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Introductory Chapter: Myasthenia Gravis - An Overview

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1. Introduction

The term myasthenia gravis (MG) is derived from the Greek terms my, asthenia, and gravis, which mean muscle, weakness, and severe, respectively. Myasthenia gravis is a rare potentially fatal chronic autoimmune disorder, in which circulating autoantibodies directed against components of the neuromuscular junction (NMJ) of skeletal muscles, most commonly nicotinic acetylcholine receptor (AChR) and associated protein in the postsynaptic membrane, will block neuromuscular transmission resulting in muscle weakness [1]. The muscle weakness is typically worsened with continued activity, improves on rest, and is of variable severity ranging from mild ocular muscle weakness to severe generalized muscle weakness involving the respiratory muscle with impending respiratory failure.

2. Historical perspective

The first reported case of MG could be traced to the Native American Chief Opechancanough, who died in 1664. “The excessive fatigue he encountered wrecked his constitution; his flesh became macerated; his sinews lost their tone and elasticity; and his eyelids were so heavy that he could not see unless they were lifted up by his attendants ...he was unable to walk; but his spirit rising above the ruins of his body directed from the litter on which he was carried by his Indians” [2, 3]. An English physician, Thomas Willis, in 1672 described a patient with a typical myasthenic fatigable weakness of limb and bulbar muscles [4]. The late 1800s certify the publishing first modern description of patients with myasthenia symptoms when Wilks in 1877 described bulbar and peripheral muscular weakness without any pathology of the central nervous system [5]. A great advance in understanding MG and its management were achieved in 1934 by Walker who found the symptoms of MG were similar to curare poisoning and was treated with a cholinesterase inhibitor, physostigmine. Walker showed that the symptoms of MG promptly improved by the administration of physostigmine [6]. In 1937, Blalock established the removal of thymus as a treatment for MG [4]. Simpson and Nastuck suggested the autoimmune etiology of MG in 1959–1960 [7, 8] depending on several observations. In the 1970s, prednisolone, azathioprine, and, later, plasma exchange were established as treatments for MG [2].

3. Epidemiology

The worldwide prevalence of MG is 100–200 per million population [9], affecting more than 700,000 people all over the world [10]. The prevalence rate

has increased since the 1950s due to improved diagnostic precision and decreased mortality rate. It occurs in both genders, in all ages from different ethnic groups with variable prevalence and annual incidence rate from one country to another. Female-to-male ratio for incidence is 3:2 in people below the age of 30 and 1:1.5 in people more than 50 years of age. Life-threatening MG crises occur approximately in 15–20% of patients, typically within the first 2 years of diagnosis [11]. Previously, MG crises were associated with 50–80% mortality rate. Currently, the overall inpatient mortality rate of MG is 2.2%, being higher in crises (4.47%). Older age and respiratory failure were the predictors for death in MG crises [12].

4. Etiology

Myasthenia gravis is an autoimmune disease mediated by organ-specific antibody. These antibodies are present at neuromuscular junction (NMJ) and directed against nicotinic acetylcholine receptor (AChR) on the postsynaptic muscle membrane in 80–90% of patients. In 3–7%, the autoantibodies are directed against another NMJ protein, muscle-specific tyrosine kinase (MuSK). Using cell-based assay may increase the rate of detection of autoantibodies in patients with negative result by standard binding and modulating technique [13]. Patients with negative antibodies against AChR and MuSK might show positive antibodies against low-density lipoprotein receptor-related protein (LRP4) [14]. Other types of antibodies might be detected in patients with MG like agrin antibodies and antibodies to collagen Q and cortactin. These antibodies are of debatable clinical importance [15]. The reason why some patients develop these autoantibodies remains unclear. Genetic predisposition linked to human leukocyte antigen complex, single nuclear polymorphism, association with thymic hyperplasia or thymoma and abnormalities in the number and function of regulatory T and B cells are probably playing a role in the etiology of MG [16–19]. Risk factors for developing MG include positive personal or family history of autoimmune disease like rheumatoid arthritis, HLA-B8, DR3, and women being less than 40 and men more than 60 years of age.

5. Pathophysiology

Normally, Ach is released in a discrete package from the motor nerve terminal at the neuromuscular junction. These Ach quanta diffuse across the synaptic cleft and bind to receptors on the folded muscle end plate membrane (**Figure 1**). Motor nerve stimulation will release many Ach quanta causing depolarization of muscle end plate membrane resulting in muscle contraction. In MG, Ach was released normally but its effect on the postsynaptic membrane reduced. The autoantibody against AChRs will result in the destruction of postsynaptic membrane and reduction in the number of available Ach receptors on the muscle end plate membrane (binding site for Ach), which in turn will lead to an inconsistent generation of muscular action potentials manifesting as muscle weakness (**Figures 2 and 3**). The process of destruction of the postsynaptic membrane is dependent on complement activation. In patients without antibodies against AChRs, a muscle-specific tyrosine kinase (MuSK), an agrin-dependent protein on muscle membrane, has been found to be the antigenic target. These

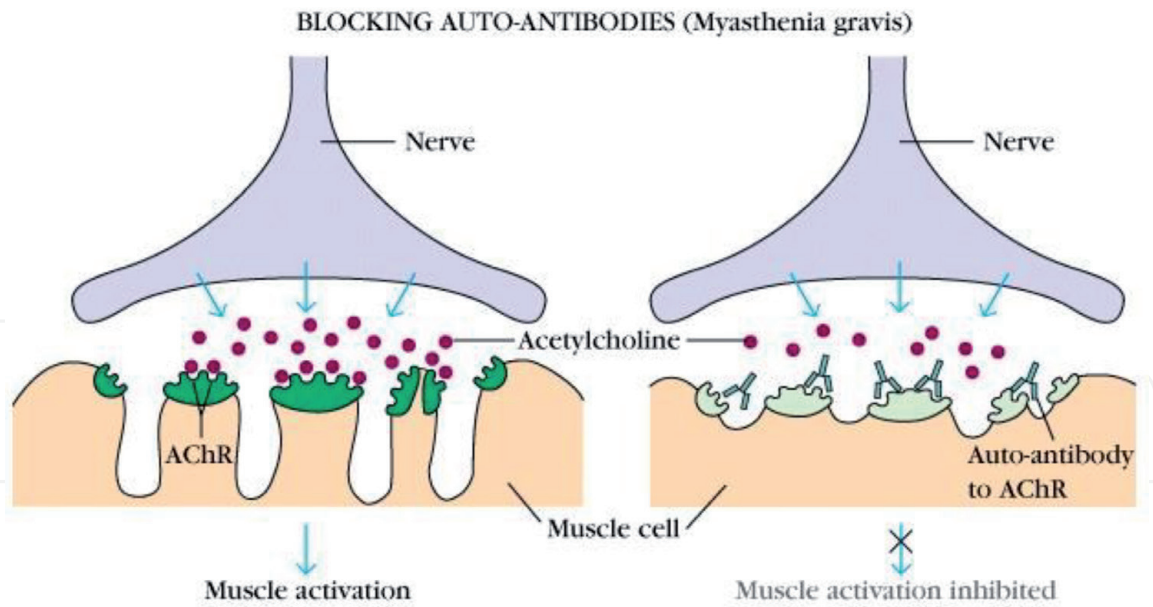


Figure 1.
Mechanism of muscle activation. Adopted from the free domain: <http://pathologicallyspeaking.blogspot.com/2015/07/speech-therapy-treatment-for-myasthenia.htm>.

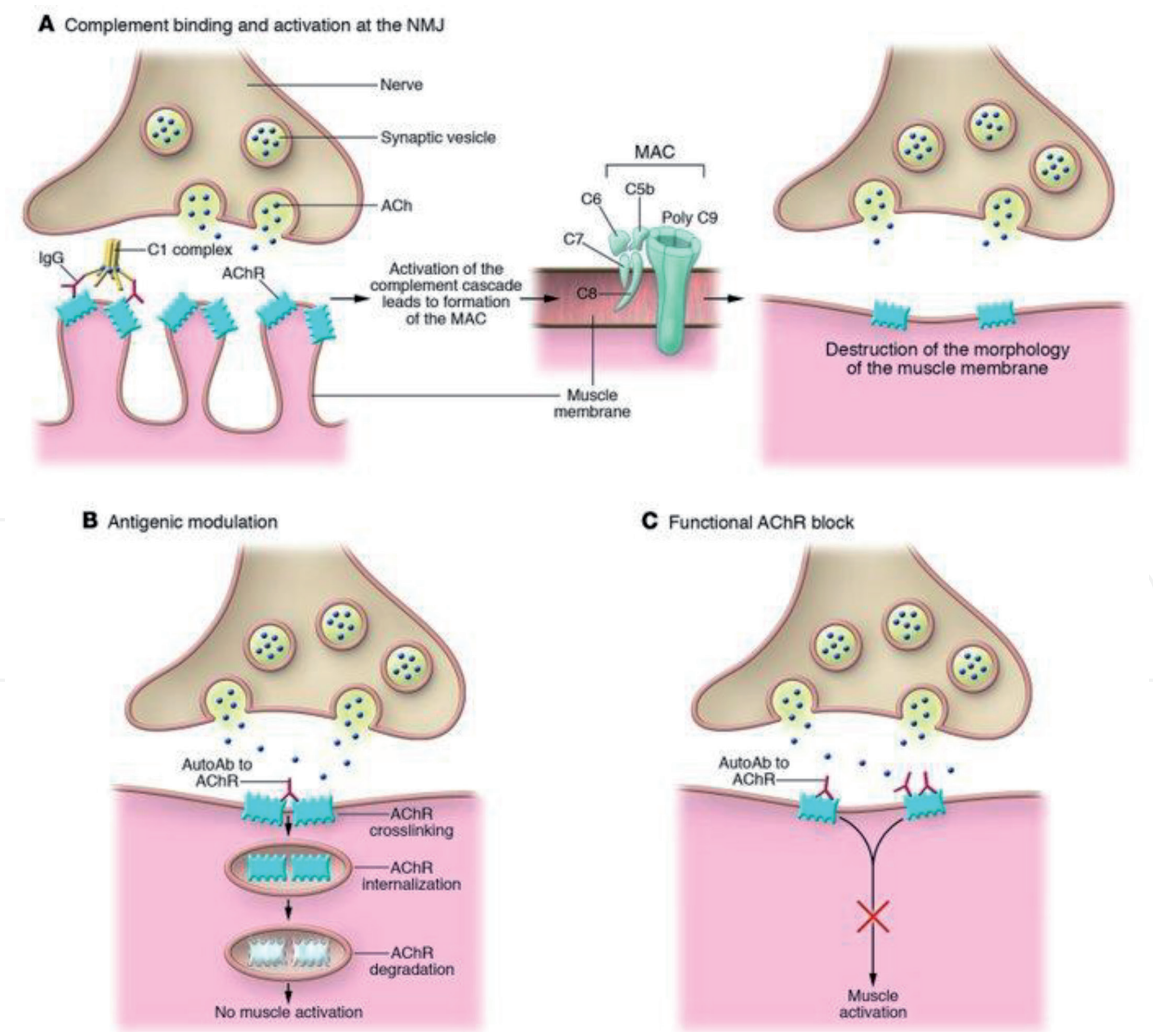


Figure 2.
Mechanisms of inhibition of neurotransmission by anti-AChR antibodies. Adopted from the free domain: <https://www.jci.org/articles/view/29894/figure/2>.

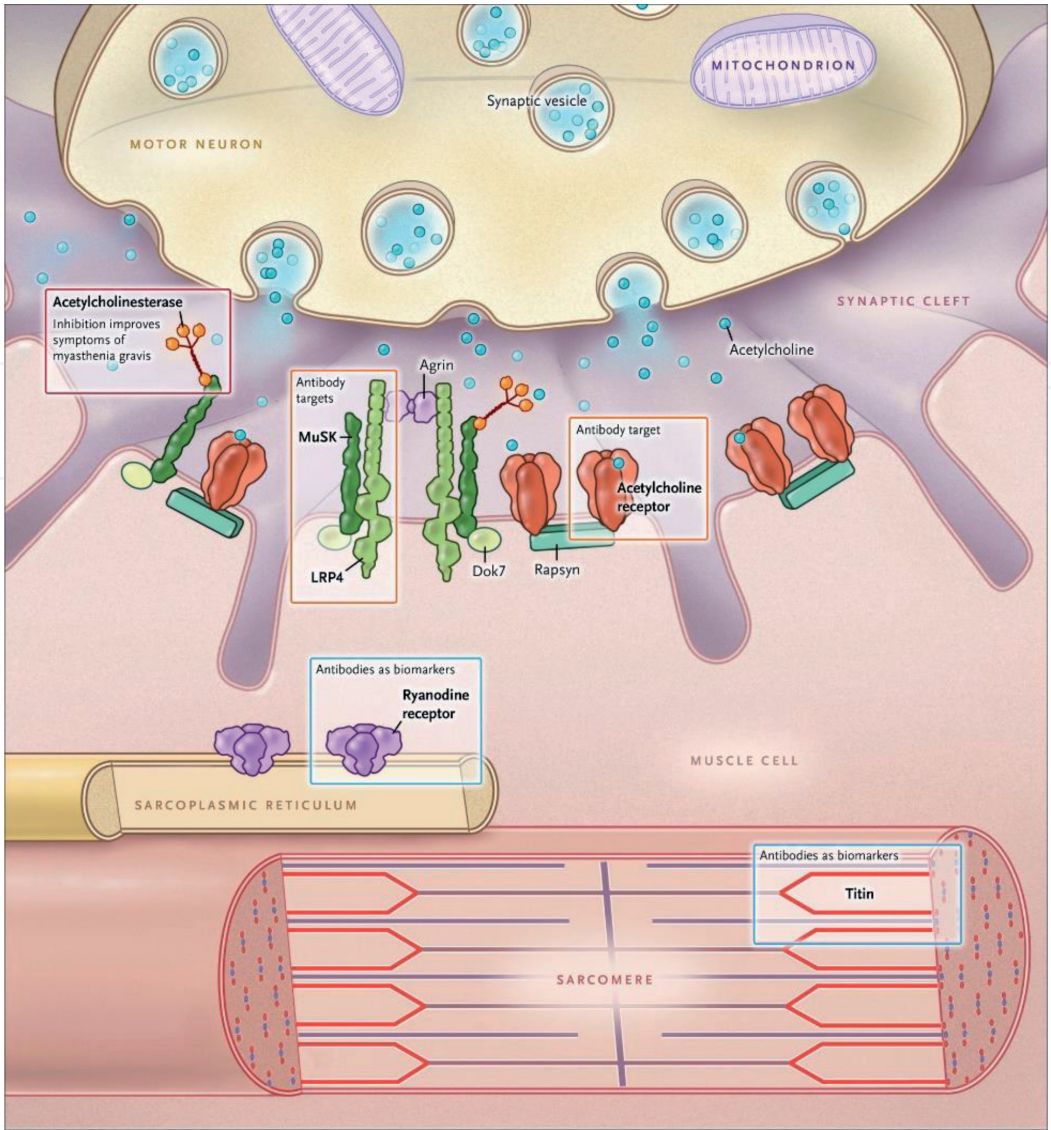


Figure 3.
Pathogenesis of MG. Adopted from the free domain: <https://www.nejm.org/doi/full/10.1056/NEJMra1602678>.

autoantibodies are T-cell dependent and there is interesting differential involvement of muscle groups, especially the extraocular muscles [20].

6. Clinical presentation

Fatigable weakness, involving specific susceptible groups of muscles, is the clinical hallmark of MG. This weakness usually fluctuates from hour to hour, day to day, worsens with activity, and improves on rest. The susceptible groups of muscles include ocular, bulbar, facial, limb muscle, axial muscle, and respiratory muscle. Clinical features resulting from the involvement of the susceptible group of muscle are summarized in **Table 1** [21].

The most common initial presenting feature of MG is ocular muscle involvement presenting as fluctuating ptosis and/or diplopia, with or without generalized weakness, in about 85% of cases [22]. The absence of ocular involvement makes the diagnosis difficult. In 50–60% of patients with isolated ocular involvement, progression to generalized weakness occurs within 2 years of the onset. The

Group of muscle	Clinical features
Ocular muscle	Fluctuating ptosis and/or diplopia
Bulbar muscle	Dysarthria, painless dysphagia, dysphonia, and masticatory weakness
Facial muscle	Facial weakness, inability to close eye firmly, drooling of saliva
Axial muscular	Flexion or extension of the neck
Limb muscle	Weakness involving the arms more than legs
Respiratory muscle	Labor breathing, orthopnea, dyspnea, and respiratory failure

Table 1.
Signs and symptoms of MG.

second most common presenting feature is bulbar muscle involvement manifesting as dysphagia, dysarthria, dysphonia, or difficulties in chewing, occurring in about 15% of cases [23]. A life-threatening respiratory muscle involvement, requiring immediate therapeutic action might occur on rare occasions. Patients with MG usually experience a variable course with intermittent worsening of symptoms precipitated by viral infection, surgery, warm weather, immunization, emotional stress, pregnancy, chronic diseases, or medications. Progression to maximum severity usually occurs with the first 2 years of onset and spontaneous long-term remission might occur in up to 10–20% of patients [22]. About 10–20% of infants born to mothers with symptomatic or asymptomatic MG present soon after birth with transient neonatal MG. It occurs as a result of transplacental passage of antibodies against NMJ receptors. The most common presenting features are hypotonia and poor feeding that resolve usually within the first months after birth [24].

7. Clinical classifications

Myasthenia gravis is classified clinically into five classes and several subclasses according to MG foundation of American clinical classification, see **Table 2** [25].

Class	Clinical description
Class 1	Any eye muscle weakness, possible ptosis, all other muscles' strength is normal
Class 2	Mild weakness of other muscles; may have eye muscle weakness of any severity
2a	Predominantly limb or axial muscles weakness or both
2b	Predominantly oropharyngeal or respiratory muscle weakness or both
Class 3	Moderate weakness of other muscles; may have eye muscle weakness of any severity
3a	Predominantly limb or axial muscle weakness or both
3b	Predominantly oropharyngeal or respiratory muscle weakness or both
Class 4	Severe weakness of other muscles; may have eye muscle weakness of any severity
4a	Predominantly limb or axial muscle weakness or both
4b	Predominantly oropharyngeal or respiratory muscle weakness or both; use of feeding tube without intubation
Class 5	Intubation needed to maintain airway

Table 2.
Clinical classification of MG.

8. Diagnosis

The diagnosis of MG might be difficult and easily missed, because of the rarity of the condition and hence unfamiliarity to physicians. Furthermore, fluctuations of muscle weakness may add to the perplexing presentation. Once MG is suspected, the following test can be requested:

8.1 Serological tests

Anti-AchR has about 100% specificity, 85% sensitivity in patients with generalized MG, and 50% sensitivity in pure ocular variety [26]. False positive results may occur in patients with thymoma without MG, small cell lung cancer, rheumatoid arthritis treated with penicillamine, and rarely in people over 70 years of age. Other serological tests include anti-MuSK antibody (positive in 50% of myasthenic patients with negative anti-AchR), anti-agrin antibody, anti-lipoprotein-related protein 4 (LRP4) antibody, antistriational antibody (present in all myasthenic patients with thymoma), and anti-cortactin antibody.

8.2 Neurophysiological studies

These studies are commonly used to detect defects in neuromuscular transmission in patients with MG. Repetitive nerve stimulation and single-fiber electromyography are the most commonly used tests. Repetitive nerve stimulation can detect 75 and <50% of generalized and ocular MG patients, respectively. On the other hand, single-fiber electromyography can detect defects in neuromuscular transmission in 95–99% of myasthenic patients and a negative result can exclude the diagnosis [27].

8.3 Radiological studies

Chest X ray, CT scan, and MRI might be recommended to evaluate patients with anterior mediastinal mass and suspected thymoma, and also to exclude brain and orbit mass lesion inducing cranial nerve palsies in ocular MG.

8.4 Pharmacological tests

In MG, the number of AChRs at the NMJ is low due to inhibition by the auto-antibody. The result is decrease in the number of interaction between Ach (release from motor nerve terminals) and its receptors on postsynaptic muscle membrane of NMJ. The Ach is metabolized by Ach esterase (AChE) enzyme. Therefore, inhibition of this enzyme will increase the Ach concentration at the NMJ and hence improve the chance of interaction between the Ach and its receptors. Edrophonium test is based on the clinical improvement of muscle weakness in myasthenic patients after intravenous administration of short-acting Ach esterase inhibitor, Edrophonium (Tensilon). Double blinding of both the patient and the examiner increases the validity of the test [28].

8.5 Ice pack test

This debatable test uses the fact that cooling might improve neuromuscular transmission. It is mainly used by ophthalmologists to assess improvement in ptosis and diplopia in myasthenic patients [29].

9. Treatment

The severity of symptoms in patients with MG will determine the strategy of the treatment using the many therapeutic options available. According to MG foundation of American clinical classification (**Table 2**), MG can be divided into three categories: mild (classes 1 and 2), moderate (class 3), and severe (classes 4 and 5). The available therapeutic options include:

9.1 Pharmacologic therapy

The cornerstone for the treatment of MG is the administration of reversible cholinesterase (AChE) inhibitor, pyridostigmine, which is more effective in patients with generalized and ocular MG and less effective in patients with positive anti-MuSK antibody. In those patients with poor response to pyridostigmine, steroid and immunosuppressive agents should be considered [30–32].

9.2 Immunosuppressive agent

All types of MG respond to corticosteroid (prednisone and prednisolone) in terms of improvement of muscle strength. Furthermore, corticosteroid may prevent progression of the disorder from ocular to generalized MG [30, 33]. Patients who do not respond to corticosteroid or who cannot tolerate it are candidates for immunosuppressive agents using azathioprine (they are first-line agents and can be used with corticosteroid), cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus [32]. Recently, promising results are shown by two monoclonal antibodies, rituximab and eculizumab. The use of rituximab in refractory MG may show clinical improvement and reduction for the need of corticosteroid and therapeutic plasma exchange [34].

9.3 Therapeutic plasma exchange (TPE)

It is the procedure by which the patient's plasma is removed and replaced by fresh plasma or albumin. This will lead to the removal of autoantibody against AChRs, leading to short-term improvement of NMJ transmission and hence muscular strength. It is useful as an acute treatment in patients with severe generalized MG, refractory MG, myasthenia crises, and as maintenance therapy in patients with juvenile MG [35].

9.4 Intravenous immunoglobulin (IVIG)

The mechanism of action of IVIG is complex and may involve inhibition of cytokines and complement deposition, competition with autoantibodies, interference with binding of Fc receptor on macrophages and immunoglobulin receptor on B cells, and interference with antigen recognition by sensitized T cells [36]. It is used as an acute treatment in patients with severe generalized MG and MuSK-MG, as a maintenance therapy in patients with refractory and juvenile MG, and in myasthenia crises [1].

9.5 Thymectomy

Myasthenic patients commonly have thymic abnormalities. Patients with generalized MG have thymic hyperplasia in 85% and thymoma in 10–15% of cases. Those patients are usually anti-AChR antibody positive. Thymectomy is indicated for all patients with thymoma and for patients aged 10–55 years who have generalized MG

but without thymoma. In fact, thymectomy is proposed as first – line therapy in most patients with generalized MG. Thymectomy not indicated in patients with antibodies to MuSK, LRP4, or agrin antibodies because the thymic pathology is different from the more common type of MG characterized by seropositivity to AChR, and also it is not indicated in patients with ocular MG during the first 2 years after diagnosis because the possibility of spontaneous remission [2].

10. Prognosis

With the recent advances in the management of MG in both supportive intensive care and specific therapeutic options, most patients enjoy normal or near normal life span. The mortality rate is about 3–4% and the risk factors for death include a short history of a progressive disease, age more than 40 years, and thymoma. Morbidity in MG results from intermittent muscle weakness, which may result in aspiration pneumonia, difficult breathing, and even respiratory failure requiring ventilator assistance and in possible side effects of medications used in the treatment.

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