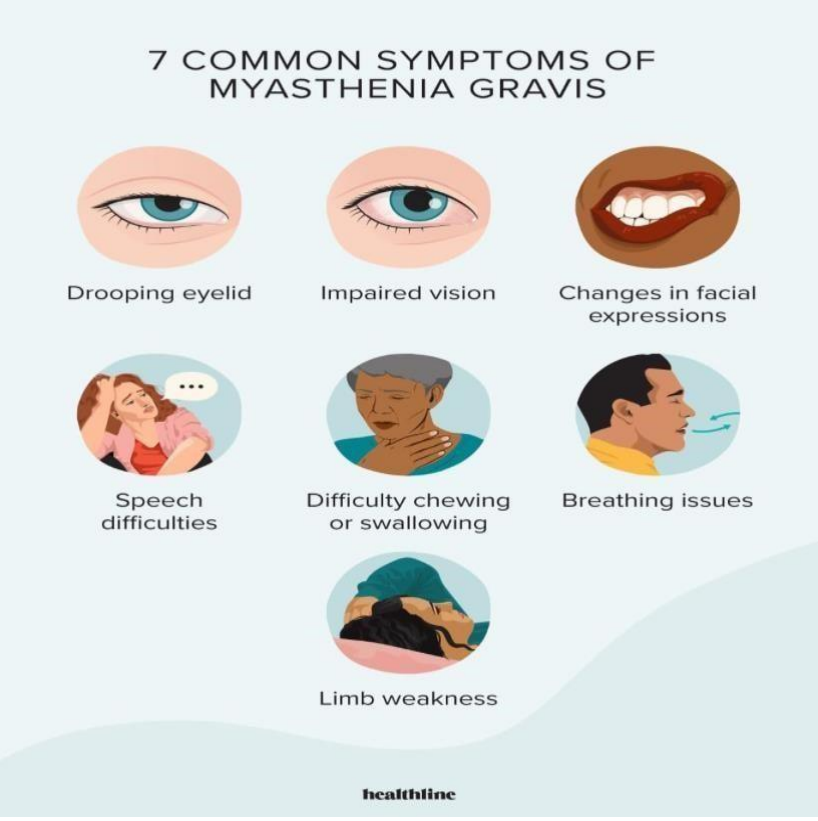

Figure No. 5: Common Symptoms of Myasthenia Gravis.

9. PREVENTION

Prevention of Myasthenia Gravis (MG) primarily focuses on avoiding triggers and managing factors that can worsen the condition, as the underlying cause of MG remains unknown and there is no known way to completely prevent it.

Preventing Onset and Flare-UpsHealthy Lifestyle: Maintaining a balanced diet, exercising regularly, avoiding smoking, and limiting alcohol can strengthen the immune system and lower the risk of autoimmune activation that might trigger MG.[81-82]

Infection Control: Infections are a common cause of MG flare-ups. Practicing good hygiene, washing hands frequently, avoiding contact with sick individuals, and staying up to date with vaccinations such as flu and pneumococcal shots can help reduce infection risk.[83-84]

Stress Management: Chronic stress can intensify MG symptoms. Techniques like yoga, meditation, and deep breathing exercises can be effective in maintaining mental and physical balance.[85-86]

Medication Awareness: Certain drugs, including some antibiotics, beta-blockers, and anesthetics, can aggravate or unmask MG. It is important to consult healthcare professionals before taking new medications and to follow prescribed treatments carefully.[87]

Avoiding Physical and Environmental Triggers: Excessive heat, cold, fatigue, and overexertion can worsen muscle weakness. Patients are advised to pace activities, rest regularly, avoid extreme temperatures, and prevent overheating.[88]

Routine Medical Care: Regular follow-ups with healthcare providers can help detect and manage early signs of worsening disease and adjust treatments promptly. Although complete prevention of MG is not yet possible, adopting these measures can significantly reduce the frequency and severity of symptoms, supporting better longterm health outcomes.[89-90]

10. CONCLUSION

Myasthenia Gravis (MG) is a chronic autoimmune disorder that disrupts communication between nerves and muscles, leading to fluctuating weakness and fatigue. Advances in diagnostics, such as antibody testing and high-resolution imaging, have improved early detection and disease monitoring. Modern therapies—including acetylcholinesterase inhibitors, immunosuppressant, monoclonal antibodies, and minimally invasive

thymectomy—have greatly enhanced symptom control and patient outcomes. Emerging treatments like complement and FcRn inhibitors, as well as cell-based therapies, promise more targeted and durable relief. Although MG cannot yet be fully prevented or cured, ongoing research, improved access to advanced therapies, and comprehensive care approaches continue to move the field toward more personalized and potentially curative management.

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62. Adachi T., El-Hattab A.W., Jain R. et al., “Enhancing Equitable Access to Rare Disease Diagnosis and Treatment around the World: A Review of Evidence, Policies, and Challenges” (2023) – Discusses global barriers to access of diagnosis and therapies in rare diseases, which is relevant to MG as a rare autoimmune neuromuscular disorder.
63. “Market Access Programs for Rare-Disease Treatments” (2025) – Describes commercial, regulatory and systemic barriers to access for advanced/rare-disease therapies (e.g., pricing, distribution networks, LMIC exclusion).
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83. Gummi RR et al., “Factors associated with acute exacerbations of myasthenia gravis” — showed that infections account for about 30% of acute MG exacerbations and are the highest single contributor.
84. Gilhus NE, “Myasthenia gravis and infectious disease” — notes that MG can be triggered and worsened by infections, and recommends active infection-prophylaxis in MG.
85. In their review of management in MG, the authors note that “stretching exercises such as Tai chi, slow-flow yoga or Pilates.

86. With emphasis also on balance maintenance" can be appropriate. A case report describes a breathing-exercise (yogic breathing) intervention offering relief for MG.
87. A review titled "Drugs That Induce or Cause Deterioration of Myasthenia Gravis" states: "Other drugs, especially certain antibiotics, anti-arrhythmics, anesthetics and neuromuscular blockers, have deleterious effects on neuromuscular transmission, resulting in increased weakness in MG or MG-like symptoms in patients who do not have MG."
88. "Temperature extremes of either hot or cold may make you feel weak. … Extremely hot temperatures, humidity, and sunlight all can make MG worse."
89. The updated international consensus guidance for MG management recommends that "for patients with stable disease, follow-up every 6 months was considered reasonable" and emphasizes close monitoring of active disease.
90. According to the patient-information page by NYU Langone Health: "Most people with MG visit their care team every few months... If you are able to control your symptoms with medication… you may follow up… every two to three months so that [the doctor] can monitor your symptoms and response to the medication."