Myasthenia Gravis – A Review

Mr. Hajare Krushna Ashok[1], Ms. Pallavi Jadhav[2]
[1, 2] Pratibhatai Pawar College of Pharmacy, Shrirampur

Abstract- *Myasthenia gravis was first recognised as a distinct clinical entity by Thomas Willis, a 17th century Oxford physician, whose 1672 account in Latin was largely unnoticed until 1903. The first modern description was made in 1877 by Samuel Wilks, a London physician. Towards the close of the 19th century, primary muscle diseases and diseases due to denervation of muscle were studied by English, French, and German physicians. The first full descriptions of myasthenia gravis were by Wilhelm Erb, of Heidelberg, and Samuel Goldflam of Warsaw. The account by Willis, and the 19th century literature of myasthenia gravis are reviewed, revealing the dominance of German physicians and neuropathologists in the early understanding of the disease. The development in pathology, aetiology, and therapy in the first half of the 20th century are described.*

Keywords- Myasthenia gravis, Autoimmune disorder, Eye infection, Opthalmic.

I. INTRODUCTION

The clinical picture of myasthenia gravis is distinctive. The typical case has muscular weakness of a particular distribution, affecting the external ocular muscles, and those of speech and swallowing, that is, the voluntary muscles innervated by the cranial nerves, the nuclei of which are located in the midbrain, pons, and medulla oblongata. Whilst the limb and trunk muscles may be weak, those of digestion and micturition are spared, as is the heart. Weakness follows exertion and improves with rest. There are other features of myasthenia gravis, the clinical spectrum of which is diverse, but the striking presentation of a typical case is bulbar paresis related to activity. Such a distinctive clinical syndrome awaited recognition by a discerning physician; one who carefully enquired into the clinical history of patients and expertly observed their clinical signs. Such a physician appeared in 17th century Oxford. His name was Thomas Willis [Gronseth GS, et.al., 2000]

Acquired myasthenia gravis is a relatively unseen disorder, with prevalence rates that have increased to about 20 per 100,000 in the US population. This autoimmune syndrome is characterized by muscle weakness that fluctuates, worsening with exertion, and improving with rest. In about two-thirds of the patients, the involvement of extrinsic ocular muscle presents as the initial symptom, usually progressing to involve other bulbar muscles and limb musculature, resulting in generalized myasthenia gravis. Although the cause of the disorder is unknown, the role of circulating antibodies directed against the nicotinic acetylcholine receptor in its pathogenesis is well established. As this disorder is highly treatable, prompt recognition is crucial. During the past decade, significant progress has been made in our understanding of the disease, leading to new treatment modalities and a significant reduction in morbidity and mortality.

Acquired myasthenia gravis (MG) is a relatively uncommon disorder, with prevalence rates that have increased to about 20 per 100,000 in the US population. A condition in which there is a quick tiredness and weakness of voluntary muscles, it is known as myasthenia gravis. This condition demonstrates a miscommunication or loss of communication or interaction between muscles and nerves.[Robertson N. et.al. 2000]

Triggers Myasthenia Gravis

To know what triggers myasthenia gravis, let us first have a look at how our muscles work. There are many, many nerves in our body. These nerves interact with the muscles by releasing neurotransmitters, which are certain type of chemicals. These neurotransmitters fit correctly into receptor sites on the muscle. These receptor sites are located at the junction where the nerves and muscles meet. In myasthenia gravis, several of the receptor sites are blocked by antibodies for a neurotransmitter known as acetylcholine. These antibodies are produced by your own immune system. As a result, some receptor sites are available for communication between nerves and muscles. This leads to weakened muscles as there are few nerve signals received.

The antibodies produced by the immune system may also be responsible for blocking a protein called tyrosine kinase. Its role is in the formation of the nerve-muscle junction. If this protein is blocked, it may lead to myasthenia gravis, as it cannot form the nerve-muscle junction.According to some researches, thymus gland may be responsible in maintaining or triggering the production of antibodies that block the neurotransmitter acetylcholine. In infancy, the thymus gland is large. In healthy adults, it is small in size. It is seen that people having myasthenia gravis have an unusually large thymus gland.Some people may get myasthenia gravis

that is not associated with acetylcholine or tyrosine kinase. This type is known as antibody-negative myasthenia gravis. This may involve antibodies made for another protein called as lipoprotein-related protein 4.In rare cases, women with myasthenia gravis may give birth to children with myasthenia gravis. This is known as neonatal myasthenia gravis. If treated quickly and efficiently, these kids usually get better within short time after their birth.Another rare form of myasthenia gravis is congenital myasthenic syndrome. In this condition, children are born with myasthenia gravis of a hereditary type.

The main focus of this special issue is the characterization of the autoimmune responses in MG, the relationship between the immunological disturbances and the clinical picture, the role of the thymus, and the specific problems related to paediatrics and anaestiology. The special issue will summarize the most recent developments in the area.Considerable data support the involvement of thymus in the aetiology of MG. P. Cavalcante et al. address the question of whether inflammation and Epstein-Barr virus (EBV) infection are frequent pathogenic features of MG thymus. By using Low-Density Array and real-time PCR, the authors show that the MG thymic transcriptome is characterized by upregulation of genes implicated in inflammation and immune response, delineating a peculiar inflammatory and antiviral signature. By using more sensitive molecular and immohistochemical techniques, the authors have implemented and improved their previous finding of an active EBV infection in MG thymus. Hence, a new pathogenic model of virus-mediated autoimmunity in MG is proposed. EBV infection may contribute to MG-specific autoimmune responses occurring within a chronically inflamed MG thymus, through its ability to promote activation, survival, and expansion of autoreactive B cells. The overall results of the study strongly suggest that inflammation and EBV infection are key events in the intrathymic pathogenesis of MG.

Patients with autoimmune MG should be further classified before initiating therapy, as treatment response varies for ocular versus generalised, early onset versus late onset, and acetylcholine receptor antibody positive versus MuSK antibody positive disease. G. O. Skeie and coworkers discuss available treatment approaches in MG. Most patients need immunosuppression in addition to symptomatic therapy. Prednisolone and azathioprine represent first-choice drugs, whereas several second-choice options are recommended and should be considered. Thymectomy should be undertaken in MG with thymoma and in generalised, early-onset MG. For MG crises and other acute exacerbations, intravenous immunoglobulin (IvIg) and plasma exchange are equally effective and safe treatments. Children and females in childbearing age need special attention regarding potential side effects of immunosuppressive therapy. MG pathogenesis is known in detail, but the immune therapy is still surprisingly unspecific, without a pinpointed attack on the defined disease-inducing antigen-antibody reaction being available.[M. N. Meriggioli, et.al. 2009]

Acquired myasthenia gravis (MG) in an organ-specific autoimmune disorder generally mediated by antiacetylcholine receptor (AChR) or less frequently by antimuscle-specific tyrosine antibodies at the neuromuscular junction.Some MG patients have antibodies that bind in a cross-striational pattern to skeletal and heart muscle tissue sections. They were known as “striational antibodies.” These autoantibodies recognize epitopes on skeletal muscle proteins including myosin, actin, actinin, and filamin.Particularly, three types of striational antibodies including those to titin, ryanodine receptor (RyR), and Kv1.4 have been investigated by many researchers. The detection of these three striational antibodies can provide more specific clinical information and are associated with the subtypes of MG patients. In this article, we describe the characteristics of these three types of striational antibodies.

Complications Of Myasthenia Gravis

The most serious complications of myasthenia gravis is a myasthenia crisis. This is a condition of extreme muscle weakness, particularly of the diaphragm and chest muscles that support breathing. Breathing may become shallow or ineffective. The airway may become blocked because of weakened throat muscles and build up of secretions. Myasthenia crisis may be caused by a lack of medicine or by other factors, such as a respiratory infection, emotional stress, surgery, or some other type of stress. In severe crisis, a person may have to be placed on a ventilator to help with breathing until muscle strength returns with treatment. [Gronseth GS, et.al., 2000]

Precautions, which may help to prevent or minimize the occurrence of myasthenia crisis include:

- Taking anticholinesterase medicines 30 to 45 minutes before meals to reduce the risk of aspiration (food entering the lung passages)
- Taking anticholinesterase medicines exactly as prescribed to help maintain the strength of the breathing muscles
- Avoiding crowds and contact with people with respiratory infections, such as a cold or the flu
- Taking in proper nutrition to maintain optimal weight and muscle strength

- Balancing periods of physical activity with periods of rest
- Using stress-reduction techniques and avoiding emotional extremes

Tell your healthcare providers about your condition when any medicines are being prescribed. Certain medicines may interfere either with the disease or the action of the medicines you take for myasthenia gravis.

Pathophysiology :

Myasthenia Gravis has been derived from the Greek and Latin word that means Grave Muscular weakness. Myasthenia Gravis is a rare autoimmune disorder involving the autoantibody against the neuromuscular junction components of the skeletal muscles.This is associated with impaired neuromuscular transmission. Due to this, there is fluctuating weakness in the skeletal muscles and the patient finds difficult to contract the muscles. According to the Myasthenia Gravis Foundation of America, it is the most common disorder of neuromuscular transmission. Its rareness can be seen from its low frequency of occurrence in the people, that is, it affects only 15 to 20 numbers of people in every 100,000 people in the United States. Women are more prone of getting diagnosed with Myasthenia Gravis at a younger age than males, who are mostly diagnosed at the age of 60 or more. It is seen in the age groups of over 40. Its symptoms are only manageable and the disease cannot be cured. To understand the pathogenesis of Myasthenia Gravis, it is essential to understand about the neuromuscular junction which is also known as the myo-neuronal junction. The junction or the synapse between the motor neuron and the muscle fiber is called as neuromuscular junction.

The muscle fiber is surrounded by the thin plasma membrane which is called as 'Sarcolemma'. The portion of the sarcolemma which interacts with the nerve ending is called as the motor end plate. This motor end plate has several folds to increase the surface area.With the help of this, it accommodates a number of acetylcholine receptors on it. These are the muscle fibers of the skeletal or striated muscles.These muscles are innervated by the spinal motor neurons (nerve ending) that do not actually touch or directly contact with the muscle but contact with the help of acetylcholine. Acetylcholine is the name of neurotransmitter that helps in the neuromuscular transmission. When the wave of action potential reaches the neuron ending, the voltage-dependent calcium channels are opened, resulting the influx of calcium ions andthis leads to fusion of synaptic vesicles containing acetylcholine with the cell membrane of nerve ending. Synaptobrevin, Syntaxin, and SNAP-25 get involved in exocytosis to release the neurotransmitter present in the vesicle. Each vesicle contains approx 5000 acetylcholine molecules. The acetylcholine then binds with the acetylcholine or nicotinic receptors which exist on the motor end plate. These receptors are ion channels which when get activated, lead to the influx of Na+ ions into the muscle cell. This further generates miniature endplate potentials (MEPPs) or the depolarization but this little depolarization is not enough to reach the threshold potential.

When this miniature end plate potential summates (MEPPs are additive), it becomes end plate potential and this end plate potential ultimately reaches to the threshold potential7. This leads to opening of voltage-gated sodium ion channel on the motor end plate. The heavy influx of sodium ions then leads to threshold potential and this further leads to the generation of action potential in the muscle and this leads the way to muscle contraction. The enzymes responsible for breakdown the acetylcholine are called as acetylcholinesterases. The development of the Myasthenia Gravis or pathogenesis starts with the destruction of acetylcholine receptor, lipoprotein-related protein 4 (LRP4), Muscle specific kinase (MuSK), or agrin at the neuromuscular junction by the antibodies. MuSK is a receptor tyrosine kinase at the motor end plate that plays a very important role in the formation of the neuromuscular junction (NMJ) . MuSK produces the signal when activated by the ligand lipoprotein-related protein 4. Its affinity for its receptor is increased by agrin. Agrin is neuron-derived heparansulfate proteoglycan. Muscle specific kinase regulates the concentration of cholinergic receptors on the postsynaptic membrane. It is very important for consideration that in 85% of people with Myasthenia Gravis, the antibodies are directed against cholinergic receptors and in 15% of people with Myasthenia Gravis; the antibodies are directed against the MuSK proteins. In both the cases, one thing is common; the numbers of cholinergic receptors get decreased. These all lead to the weakness of muscle. Another important thing to remember is that in all the diseases related to the disruption of neuromuscular transmission like Myasthenia Gravis, there is the painless muscular weakness. In a normal individual, the end plate potential always goes above the threshold potential and results in an action potential. The amplitude of endplate potential that is needed above the threshold value to generate the action potential (muscle fiber-action potential) is known as the safety factor. In Myasthenic people, this safety factor gets reduced and this manifests as muscular weakness. This is all due to the reduction in the number of the cholinergic receptors.[M. N. Meriggioli, et.al., 2009]

Causes :

Antibodies

Myasthenia gravis is an autoimmune disease, which means the immune system—which normally protects the body from foreign organisms—mistakenly attacks itself.

Myasthenia gravis is caused by an error in the transmission of nerve impulses to muscles. It occurs when normal communication between the nerve and muscle is interrupted at the neuromuscular junction—the place where nerve cells connect with the muscles they control.

Neurotransmitters are chemicals that neurons, or brain cells, use to communicate information. Normally when electrical signals or impulses travel down a motor nerve, the nerve endings release a neurotransmitter called acetylcholine that binds to sites called acetylcholine receptors on the muscle. The binding of acetylcholine to its receptor activates the muscle and causes a muscle contraction.

In myasthenia gravis, antibodies (immune proteins produced by the body's immune system) block, alter, or destroy the receptors for acetylcholine at the neuromuscular junction, which prevents the muscle from contracting. This is most often caused by antibodies to the acetylcholine receptor itself, but antibodies to other proteins, such as MuSK (Muscle-Specific Kinase) protein, also can impair transmission at the neuromuscular junction.

The thymus gland

The thymus gland controls immune function and may be associated with myasthenia gravis. It grows gradually until puberty, and then gets smaller and is replaced by fat. Throughout childhood, the thymus plays an important role in the development of the immune system because it is responsible for producing T-lymphocytes or T cells, a specific type of white blood cell that protects the body from viruses and infections.

In many adults with myasthenia gravis, the thymus gland remains large. People with the disease typically have clusters of immune cells in their thymus gland and may develop thymomas (tumors of the thymus gland). Thymomas are most often harmless, but they can become cancerous. Scientists believe the thymus gland may give incorrect instructions to developing immune cells, ultimately causing the immune system to attack its own cells and tissues and produce acetylcholine receptor antibodies—setting the stage for the attack on neuromuscular transmission.

Signs and symptoms :

Myasthenia gravis (MG) weakens and fatigues the body's *voluntary muscles* (those we can move at will). It does not damage the musculature of the heart or the gastrointestinal tract.

MG can affect any of the body's voluntary muscles, but it tends to affect the muscles that control movement of the eyes and eyelids, causing *ocular* weakness. Consequently, a partial paralysis of eye movements *(ophthalmoparesis)*, double vision (*diplopia*), and droopy eyelids (*ptosis*) are usually among the first symptoms of MG. More than 50% of patients present with ocular symptoms of ptosis and/or diplopia. Of those who present with ocular manifestations, about half will develop generalized disease within two years. [1,2,3]

In generalized MG, weakness tends to spread sequentially from the face and neck to the upper limbs, the hands, and then the lower limbs. It may become difficult to lift the arms over the head, rise from a sitting position, walk long distances, climb stairs, or grip heavy objects.

Weakness and fatigue in the neck and jaw also can occur early in MG. This *bulbar* weakness — named for the nerves that originate from the bulblike part of the brainstem — can cause difficulty with talking (dysarthria), chewing, swallowing (dysphagia), and holding up the head. About 15% of patients present with bulbar symptoms. Bulbar weakness tends to give speech a slurred, nasal quality. It also can lead to frequent choking spells and make eating unpleasant and tiresome.

Limb weakness alone is highly uncommon and can be seen in only 5% of MG patients. In some rare cases, weakness may spread to muscles in the chest that control breathing

This disease starts gradually and does not involve sudden weakness. On sustained or repeatedly movement or muscle contraction, patient movement decreases gradually and this is the very important point to consider as it differentiates this disease from Lambert Eaten Syndrome. The initial symptoms which a patient presents to the doctor are extraocular motor disturbances, due to which patient develops ptosis (drooping eyelid) or diplopia (as extraocular muscles are weak, so eyeball cannot move; due to which there is perception of two images of a single object) and this occurs in majority of patients that is approximately 85% of patients. Ptosis can be unilateral or bilateral and this is shown in Figure 1 and 2. Weakness is limited to the ocular muscles in about 10 to 40% of patients and the rest of the patients have the progressive weakness

for the first two years that involves oropharyngeal and limb muscles. There is fluctuating muscle weakness which is a main characteristic feature of Myasthenia gravis that differentiates it from other disorders having the similar weakness. Patients come to the physician with a specific muscular weakness rather than generalized fatigue.

Weakness in the bulbar muscles can be seen during the disease progression in 60% of patients and this is presented as difficulty in chewing, swallowing of food (dysphagia), motor speech disorder or impaired speech production (dysarthria).In 15 % of patients, bulbar symptoms may be the initial presentation. The disease rarely involves respiratory muscles and if becomes severe, then myasthenia crisis may occur. When it involves proximal muscles, then arms get more affected than legs. Neck and extensor muscles are commonly affected and due to this, the weight of the head overcomes the extensor and the patient suffers from 'dropped head syndrome.

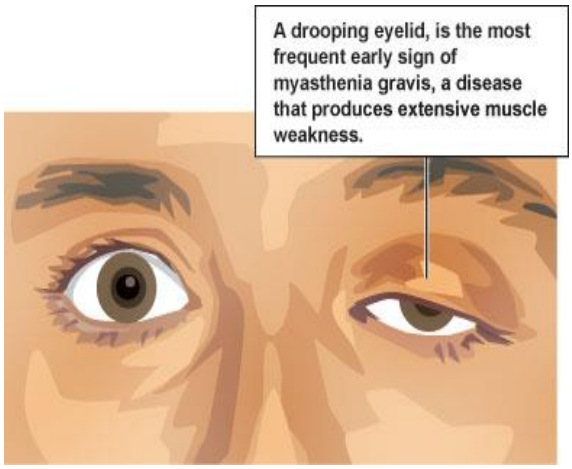

Fig 1

Historical Aspect :

The first reported case of MG is likely to be that of the Native American Chief Opechancanough, who died in 1664. It was described by historical chroniclers from Virginia as "the excessive fatigue he encountered wrecked his constitution; his flesh became macerated; the 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"In 1893, Samuel Goldflam (Warsaw, Poland) described three cases with complete description of myasthenia and also analyzed the varying presentations, severity, and prognosis of his cases. Due to significant contributions of Wilhelm Erb and later of Samuel Goldflam, the disease was briefly known as "Erb's disease" and later for a brief time, it was called "Erb-Goldflam syndrome" The first two words of this syndrome gradually got accepted as the formal name of this disorder. He also demonstrated a phenomenon, that later came to be known as "Mary Walker effect" after she herself observed and described the same finding in 1938 [Gronseth GS, et.al., 2000].

This was reported as "if you stimulate one group of muscles to exhaustion, weakness is apparent in muscles that are not stimulated; an evidence of a circulating factor causing neuromuscular weakness".In 1934, Mary Walker realized that MG symptoms were similar to those of curare poisoning, which was treated with physostigmine, a cholinesterase inhibitor. She demonstrated that physostigminepromptly improved myasthenic symptoms. In 1937, Blalock reported improvement in myasthenic patients after thymectomy. Following these discoveries, cholinesterase inhibitor therapy and thymectomy became standard and accepted forms of treatment for MG.[Pascuzzi RM. Et.al., 1994].

Classification of MG:

Clinical Classification

The Myasthenia Gravis Foundation of America (MGFA) clinical classification divides MG into 5 main classes and several subclasses. It is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy. It should not be used to measure outcome and is as follows.[Gronseth GS, et.al., 2000]

Class I MG is characterized by the following:

any ocular muscle weakness.
may have weakness of eye closure.
all other muscle strengths are normal.
Class II MG is characterized by the following:
mild weakness affecting muscles other than ocular muscles,
may also have ocular muscle weakness of any severity.

Class IIa MG is characterized by the following:
predominantly affecting limb, axial muscles, or both
may also have lesser involvement of oropharyngeal muscles.

Class IIb MG is characterized by the following:
predominantly affecting oropharyngeal, respiratory muscles, or both,
may also have lesser or equal involvement of limb, axial muscles, or both.

Class III MG is characterized by the following:

moderate weakness affecting muscles other than ocular muscles,
may also have ocular muscle weakness of any severity.

1. early-onset MG: age at onset <50 years. Thymic hyperplasia, usually females,
2. late-onset MG: age at onset >50 years. Thymic atrophy, mainly males,
3. thymoma-associated MG (10%–15%)
4. MG with anti-MUSK antibodies,
5. ocular MG (oMG): symptoms only affecting extraocular muscles,
6. MG with no detectable AChR and muscle-specific tyrosine kinase (MuSK) antibodies.

MG patients with Thymoma almost always have detectable AChR antibodies in serum. Thymoma-associated MG may also have additional paraneoplasia-associated antibodies (e.g., antivoltage-gated K+ and Ca++ channels, anti-Hu, antidihydropyrimidinase-related protein 5, and antiglutamic acid decarboxylase antibodies

About 15% of generalized MG patients do not have anti-AChR antibodies in current lab assays. In 40% of this subgroup, antibodies to MuSK and another postsynaptic neuromuscular junction (NMJ) protein, are found. They have atypical clinical features like selective facial, bulbar, neck, or respiratory muscle weakness with occasional marked muscle atrophy and with relative sparing of the ocular muscles. Respiratory crises are more common with involvement of muscle groups like paraspinal and upper esophageal muscles. Enhanced sensitivity, nonresponsiveness, or even clinical worsening to anticholinesterase medications has also been reported. Disease onset is earlier with female predominance and thymus histology is usually normal .Seronegative MG lacks both anti-AChR and anti-MuSK antibodies and forms a clinically heterogenous group with purely ocular, mild generalized, or severe generalized disease. Some patients may have low-affinity anti-AChR antibodies, nondetectable by current assays. They are essentially indistinguishable from patients with anti-AChR antibodies in terms of clinical features, pharmacological treatment response, and possibly even thymic abnormalities.[Pascuzzi RM. Et.al., 1994]

Diagnostic Tests:

Edrophonium or tensilon test: The drug edrophonium is very commonly used for testing the improvement in the muscle strength. Edrophonium is a short acting and rapid acting anticholinesterase inhibitor that is it starts the action within 30 seconds and shows the action for approximately 5 minutes. When we perform this test, an important thing that should be taken into the consideration is that we should have atropine ready at the bedside. As edrophonium exerts muscarinic effects like salivation, excessive lacrimation, bradycardia, bronchospasm, etc. and can threaten the life. The edrophonium test is considered to be positive only when there is the undeniable improvement in the muscle strength. Generally, the patients who have cranial muscles weakness or restricted extra-ocular movement show a positive result. In other muscles, the muscarinic effect of edrophonium can complicate the measurement of muscle strength and makes the result difficult for interpretation. At initial, 2 mg should be given intravenously followed by 2 mg, 3 mg, and 3 mg if required. There should be one minute period of observation after each dose. If in any dose, there is a significant improvement in the strength of muscle, then we consider the test as positive else negative. The sensitivity of this test has been found to be 71.5% to 95% for the diagnosis of myasthenia gravis.

Ice Pack Test:

This test is generally performed for those myasthenic people who have ptosis with contraindication of edrophonium. It is a non-pharmacological test.

Electrophysiological Test:

There are two tests under this category and they are single fiber electromyography and repetitive nerve stimulation study. In repetitive nerve stimulation study, the amplitude of action potentials is measured when a muscle is repetitively stimulated 5 times at a frequency of 2 to 5 Hz. A decrease in the amplitude of the signal by greater than or equals to 10% between the first and the fifth evoked muscular action potential is considered as the positive test for Myasthenia gravis. The test comes to be abnormal in the 50% people with ocular myasthenia gravis and 75% people with generalized myasthenia gravis .

Single fiber electromyography is the most commonly used electrophysiological diagnostic test for myasthenia gravis. Whenever possible, it should be done on weak muscles. In this, the action potential of muscle fiber generated by the same motor neuron is recorded by the help of special needle (25 µm diameter) electrode. This technique helps to record and identify the action potential of individual muscle fiber having innervations of a same motor neuron. The selectivity of the test increases further by using the high-pass filter of 500 Hz. We look at the jitter value in the Myasthenia gravis patient. The jitter value is the variation in the action potential of the second related to the

first. The jitter value increases in the myasthenia as the safety factor reduces. The sensitivity of the test in Myasthenia gravis people is 95 to 99%, if appropriate muscles (facial and limb muscle) are examined. Diseases like myositis, peripheral neuropathy, and motor neuron diseases can interfere with the results.[]

Immunological Test:

There are different types of antibodies that are present and found in the myasthenia gravis people. Examples are acetylcholine receptor antibodies, MuSK antibodies, Anti-striated muscle antibodies, antibodies against titin (skeletal muscle protein), etc. In 10 % of patients, results are seronegative. In these patients, diagnosis is done on the basis of clinical features, response to anticholinesterases and electrophysiological tests. There is one antibody named antistriational antibodies that are nonpathogenic and are directed against contractile elements of the skeletal muscle. More than 90% of the patients with myasthenia gravis and thymoma have these antibodies and one-third of patients with thymoma without Myasthenia gravis are having antistriated antibodies. Those who do not have thymoma but they are having Myasthenia gravis, also have this antibody. In younger patients, these antibodies can prove to be useful in patients with thymoma. It has been demonstrated that in 80% of patients who are myasthenia gravis but thymoma have these antibodies. The main role is of those antibodies which are directed against acetylcholine receptors and muscle specific tyrosine kinase receptors; more than 80% of patients with generalized Myasthenia gravis and more than 10% of patients with ocular Myasthenia gravis have serum positive acetylcholinergic receptor antibodies. The concentration of these antibodies is low or may be absent at early stage or symptoms onset and elevate at the later stage. Sometimes, acetylcholine receptor binding antibodies elevate in the persons with inflammatory neuropathy, thymoma without Myasthenia gravis, rheumatoid arthritis patients taking D- penicillamine, amyotrophic lateral sclerosis, SLE (systemic lupus erythematosus) and the relatives of the patients with Myasthenia gravis. So in a nutshell, we can say that an increased concentration of acetylcholine receptor directed antibodies with relevant clinical presentations confirms the diagnosis of Myasthenia gravis. In about 40% of patients who are seronegative for acetylcholine receptors antibodies, have seropositive for anti-muscle protein tyrosine kinase proteins antibodies. Some other patients, who are seronegative for these two types of antibodies, have antibodies against agrin. Agrin is a molecule that is produced by motor neurons and induces the aggregation of nicotinic ion channel (acetylcholine receptors) on the motor end plate. Lipoprotein-related protein 4 acts as a receptor for agrin. Antibody against this receptor is present in the patient (2-27%) who is seronegative to nicotinic cholinergic receptor and muscle specific tyrosine kinase antibodies.[Pascuzzi RM. Et.al., 1994]

CT SCAN, Radiography and MRI :

Radiography is the heart and core of the modern medicine. Chest CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) is necessary for all the individuals with the Myasthenia gravis to confirm the presence or absence of thymic hyperplasia or thymoma. Radiography may identify the thymoma as anterior mediastinal mass. Smaller thymoma is many times not detected by radiography. CT or MRI of brain and orbit become even more important if the patient has ocular Myasthenia gravis to figure out the mass lesions compressing the cranial nerve.[Gronseth GS, et.al., 2000]

Treatment of Myasthenia gravis:

With the continued research and findings in the field of molecular immunology and versatile immune response, it has become easier to manage the conditions and its manifestations. Treatment depends on different numbers of factors like the severity of disease, characteristics of the patient, the degree of functional impairment, etc. There are basic therapies that are used for the treatment or the management of Myasthenia gravis. These are the treatment of disease with the acetylcholinesterase inhibitor, treatment with the corticosteroid and other nonsteroidal immunosuppressant drugs, intravenous immune globulin and surgical removal of thymus that is called as Thymectomy, use of immunosuppressant drug and plasmapheresis. So, description about all is given below.[Vernino S, et.al., 2004]

Non Steroidal Immunosuppressant Drugs:

Drugs like azathioprine and cyclophosphamide prevent the clonal expansion of T and B lymphocytes. Azathioprine is a purine antimetabolite that has more immunosuppressant action than the antitumor action. It affects the differentiation and function of T cells selectively. Immune cells take the azathioprine and convert it into an active metabolite that is 6-mercaptopurine17. 6-mercaptopurine then undergoes further transformations and inhibits the de novo purine synthesis and cause damage to the DNA. It has been found useful in 70 to 90 percent of patients with the Myasthenia gravis. Patients, who do not respond to corticosteroid, respond to azathioprine. It

generally takes very long period to show the effects, usually 10-15 months. Leukopenia and hepatotoxicity are the major side effects. Cyclophosphamide is used both orally and intravenously. It tends to cause less damage to platelets; rather it causes alopecia and cystitis. After one year, many patients become asymptomatic. Cyclosporine is a cyclic polypeptide that has greatly increased the success of organ transplantation. It selectively inhibits T cell proliferation, a response of inducer T cells to IL-1 and IL-2 production. It is generally used with corticosteroids or methotrexate. Maximum effectiveness comes after 6 to 7 months of treatment.

The newer drug mycophenolatemofetil (MMF) which is a prodrug of mycophenolic acid inhibits the inosine monophosphate dehydrogenase, which is an enzyme that is important for the de novo synthesis of guanosine nucleotides in the T and B cell.

Corticosteroids:

Corticosteroids were the first and most commonly used immunosuppressant medications in MG. Prednisone is generally used when symptoms of MG are not adequately controlled by cholinesterase inhibitors alone. Good response can be achieved with initial high doses and then tapering it to the lowest dose to maintain the response. Temporary exacerbation can occur after starting high doses of prednisone within the first 7–10 days which can last for several days.In mild cases, cholinesterase inhibitors are usually used to manage this worsening. In cases known to have severe exacerbations, plasma exchange or IVIg can be given before prednisone therapy to prevent or reduce the severity of corticosteroid-induced weakness and to induce a more rapid response. Oral prednisone might be more effective than anticholinesterase drugs in oMG and should therefore be considered in all patients with oMG.[Pascuzzi RM. Et.al., 1994]

Long-Term Immune Therapies : The goal of immune-directed therapy of MG is to induce a remission or near remission of symptoms and maintain it**.**

Intravenous Immunoglobulin Therapy (IVIg):

It involves isolating immunoglobulins isolated from pooled human plasma by ethanol cryoprecipitation and is administered for 5 days at a dose of 0.4 g/kg/day, fewer infusions at higher doses are also used. The mechanism of action of IVIg is complex. Factors include inhibition of cytokines competition with autoantibodies, and inhibition of complement deposition. Interference with the binding of Fc receptor on macrophages, Ig receptor on B cells, and interference with antigen recognition by sensitized T cells are other mechanisms.More specific techniques to remove pathogenic anti-AChR antibodies utilizing immunoadsorption have been developed recently, which offer a more targeted approach to MG treatment. Clinical trials showed significant reduction of blocking antibodies with concomitant clinical improvement in patients treated withimmunoadsorption techniques.[Gronseth GS, et.al., 2000]

Plasmapheresis

It improves strength in most patients with MG by directly removing AChR from the circulation Typically one exchange is done every other day for a total of four to six times. Adverse effects of plasmapheresis include hypotension, paresthesias, infections, thrombotic complications related to venous access, and bleeding tendencies due to decreased coagulation factors.[Vernino S, et.al., 2004]

Short-Term Immunomodulating Therapies

Plasma exchange and intravenous immunoglobulin have rapid onset of action with improvement within days, but this is a transient effect. They are used in certain situations such as myasthenic crisis and preoperatively before thymectomy or other surgical procedures. They can be used intermittently to maintain remission in patients with MG who are not well controlled despite the use of chronic immunomodulating drugs.

Surgical Management

Some people with myasthenia gravis have a tumor in the thymus gland. If you have a tumor, called a thymoma, doctors will surgically remove your thymus gland (thymectomy).

Even if you don't have a tumor in the thymus gland, removing the gland might improve your myasthenia gravis symptoms. However, the benefits of thymectomy can take years to develop.

A thymectomy can be performed as an open surgery or as a minimally invasive surgery. In open surgery, your surgeon splits the central breastbone (sternum) to open your chest and remove your thymus gland.

Minimally invasive surgery to remove the thymus gland uses smaller incisions. It might also involve:

- Video-assisted thymectomy. In one form of this surgery, surgeons make a small incision in your neck or a few small incisions in the side of your chest. They then use a long, thin camera (video endoscope) and small instruments to see and remove the thymus gland.
- Robot-assisted thymectomy. In this form of thymectomy, surgeons make several small incisions in the side of your chest and remove the thymus gland using a robotic system, which includes a camera arm and mechanical arms.

These procedures might cause less blood loss, less pain, lower mortality rates and shorter hospital stays compared with open surgery.

Thymectomy —Surgical treatment is strongly recommended for patients with thymoma. The clinical efficacy of thymectomy in other situations has been questioned because the evidence supporting its use is not solid. Surgical treatment is strongly recommended for patients with thymoma. The benefit of thymectomy evolves over several years. Thymectomy is advised as soon as the patient's degree of weakness is sufficiently controlled to permit surgery. Patients undergoing surgery are usually pretreated with low-dose glucocorticoids and IVIg. Thymectomy may not be a viable therapeutic approach for anti-MuSK antibody-positive patients because their thymi lack the germinal centers and infiltrates of lymphocytes that characterize thymi in patients who have anti-AChR antibodies. This supports a different pathologic mechanism in anti-MuSK Ab-positive and anti-AChR Ab-positive MG.[Vernino S, et.al., 2004]

Rehabilitation

A rehabilitation program in combination with other forms of medical treatment can help relieve symptoms and improve function in MG. The primary goal is to build the individual's strength to facilitate return to work and activities of daily living. The intensity and progression of the exercise depend on the stage of the disease and overall health. An interdisciplinary approach including neuromuscular medicine, physical medicine and rehabilitation, and respiratory therapy is recommended. Physical therapy is beneficial for long-term restoration of muscle strength. Graded strengthening exercises help the individual remain as functional as possible. Occupational therapy helps the individual adapt to new ways of performing daily living tasks using energy conservation and compensatory techniques. There is speech therapy for training of esophageal speech following a tracheostomy. Vocational counseling may be needed if the current job requirements cannot be met. Psychological interventions to cope with the illness may be necessary.

Medications

- **Cholinesterase inhibitors.** Medications such as pyridostigmine (Mestinon, Regonal) enhance communication between nerves and muscles. These medications aren't a cure, but they can improve muscle contraction and muscle strength in some people.

Possible side effects include gastrointestinal upset, diarrhea, nausea, and excessive salivation and sweating.

- **Corticosteroids.** Corticosteroids such as prednisone (Rayos) inhibit the immune system, limiting antibody production. Prolonged use of corticosteroids, however, can lead to serious side effects, such as bone thinning, weight gain, diabetes and increased risk of some infections.
- **Immunosuppressants.** Your doctor might also prescribe other medications that alter your immune system, such as azathioprine (Azasan, Imuran), mycophenolatemofetil (Cellcept), cyclosporine (Sandimmune, Gengraf, others), methotrexate (Trexall) or tacrolimus (Astrograf XL, Prograf, others). These drugs, which can take months to work, might be used with corticosteroids.

Side effects of immunosuppressants, such as increased risk of infection and liver or kidney damage, can be serious.[Pascuzzi RM. Et.al., 1994]

II. CONCLUSION

We reviewed the characteristics of three types of striational antibodies (Table 1). Although 20 years have passed since the discovery of anti-titin antibodies in MG patient, the detection of striational antibodies is not routinely tested in the clinical management by all neurologist. Recently, several therapies for MG have emerged, including rituximab and antigen-specific apheresis whereas other treatments await clarification of efficacy and their role in MG [1]. The treatment of MG should be individualized according to clinical presentation or subtype, and requires a comprehensive assessment of the patient’s functional impairment and the effect of MG on his or her daily life. The detection of striational antibodies can provide information that is useful for the classification and management of MG patients.

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