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Review Article

A REVIEW ON MYASTHENIA GRAVIS

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ABSTRACT

Myasthenia gravis is an autoimmune disorder and a disease of neuromuscular transmission in which antibodies attack the cholinergic receptors and some specific components of the neuromuscular junction of the skeletal muscles. It involves painless muscular weakness and is a very rare condition. The patient is unable to contract the muscle and feels tired. Most often, the muscles which get affected are the extra-ocular muscles and the bulbar muscles due to which the patient has drooping eyelid, diplopia, difficulty in chewing, difficulty in swallowing and slurring of speech. This disease often affects women who are under the age of 35 and the men who are about 60 years old or more. Most often, there are some thymic abnormalities such as thymoma or thymic hyperplasia in the patients with Myasthenia gravis. Different types of tests are available to diagnose Myasthenia gravis like the tensilon test, electrophysiological tests, etc. more. Still, the research is going on the molecular immunology but a lot have to be discovered yet about Myasthenia gravis.

Keywords: Cholinergic, Tyrosine, Thymoma, Ptosis, Autoimmune

INTRODUCTION

The most common and the most prevalent medical disorder related to dysfunction of neuromuscular transmission is Myasthenia gravis (MG). It is a rare autoimmune disorder which involves autoantibody against the components of neuromuscular junction of the muscles and the muscles involved are the skeletal muscles[1]. Components like nicotinic or acetylcholine receptors and muscle specific tyrosine kinase are usually attacked by the antibodies. Though it is an acquired autoimmune disorder but it sometimes involves genetic reasons. Most of the patients present with symptoms like drooping eyelids, diplopia, difficulty in chewing and swallowing, etc. It is a condition which cannot be cured; however, the symptoms are managed by drugs and other techniques. Diagnosis is very important to detect the severity of disease, type or the class of Myasthenia gravis and accordingly, the treatment is initiated[2]. The most important feature of this disease is the painless muscular weakness. With the advancement in the knowledge of its pathophysiology and molecular immunology, it is becoming easier to treat the condition by various methods and this has led to a decrease in the mortality and morbidity. This article encompasses through the pathophysiology, symptoms, diagnosis, management and most important; the classification of Myasthenia gravis which has been given by Myasthenia Gravis Foundation of America that has made its management a lot easier[3].

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[4]. 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[5]. 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[6]. 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 and

this 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 potential[7]. 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) [8]. 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 heparan sulfate 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[9].

Signs and symptoms

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'[10].

Clinical classification of Myasthenia gravis

A task force was formed named Myasthenia Gravis Foundation of America by the Medical Scientific Advisory Board (MSAB) in May 1997 to fulfill the needs of grading system, universally accepted classifications, and analytical procedures for the managements of myasthenia gravis patients who are receiving the therapy and for utilization in the therapeutic research trial and this led to the development of Myasthenia Gravis Foundation of America Clinical Classification that is MGFA classification. This classification involves classes and subclasses and is given in Table 1. The table should not be used to measure the outcome[11].

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[12].

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[13].

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[14].

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 nerves[15].

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[16]:

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-mercaptopurine[17]. 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 mycophenolate mofetil (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.

Corticosteroid

It is used when the symptoms are not managed with the acetylcholinesterase inhibitor. More than 75% of patients get improvement in the symptoms from the prednisone therapy. The best response comes after 6 to 8 weeks of treatment and in those patients who have recent onset of symptoms. Patients with thymoma have a very good response before or after the thymectomy. To bring a good response, a daily dose of 1.5 to 2 mg/kg is required. Many people suffer from weakness and exacerbations mainly within 8 to 10 days and it remains for usually 7 days. Treatment is started at a low dose to minimize the exacerbations and further increased until improvement occurs. Oral prednisone may be more effective than anticholinesterase drug and hence can be used for patients having ocular Myasthenia gravis.

Plasma Exchange

This has proved itself to be useful in many patients with Myasthenia gravis. In this, the plasma containing acetylcholinergic receptor antibodies is separated from whole blood and is replaced by albumin or fresh frozen plasma. The process needs catheterization of the large caliber veins and removes the antibodies directed against receptors on the muscle end plate. This treatment solely depends on the clinical presentations of the patients. It is a short-term intervention which is useful for the management of symptoms from getting worsen. Almost every patient with acquired Myasthenia gravis has shown improvement temporarily after this method. Maximum benefit or result can come as early as after 1st treatment and as late as the fourteenth exchange. The improvement only lasts for weeks or months and then effect gets lost until thymectomy or immunosuppressive therapy is given to the patient[18].

Intravenous Immunoglobulin Therapy

It has been utilized in a number neuromuscular transmission disorders including acute and chronic inflammatory neuropathy. This method involves the isolation of immunoglobulins from pooled human plasma by the help of ethanol cryoprecipitation and it is administered for 5 days at the dose of 0.4g/kg/day. Its mechanism of action is complicated to understand but possible mechanisms include the down-regulation of antibody production which is directed against cholinergic receptors at the NMJ or on the muscle end plate and an introduction of anti-idiopathic antibodies. Improvement is seen in 50 to 100 % of patients, usually begins within one week and lasts for a couple of months or years. Usually, it is considered as safe; however, it causes rare complications such as increased blood viscosity and some other problems related to a large volume of infused preparation. When compared to plasma exchange, immunoglobulin therapy has fewer cost advantages with a cost-benefit ratio of 2:1. Very recently, some subcutaneous preparations have been made available so as to benefit those patients with Myasthenia gravis who have problems related to the intravenous access of the vein[19].

Table 1: Classes and symptoms of Myasthenia gravis[20]

CLASSES	CLINICAL CHARACTERISTICS
CLASS 1	Any ocular muscle weakness
CLASS 2	Mild weakness other than ocular muscle
CLASS 2A	Predominantly affects limb, axial muscles or both
CLASS 2B	Predominantly affecting oropharyngeal muscles and respiratory muscle
CLASS 3	Moderate weakness affecting other than ocular muscle
CLASS 3A	Predominantly affecting limb, axial muscles or both
CLASS 3B	Predominantly oropharyngeal and respiratory muscles
CLASS 4	Severe weakness other than ocular muscles
CLASS 4A	Predominantly involves limb, axial muscles or both
CLASS 4B	Predominantly oropharyngeal and respiratory muscles
CLASS 5	Defined by the need for intubation with or without ventilation

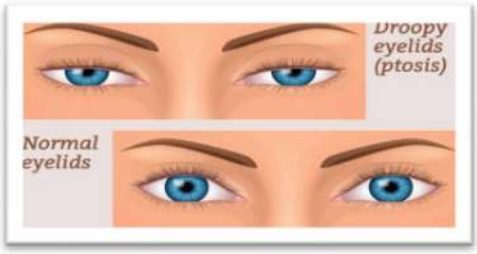

Figure 1: Bilateral Ptosis[21]

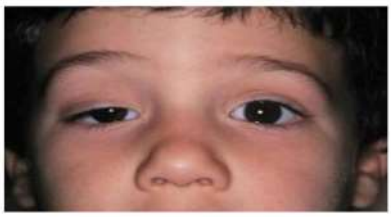

Figure 2: Unilateral Ptosis[22]

CONCLUSION

Myasthenia gravis is a rare disorder of immune system in which the immune system starts producing antibodies which are directed towards the components of the neuromuscular junction. They attack mostly the cholinergic receptors and the muscle-specific tyrosine kinase. It is a condition which involves different treatment approaches like anticholinesterase inhibitors, thymectomy, steroids, etc. These are all very necessary so as to prevent the life-threatening situations like Myasthenia crisis. Treatment only manages the symptoms but is not helpful to eradicate the root cause of the disease. We can also take some help of Ayurveda rather hyping up the Allopathic treatment. Its symptoms can relapse or remit in any patient.

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