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# INSIGHT INTO MYASTHENIA GRAVIS

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**ABSTRACT**

Myasthenia gravis (MG) is an autoimmune condition that manifests through muscle weakness and fatigue. It is B-cell-mediated and due to antibodies against the acetylcholine receptor at the postsynaptic membrane of the neuromuscular junction, muscle-specific kinase, lipoprotein-related protein 4, or agrin. The symptoms of the disease include ptosis, dysphagia, diplopia, and generalized muscle weakness with special predilection towards muscles controlling the eyes, face, throat, and limbs. Antibody testing, clinical assessment, electromyography, and imaging techniques for identification of thymomas, which sometimes are associated with this disease, have led to its diagnosis. The treatments include anticholinesterase drugs, immunosuppressive therapies, plasmapheresis, intravenous immunoglobulins, and thymectomy in some cases. Though MG can be lethal in the sense that it compromises the respiratory system, for most individuals, it is possible to sufficiently alleviate their symptoms with appropriate treatment. Ongoing research that fine-tunes the diagnostic and treatment modalities helps to enhance the quality of life and prognosis of patients suffering from this difficult illness.

## INTRODUCTION:

Myasthenia gravis (MG) is one of the most prevalent conditions disrupting neuromuscular transmission. The key characteristics of the illness include sudden weakness and fatigue, extraocular muscles, bulbar functions, and limb and respiratory muscles. It results from an immune response to the post-synaptic membrane of the NMJ [1]. While usually treatable and curable, MG can bring on severe morbidity and death, typically averted or lessened by timely diagnosis and effective therapy [2]. Most patients present with weakness of the eye muscles at onset of MG. This often leads to ptosis and diplopia. If the weakness is confined to ocular muscles, the disease is Called as 'ocular myasthenia'. Oropharyngeal weakness may lead to chewing and swallowing and articulation problems. In generalized MG, the proximal muscle groups typically have more severe limb girdle weakness than the distal muscle units [3]. These days, any one of the wide range of autoimmune diseases having a post synaptic impairment of neuromuscular transmission is collectively called "Myasthenia gravis." With its own unique features and particular needs in treatment, these myasthenic syndromes are grouped into the following categories [3]:

(1)Course type: -Ocular (in around 20% of patients with MG)- Generalized or

oropharyngeal (2)Age of onset: Onset before puberty -Onset early before the age of fifty, Onset late after the age of fifty (3) Antibody specificity: -anti-AChR -seronegative MG (4) Thymus pathology: - atrophic or normal thymus pathology -Thymitis

Myasthenic weakness tends to fluctuate in the day, getting worse at the end of the day and lesser at the morning time, particularly if the muscles are exercised for a long time[1]. Even though it is one of the most frequent medical complaints, myasthenia gravis-related fatigue shares many features unique to this disorder, such as weakness of localized groups of muscles that worsens later in the day and worsens with repeated exercise.Sixty percent of the cases present with asymmetric ptosis and changeable diplopia, and in most of the cases, these symptoms will extend to other muscles, giving fluctuating dysarthria, dysphagia, troubling eating, and dyspnea. While limb involvement is less common, it usually results in proximal weakness [32].

**Historical perspective**: The first written account of any person ever known to have had MG was that of Native American Chief Opechancanough, who died in 1664. He was put through utmost exhaustion, which absolutely destroyed his constitution: so that the flesh on his bones became macerated; the sinews lost their tone and elasticity, and his eyelids were so heavy that unless raised up by his attendants, he could not see. He could not walk, but above the ruin of his body the spirit broke into the daylight where it governed on the litter supported by his Indians. In the year 1672, an English physician by name Thomas Willis registered a case classic myasthenic fatigable weakening of bulbar and leg muscles. The first report of patients with symptoms of myasthenia was published in the late 1800s, and Wilks described in 1877 bulbar and peripheral muscular myasthenia**.**

**Epidemiology**: Myasthenia gravis is the most common disease of the neuromuscular junction. According to the epidemiological studies of myasthenia gravis, its prevalence is reported to be 2-7/10000 population in the UK[13] and about 1.5/10000 in central and western virginia[14]. In a very large population based study of the epidemiology of myasthenia gravis in greece[15], the average annual incidence was reported to be 7.40/million population/year [women 7.14;men 7.66], and the point prevalence rate was found to be 70.63/million[women-81.58;men-59.39]. Myasthenia gravis can occur at any age, but it has a bimodal peak of incidence, with the first peak in the third decade, predominantly affecting women, and the second peak in the sixth and seventh decades, predominantly affecting men. It has been suggested that incidence falls after 70 years of age. However, recently in a population-based UK study in which AChR antibody served as a tool for diagnosis it was demonstrated that myasthenia gravis was largely underdiagnosed in people aged >75 years[16].

**Classification of MG in humans:** Subgrouping is crucial because of differences in clinical presentation, diagnosis, best treatment, and results among human patients of MG. It is performed on the mechanism of the disease caused by autoimmune processes, type or types of protein involved, status of thymus gland, genetic feature, response to treatment, and presence of selective versus generalized muscle involvement. These subgroups are; AChR autoantibody negative MUSK or LRP4 autoantibody positive MG, seronegative MG, early onset, late onset, or thymoma-associated MG and AChR autoantibody positive ocular MG [35–37]. Table 1: Classification of myasthenia gravis subgroups in human [36].

**Pathophysiology:** The impulses are relayed to the muscle cells by the site commonly referred to as the neuromuscular junction or nmj. It is the place of chemical communication between a nerve fiber and a

muscle. The initiation of an action potential leads to the transmission of neurotransmitters and actualization of Ach molecules at the nmj, which diffuse across the synapse, bind with receptors on the striated muscle, and depolarize the postsynaptic membrane causing muscular contraction[4]. (Fig 1) The transfer mechanism of an impulse to adjacent muscle fibers across the neuromuscular junction for nerve terminals includes the process of releasing presynaptic acetylcholine. This binding of postsynaptic receptors to this transmitters causes activating of voltage-gated calcium channels such that it gives way for influx into the terminal nerve of the calcium ion, therefore, causing release from the synaptic vesicle with presynaptic membranes containing acetylcholine. The binding of ACh to the receptors in the postsynaptic membrane opens up the ACh cation-specific channel, resulting in the limited space depolarization that leads to the activation of the voltage-gated sodium channels adjacent to it. Thus, the chemical reaction is localized to an electric signal-the action potential of the muscle fiber.(Fig 2)

Pathogenesis of MG(Fig 3 and Fig 4) :

**Generation of Autoantibodies:** Autoantibodies disrupt the structural components of the NMJ, thereby impairing neuromuscular transmission. The main targets of pathogenic Autoantibodies for MG are LRP4, muscle-specific kinase, and nicotinic cholinergic receptors. Most cases are due to IgG1 and IgG3 autoantibodies against the acetylcholine receptor. Complement-mediated injury and increased acetylcholine receptor turnover lead to the loss of acetylcholine receptors from the postsynaptic membrane [28].

**Role of cytokines and T-cells:** At the NMJ, activated T cells, B cells, plasma cells, and cytokines produce pathogenic autoantibodies and induce inflammation. All such events are important. The pathogenesis of MG can be worsened by a host of potential conditions. These include follicular Th (Tfh) cells, which drive B cells and plasma cells to produce autoantibodies; regulatory T (Treg) cells, which are dysfunctional and activate the immune system; and T helper type 17 (Th17) cells, which mediate chronic inflammation. Whereby the presence of more Th2 and Treg cells decrease the disease course, the presence of more Th1 and Th17 cells enhance the pathophysiology of MG[29].

**Thymus Abnormalities:** The disease pathogenesis is most probably linked to the thymus. The production of anti-acetylcholine receptor antibodies seems localized in the thymus. B cells responsible for the production of anti-acetylcholine receptor antibodies are mostly located within germinal centers, seen in most of the patients that harbor the corresponding antibodies. The altered structure and function of the MG thymus make it a prototype for tertiary lymphoid neogenesis. This is an optimal interaction of lymphocytes and antigen-presenting cells that should elicit an immune response. Thymus dysfunction accounts for about 75% of patients with MG. While 10% of the population carries thymic tumors, or thymomas, the thymus is "hyperplastic" with active germinal centers in approximately 65% of cases[30].

**Genetics:** Almost 35% of monozygotic MG twins have concordance. This reflects that the condition is mainly due to environmental causes. However, it cannot be inherited based on Mendelian inheritance. MG presents up to 1000 times more among family members of patients with MG as compared to the general population[31].

**General Symptoms:**

1. Voluntary muscles are variably weak.
2. Visits with progressive weakness on muscle use.
3. Symptoms caused by rest.
4. Ocular features:

-Diplopia[diploptosis].

-Ptosis.

5. Oro-pharyngeal features:
-Dysphagia.
-Dysarthria.
-Difficulty in mastication.
6. Limb girdle weakness: more common in proximal than distal muscle groups.

**Subtypes with characteristic symptoms:**
Anti-MUSK-positive MG
Predominantly oropharyngeal, facial, neck, and respiratory muscle weakness. Facial and tongue atrophy may be present. At greater risk of myasthenia crisis. Seronegative MG
Symptoms present without detectable standard antibodies. Co morbidities and Associated Issues

1. Sleep disturbances and at higher risk of sleep apnea.
2. Pain from poor posture due to weakness.
3. Higher risk of myocarditis and other inflammatory muscle disorder.
4. Associated with other autoimmune diseases [eg.,thyroiditis, rheumatoid arthritis, lupus].

**Epidemiological trends:** Increasing incidence in elderly populations, often presenting atypically.

**Severity:** The Osterman original classification splits adult myasthenia gravis into groups according to the severity of the disease [17]. Ocular myasthenia gravis - the disease affects only the ocular muscles. Generalized myasthenia gravis, of mild [a] or moderate [b] severity, Severe generalized. Myasthenic crisis with respiratory failure. Recently, this classification has been modified by an ad hoc committee of the American myasthenia gravis foundation[18] for the purpose of standardising it for research use into following types: Any ocular weakness; may have weakness of eye closure ; strength of all other muscles being normal. Mild weakness other than ocular muscles,+/_ weakness of ocular muscles of any severity. Limb and/or axial predominant. Oropharyngeal and/or respiratory predominantly.

• Moderately weak; the weakness could involve muscles other than ocular, may also include ocular weakness
a. Limb and/or axial predominant
b. Oropharyngeal and/or respiratory predominant

● Severely weak; the weakness could involve muscles other than ocular, may also include ocular weakness. This is a form of intubation with or without mechanical ventilation except those used for routine postoperative care [18].

**Clinical signs**

❖ OCULAR SIGN: Ptosis [Eyelid Drooping]: Often one of the first signs, ptosis arises from weakness of the muscles which elevate the eyelids, Diplopia [Double vision]: Weakness of the extraocular muscles can also cause double vision, especially upon prolonged activities such as reading or driving

❖ Bulbar signs

➢ Dysarthria [speech difficulties]: Weakness in the muscles related to speech often leads to slurred or nasal speech.

➢Dysphagia [swallowing difficulties]: Involvement of oropharyngeal muscles could present with dysphagia. There is always the danger of aspiration.

❖ Facial and Neck muscle weakness: Facial weakness: A patient would look like his or her smile was "gnawed off." There might even be an expressionless face because the facial muscles are weak.

➢Neck weakness: Holding the head erect can become difficult; thus, one will have to endure a dropped head posture. Limb and Respiration muscles weakness: Limb weakness: It is rare when the patients develop limb weakness at the early stage of onset that impinges on day-to-day activity

➢Respiratory muscles weakness: When very severe, it can compromise respiratory muscles which would culminate in Myasthenic crisis.

**Clinical presentations:**

**Invasive studies:** In a patient who has corresponding clinical features, the presence of high levels of anti-AChR binding antibodies usually also makes the diagnosis of MG. However, normal concentrations of antibody cannot rule out the diagnosis. Anti-AchR binding antibodies were detected in 55% of patients with only ocular symptoms and in 80% to 85% of patients with generalized MG. These are the most common and best-studied antibodies in MG. Crosslinking to cholinergic receptors accelerates their endocytosis and degradation through the binding to an activating complement that ruptures the postsynaptic membrane[22].

**Electrodiagnosis:** The repetitive stimulation test is a clinically very useful and often used neurophysiological examination used in NMJ disorders, such as MG[24]. The abductor digiti minimi, tibialis anterior, upper trapezius, deltoideus, orbicularis oculi, and nasalis muscles are frequently used for repeated stimulation. Repetitive stimulation is used to measure the variations of CAMP, which is compound muscle action potential. Low frequency (<5-Hz) RNS may be used in the diagnosis of myasthenia gravis and other postsynaptic conditions. The sensitivity of the present study for MG ranges from 10% to 17% for ocular MG and between 53% and 100% for generalized MG[23]. Ice pack test. Non-pharmacological ice pack test can be provided to the patients with ptosis when edrophonium testing is not possible. This involves placing an ice pack on the eye for two to five minutes for observing improvement of ptosis[12]. Other Tests. Myasthenia gravis may involve muscles in inspiration and expiration. Irrespective of the clinical signs of the condition, pulmonary involvement almost exists in each MG patient. Generally, iodinated contrast agents are not used in the routine examination of a patient with MG because it may worsen myasthenic symptoms. Second autoimmune disease occurs in 15% of patients and has been seen in those with early onset myasthenia gravis and in patients with thymic hyperplasia[27].

**Treatment:**

**Symptomatic treatment:**

**Acetylcholinesterase inhibitors:** The 19th century discovery and medical application of acetylcholinesterase inhibitors led to the breakthrough of the patient with generalized MG. Such a dramatic and transient improvement began within minutes after administration, and although not being long-lived for the otherwise 56-year-old woman, did allow support of Walker's hypothesis formulated in 1934: that physostigm, as the substance he utilized as the partial antagonist for curare, actually could oppose curare poisoning-like symptomatology of MG[2].

Activation of the muscarinic cholinergic side effects of nicotinic receptor leads to muscle cramps and fasciculations. Side effects due to activation of the ACh muscarinic receptor include gastrointestinal disturbances, increased bronchial secretions, lacrimation, hyperhidrosis, and bradycardia. Use of glycopyrrolate or loperamide can possibly minimize the muscarinic adverse effects. AChE inhibitor treatment could be withdrawn when the patient is placed into clinical remission or side effects become incapacitating. Paradoxical weakness can be caused by very high doses of AChE inhibitors.

**Corticosteroids:** For those patients who remain symptomatic on AChE inhibitors or for whom improved control of symptoms is desired, corticosteroids are the first line of immunosuppressive therapy. In addition, 70–80% of patients on steroids go on to experience significant improvement or even complete remission of symptoms compared with 10–20% who improve spontaneously. This would thus suggest that an early start on steroid therapy in the disease course could potentially lead to early and sustained remission.

| MG subgroups | Autoantibody target | Age of Onset | Sex | Haplotype associations | Thymic status |
|---|---|---|---|---|---|
| Early onset | AChR | <50 Years | Female predisposition | various | Hyperplasia common |
| Late onset | AChR [titin, Ryanodin receptor] | >50 Years | Male predisposition | various | Atrophy common |
| Thymoma | AChR [titin, Ryanodin receptor] | Any Age | _ | _ | Lymphoepithel-ioma |
| MUSK | MUSK | Any Age | Female predisposition | DRB1:14 DRB1:16 DQB1:5 | Normal |
| LRP4 | LRP4 | Any age | _ | _ | Normal |
| Ocular | variable | Any age | _ | _ | Normal |
| Seronegative | Unknown | Any age | _ | _ | Normal or hyperplasia |

**Table 1: Classification of myasthenia gravis subgroups in human**

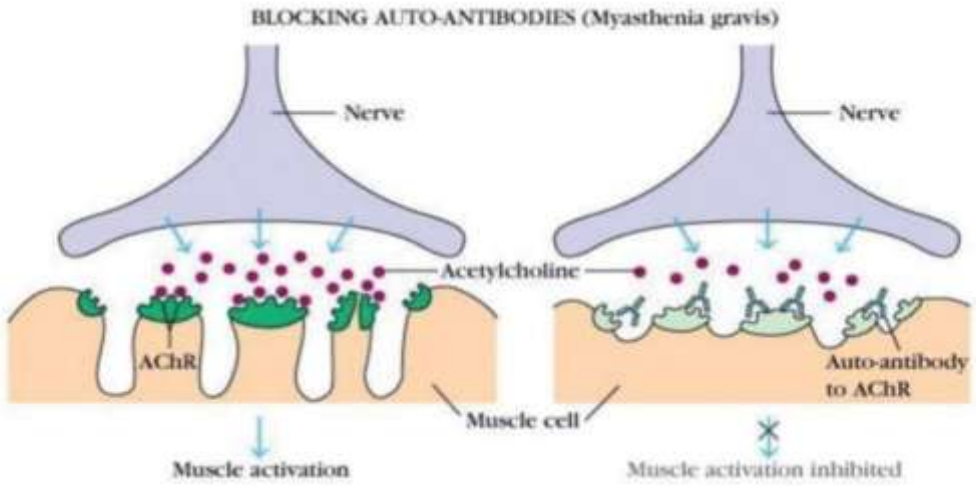


**Fig 1: Mechanism of Muscle action**

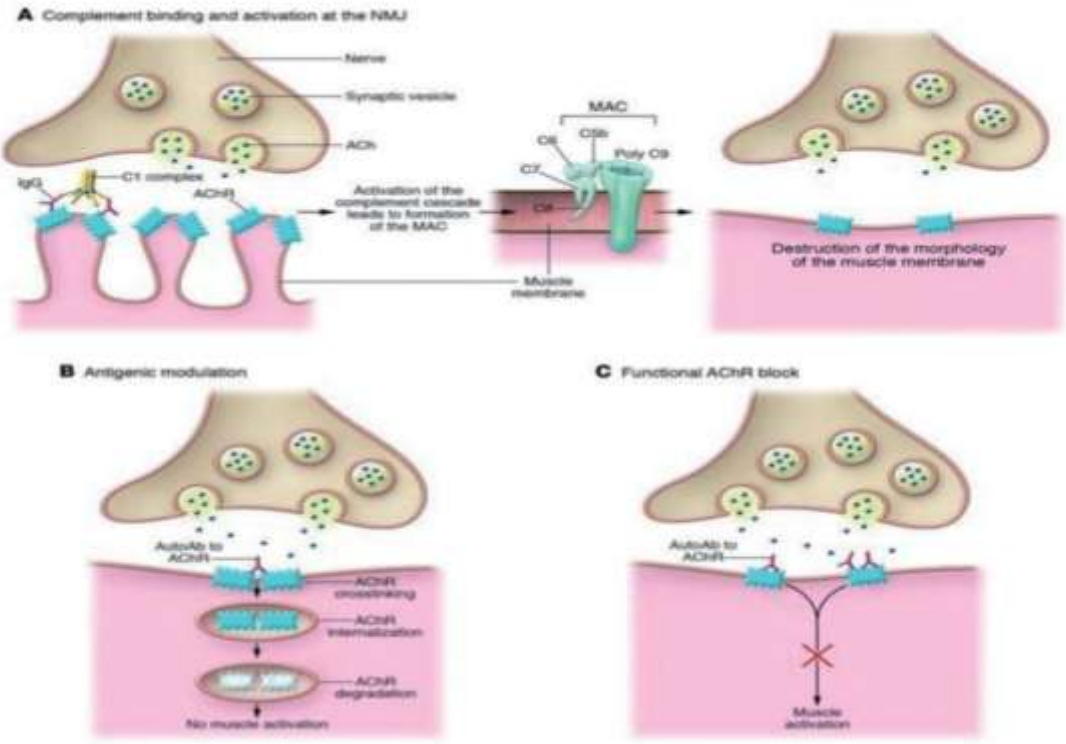


**Fig 2: Mechanism of inhibition of neurotransmission by anti-AChR antibodies**.

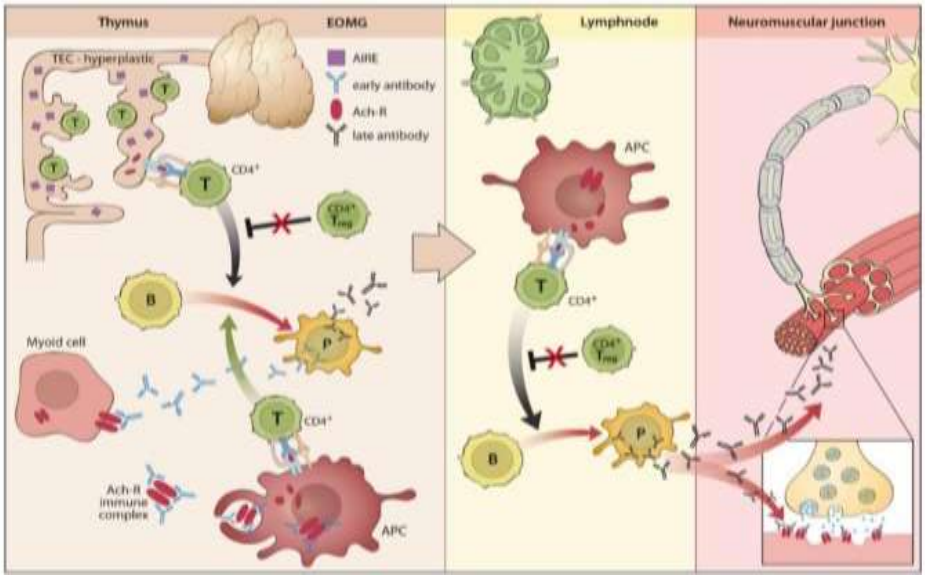


**Fig3: Pathogenesis of early-onset MG(EOMG) with lymphofollicular hyperplasia (LFH)**

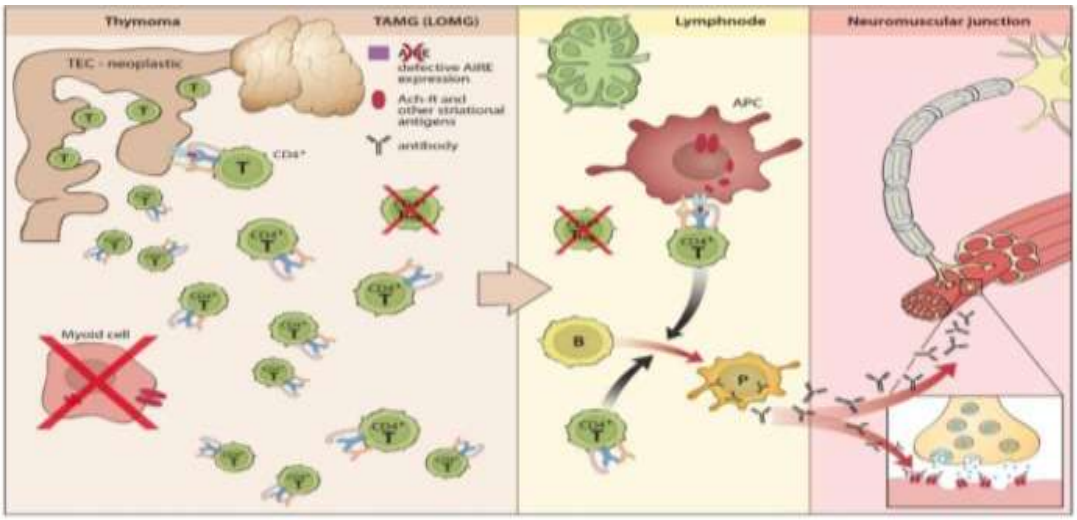


**Fig 4: Pathogenesis of thymoma-associated (and late-onset) MG (TAMG, LOMG)**

Most patients benefit from the first effects of corticosteroids within the first two weeks, and clinical response can start in as short a time frame as a few days. The maximum recovery on corticosteroids comes within the first six months, while some may require corticosteroids for up to a year and even longer than two years. Two major modalities in the administration of oral corticosteroids include the low-dose, step titration program and the high-dose, rush induction program[2].

**Immunosuppressive Treatment:** These two corticosteroids, prednisone and prednisolone enhance muscle strength in all varieties of MG. Corticosteroids may also halt the progression of ocular to generalized MG [7,9].In nonresponsive or intolerant to corticosteroid, other immunosuppressive drugs such as cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus[8], or azathioprine (first-line medications which may be administered concomitantly with corticosteroid). Recently, two monoclonal antibodies, eculizumab and rituximab, have been promising. Clinical improvement and reduction in the requirement for corticosteroid and therapeutic plasma exchange may be noted when rituximab is administered in refractory MG[10]. Neuro muscular Transmission: The voltage-gated presynaptic calcium channels open when the axonal action potential depolarizes the terminal branches. Upon entry of calcium, acetylcholine [ACh] is released from the immediate quantum reserve into the synaptic cleft.The ACh diffuses to the postsynaptic membrane and binds to ACh receptors [AChR] at the crests of the folds. Thus, it depolarises the postsynaptic membrane to the depth of the Na-channels of the postsynaptic folds. The following end-plate potential [EPP] results in the generation of an action potential in the muscle fiber, which then transmits this to the sarcolemma and thus, sets off a chain of events leading to the contraction of the muscle fibers. Acetylcholinesterase [AChE] breaks down ACh into its constituent parts, which are reabsorbed by the terminal and resynthesised into ACh. The "safety factor" of neuromuscular transmission that ensures uninterrupted recurrent contraction of muscle fibers is that the EPP is much larger than the threshold of depolarization of the sarcolemma-a condition ensured by the massive number of ACh quanta released and the special arrangement of the postsynaptic membrane. The release of the protein agrin from the terminal controls the AChR

clustering and other important end-plate characteristics. Muscle-specific tyrosine kinase [MUSK] is activated by Agrin when it associates with low-density lipoprotein receptor-related protein 4 [LRP4]. Our very brief overview cannot do justice to the normal anatomy and physiology of the synapse; for those, consult more extensive reviews.

**Plasmapheresis:** It directly removes AChR from the blood, thus improving strength in most MG patients[4]. The average number of exchanges is four to six, and one exchange per other day is normally performed. Other side effects of plasmapheresis include hypotension, paresthesias, infections, thrombotic complications due to venous access, and bleeding tendencies due to decreased coagulation factors[5]. This immunosuppressive therapy must be continued, as remission will not last long beyond four to ten weeks. The equipment involved in plasmapheresis is expensive. Thus, plasmapheresis may be unavailable in a few places due to the nature of the expensive equipment. This includes hypotension, disturbances in coagulation, and intravenous site difficulty, such as the placement of a central line[19].

**Therapeutic plasma exchange[TPE]:** This procedure eliminates the patient's plasma and utilizes fresh plasma or albumin instead. Autoantibodies against AChRs will therefore be removed; this will increase NMJ transmission, hence muscle strength in the short term. It can be utilized as maintenance therapy for the juvenile MG sufferer and as acute therapy for those patients suffering from severe generalized MG, resistant MG, and myasthenia crises.

**Thymectomy:** All 10–15% of MG patients who have a thymoma should undergo a thymectomy. Whereas this does so much less frequently than those having a hyperplastic thymus, spontaneous improvements in MG are sometimes seen even in such patients[20]. Thymectomy has a primary rationale for the patients-the eradication of potentially invasive tumor. After resection of a thymoma[21], some patients without, or with very weak MG symptoms, have shown a dramatic worsening of MG with an elevation of AChR autoantibodies. There are two distinct roles of thymectomy in myasthenia gravis: Thymectomy for thymic tumors associated with about 10% of myasthenia gravis patients and Thymectomy as a treatment for myasthenia gravis in itself. Because thymic tumors may locally spread, thymectomy should always be performed at the first sign. For decades myasthenia gravis [in whom thymoma is not identified] has been treated with thymectomy. In a more recent study, response was unaffected by age[34]; however other studies have indicated that younger age and the absence of thymoma predict a better response[33]. All 10–15% of MG patients with a thymoma should receive a thymectomy. While this is much less common than in patients with a hyperplastic thymus, occasional improvement of MG has been noted in such patients[20]. The primary reason for surgery in thymoma patients is to remove a tumor that could be invasive. After a resection of a thymoma[21], some patients who were asymptomatic or had very weak symptoms of MG have had a dramatic worsening of MG with an increase in AChR autoantibodies. There are two different aspects of thymectomy in myasthenia gravis: Thymectomy for thymic tumors associated with about 10% of myasthenia gravis patients and Thymectomy for the treatment of myasthenia gravis per se. Because thymic tumors can invade locally, thymectomy should always be done in response to the first sign. For decades thymectomy has been used to treat myasthenia gravis[when thymoma is not a factor]. The response was no different in an age-related response in a latest study[34], but most other studies reveal that young age and the absence of thymoma

predict a much better response to thymectomy[33].

**Treatment of myasthenic crisis:** Hospitalization and very careful observation of respiratory and bulbar functions are necessary in cases where myasthenic crisis is about to occur. A patient should be admitted with the option to be transferred to the intensive care unit in case of symptoms which may show a crisis. Plasma exchange (PLEX) and human immunoglobulin (IVIg) is short-term treatments for these disorders. In most cases, this is initiated by the administration of corticosteroids or another immunosuppressive medication or by increasing their dose at the same time[25]. Since they cause an accumulation of respiratory secretions, acetylcholinesterase inhibitors make airway management difficult and should not be administered intravenously during crisis; they are all withdrawn when the patient is intubated[26]. A patient usually needs mechanical ventilation for five to seven days after intubation. Reintubation usually happens when a patient is extubated after only a few days of mechanical ventilation. Thus, in this case, a conservative approach to extubating is recommended [26].

## CONCLUSION

Myasthenia Gravis is an autoimmune disease; it impairs the NMJ of skeletal muscle by the production of autoantibodies against the junction. Clinical hallmark of MG is fluctuating fatigability and weakness, which characteristically affects the ocular, bulbar and limb skeletal muscle groups. It can occur at any age, even in childhood, but the patients who are mostly at risk are older males over 60 years, and young adult females under 40 years. There are no treatments for MG. Medicine controls the disorder, plasmapheresis, thymus removal, IVIG, and rest that diminish muscle weakness. An application of treatment can control symptoms and regulate a response of the immune system. Most patients are able to have a significant regain in muscle strength and can live relatively normal or nearly normal lives. Emerging new therapies aim at specific pathways of the immune system. Future treatments may apply themselves through the studies of gene-based medicine.

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