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Myasthenia gravis

R. Jona methusala, P. Anusha

M. Pharm(Ph.D), B. Pharmacy

Dr. Kv subba reddy institute of pharmacy

ABSTRACT

Myasthenia gravis is an autoimmune disorder caused by autoantibodies against the nicotinic acetylcholine receptor on the postsynaptic membrane at the neuromuscular junction and characterised by weakness and fatigability of the voluntary muscles. It has a bimodal peak of incidence with first peak in the third decade and the second peak in the sixth decade. It is probably underdiagnosed in the very old population. Our understanding of the pathogenesis, immunology, and molecular biology of myasthenia gravis has greatly improved in last three decades. It is almost always possible to establish the diagnosis of myasthenia gravis with the current tests. The modern treatment is highly successful and the mortality of treated myasthenia gravis is practically zero. However, there are still important gaps in our knowledge of the origin of myasthenia gravis, the factors that contribute to chronic disease, and the way to cure the disease. In this article the current knowledge of the various aspects of myasthenia gravis are outlined.

KEYWORDS

AChR, acetylcholine receptor, EPP, endplate potential, MRI, magnetic resonance imaging, MuSK, muscle specific protein kinase, myasthenia gravis, autoimmune disorder.

INTRODUCTION

Myasthenia gravis is a potentially serious but treatable organ specific autoimmune disorder characterised by weakness and fatigability of the voluntary muscles that is caused by autoantibodies against the nicotinic acetylcholine receptor (AChR) on the postsynaptic membrane at the neuromuscular junction.[1][2] Thomas Willis (1672) was probably the first to describe patients with weakness of limb muscles increasing during the course of the day and progressive tongue weakness provoked by "long, hasty or laborious speaking".[3] It was more than two centuries later when another patient with bulbar and limb muscle weakness who died of respiratory failure was reported.[4] The lesion was initially thought to be in the medulla oblongata but necropsy did not show any abnormality in the medulla. Subsequently, several case reports describing patients with the early or predominant bulbar weakness, and those with the weakness worsening during the course of the day appeared in the literature. Jolly (1895) described a progressive decline in the tetanic tension of the indirectly stimulated muscles with the repeated stimulations that improved with rest. He gave the disease its name: myasthenia gravis pseudoparalytica.[5] The earlier reports suggested a "toxin probably of

microbial origin"[6] or "some toxic, probably autotoxic, agent"[7] causing damage of the lower motor neurons to produce myasthenic weakness. The demonstration by Dale and Feldberg of acetylcholine as a neurotransmitter at the motor endplate paved way for the future developments in pathogenesis, diagnosis, and the treatment of myasthenia gravis.[8] Harvey and Marsland described the decremental response of the evoked muscles to repeated stimuli in myasthenia gravis. Simpson proposed a new theory that myasthenia gravis was an autoimmune disorder based on its association with the other autoimmune diseases, the thymic abnormalities noted in myasthenia gravis, and the fluctuating course of the disease.[9] That the damage in myasthenia gravis is at the postsynaptic level was demonstrated by Engel and Santa in ultrastructural studies of the motor endplate. Neostigmine, an orally administered anticholinesterase, was first used in myasthenia gravis in 1935.[10] Subsequently, corticosteroids and other immunosuppressants,were found to be useful in treatment and Blalock reported beneficial effects of thymectomy.Lindstorm and his team demonstrated circulating antibodies directed against the AChR protein in up to 87% of cases of myasthenia gravis.Recently, antibodies that bind to MuSK, a muscle specific protein kinase, have been described in a subgroup of patients with myasthenia gravis who do not have antibodies against AchRs.[11]

Muscular weakness and fatigability are the hallmarks of myasthenia gravis. They are caused by an antibody-mediated autoimmune attack directed against AChRs at neuromuscular junctions[12]. There are several mechanisms by which the autoantibodies reduce the number of available AChRs at neuromuscular junctions. The molecular structure of nicotinic AChR is now well characterised and the receptor has been purified from a variety of sources, including human muscle.[13] An experimental model of myasthenia gravis has been produced by immunisation of animals with AChRs. This has greatly helped our understanding of the disease mechanisms. There have been significant advances in the diagnosis and treatment of myasthenia gravis. It used to be a very disabling and often fatal (and, hence, the name gravis) disease in the past. However, modern immunotherapy has dramatically improved the prognosis and nearly all patients are now able to lead full, productive lives.[14]

Despite these advances, there are still important gaps in our knowledge. We do not know the factors that initiate and maintain the autoimmune response in myasthenia gravis. A large amount of work is in progress to elucidate these mechanisms.[15]

What is Myasthenia Gravis?

Myasthenia is a neuromuscular disorder that causes weakness in the skeletal muscles, which are the muscles that allow your body to move. MG is a relatively uncommon condition that affects about 20 people out of every 100,000 in the United States. However, because it is underdiagnosed, the prevalence may be higher.

FIG.1 Myasthenia Gravis

Who Might Get Myasthenia?

Myasthenia gravis primarily affects women between the ages of 20 and 40 and men between 50 and 80. Teenagers account for approximately one-tenth of all cases. The disease can affect people of all ages, but it is uncommon in children.

These factors raise the risk:

- History of other autoimmune diseases, such as rheumatoid arthritis and lupus Infections
- Medications for malaria, heart arrhythmias, and cancer
- Surgical procedures
- Thyroid disease

What Causes Myasthenia?

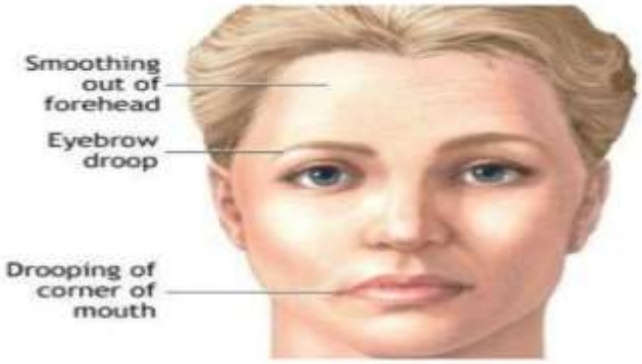
1. Antibodies

Myasthenia is caused by a faulty nerve impulse transmission to the muscles. It happens when normal nerve-muscle communication is disrupted at the neuromuscular junction—the point at which nerve cells connect with the muscles they control.

2. Thymus gland

The thymus gland regulates immune function and may be linked to myasthenia gravis. It gradually grows until puberty, shrinks, and is replaced by fat. The thymus plays an important role in developing the immune system throughout childhood because it is responsible for producing the T cells, a type of white blood cell that protects the body from viruses and infections.

SIGNS&SYMPTOMS



SYMPTOMS:

- The first noticeable symptom is weakness of the **eye muscles**, difficulty in swallowing and slurred speech may also be the first signs.
- Muscles that control eye and eyelid movement, facial expressions, **chewing, talking and swallowing** becomes weaker.
- The muscles that control **breathing** and neck and limb movements can also be

FIG.2 Signs&Symptoms

ETIOLOGY

There are four classes based on the etiology:

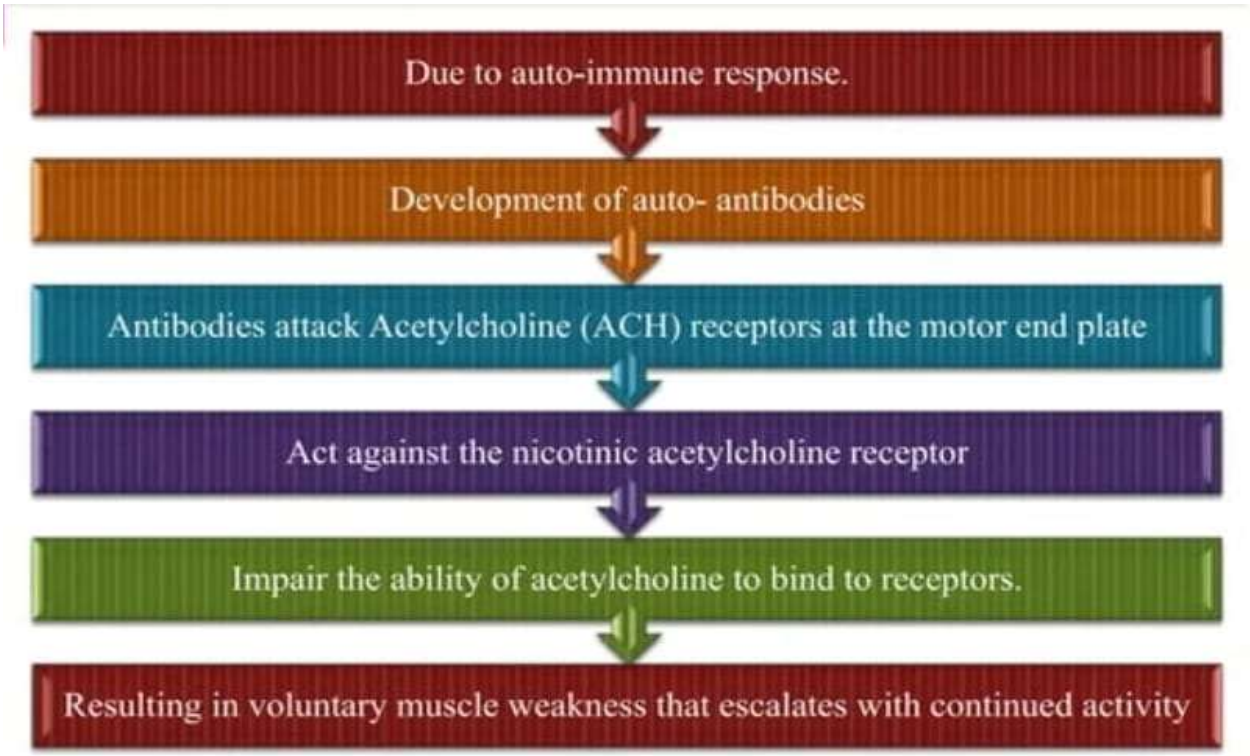
1.Acquired autoimmune.

2.Transient neonatal caused by the passive transfer of maternal anti-AChR antibodies

3.Drug induced: D-penicillamine is the prototype of drug induced myasthenia gravis. Clinical presentation may be identical to typical acquired autoimmune myasthenia gravis and the antibody to AChR may be found.25 Disease tends to remit after cessation of the drug. Other drugs that can cause myasthenia-like weakness or that exacerbate weakness of myasthenia gravis include curare, aminoglycosides, quinine, procainamide, and calcium channel blockers.

4.Congenital myasthenic syndromes (AChR deficiency, slow channel syndrome, and fast channel syndrome) are distinct heritable disorders of postsynaptic neuromuscular transmission with characteristic age of onset, pathology, electrophysiology, and treatment. [19]

PATHOPHYSIOLOGY



EPIDEMIOLOGY

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. This autoimmune disease 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 muscles (EOMs) presents as the initial symptom, usually progressing to involve other bulbar muscles and limb musculature, resulting in generalized myasthenia gravis (gMG). In about 10% of myasthenia gravis patients, symptoms are limited to EOMs, with the resultant condition called ocular MG (oMG). Sex and age appear to influence the occurrence of myasthenia gravis. Below 40 years of age, female : male ratio is about 3 : 1; however, between 40 and 50 years as well as during puberty, it is roughly equal. Over 50 years, it occurs more commonly in males. Childhood MG is uncommon in Europe and North America, comprising 10% to 15% of MG cases.[22] In Asian countries though, up to 50% of patients have onset below 15 years of age, mainly with purely ocular manifestations.

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 1672, the English physician Willis first described a patient with "fatigable weakness" involving ocular and bulbar muscles described by his peers as "spurious palsy."

In 1877, Wilks (Guy's Hospital, London) described the case of a young girl after pathological examination as "bulbar paralysis, fatal, no disease found.

In 1879, Wilhelm Erb (Heidelberg, Germany) described three cases of myasthenia gravis in the first paper dealing entirely with this disease, whilst bringing attention to features of bilateral ptosis, diplopia, dysphagia, facial paresis, and weakness of neck muscles .

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 physostigmine promptly 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 otreatmentfor MG.

In 1959-1960, Nastuk et al. and Simpson independently proposed that MG has autoimmune etiology.

In 1973, Patrick and Lindstrom were able to induce experimental autoimmune MG (EAMG) in a rabbit model using muscle-like acetylcholine receptor (AChR) immunization.

In the 1970s prednisone and azathioprine were introduced as treatment modalities for MG followed by plasma exchange that was introduced for acute treatment of severe MG, all supporting the autoimmune etiology.[24]

CLASSIFICATION OF MG

Subtypes of MG are broadly classified as follows:

(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 muscle,[25]

(6)MG with no detectable AChR and muscle-specific tyrosine kinase (MuSK) antibodies.

CLINICAL CLASSIFICATION

The Myasthenia Gravis Foundation of America (MGFA) clinical classification divides MG into 5 main classes and several subclasses [26]. 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.

Class I MG is characterized by the following:

(i)any ocular muscle weakness.

(ii)may have weakness of eye closure.

(iii)all other muscle strengths are normal.[27]

Class II MG is characterized by the following:

(i)mild weakness affecting muscles other than ocular muscles,

(ii)may also have ocular muscle weakness severity.

Class IIa MG is characterized by the following:

(i)predominantly affecting limb, axial muscles, or both

(ii)may also have lesser involvement of oropharyngeal muscles.

Class IIb MG is characterized by the following:

(i)predominantly affecting oropharyngeal, respiratory muscles, or both,

(ii)may also have lesser or equal involvement of limb, axial muscles, or both.

Class III MG is characterized by the following:

(i)moderate weakness affecting muscles[28] other than ocular muscles,

(ii)may also have ocular muscle weakness of any severity.

Class IIIa MG is characterized by the following:

(i)predominantly affecting limb, axial muscles, or both,

(ii)may also have lesser involvement of oropharyngeal muscles.

Class IIIb MG is characterized by the following:

(i)predominantly affecting oropharyngeal, respiratory muscles, or both,

(ii)may also have lesser or equal involvement of limb, axial muscles, or both.

Class IV MG is characterized by the following:

(i)severe weakness affecting muscles other than ocular muscles,

(ii)may also have ocular muscle weakness of any severity.

Class IVa MG is characterized by the following:

(i)predominantly affecting limb, axial muscles, or both.

(ii) may also have lesser involvement of oropharyngeal muscles.

Class IVb MG is characterized by the following:

(i)predominantly affecting oropharyngeal, respiratory muscles or both,

(ii)may also have lesser or equal involvement of limb, axial muscles, or both.[29]

Class V MG is characterized by the following:

(i)intubation with or without mechanical ventilation, except when employed during routine postoperative management,

(ii)the use of feeding tube without intubation places the patient in class.

ETIOPATHOGENESIS OF MYASTHENIA GRAVIS

It is important to understand the basic concepts of anatomy and physiology of the neuromuscular junction to comprehend the aetiopathogenesis of myasthenia gravis and related disorders.

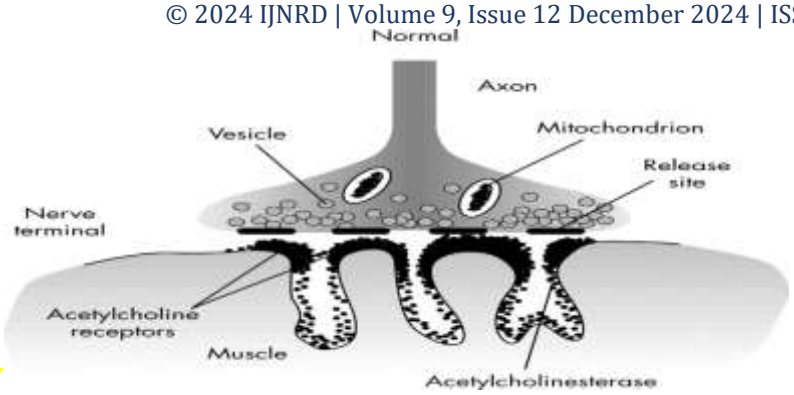


Fig.5 Normal Neuromuslar Junction

ANATOMY OF A NORMAL NEUROMUSCULAR JUNCTION

The synaptic junction involving a motor nerve terminal and the muscle membrane is the most extensively studied synapse. Its principal job is to amplify a relatively weak nerve impulse to a strong electrical impulse in the muscle capable of producing a muscle contraction. There are three important components of the neuromuscular junction:[30] presynaptic, synaptic, and postsynaptic.

Presynaptic

The presynaptic neuromuscular junction comprises a motor nerve terminal and the structures contained in it. Acetylcholine is synthesised in the nerve terminal from acetyl CoA and choline by the enzymatic action of choline transferase. It is packaged in the vesicles and is released into the synaptic cleft on arrival of a nerve impulse. Each vesicle contains from nearly 8000 to 13 000 acetylcholine molecules, termed the "quanta". Release of the acetylcholine into synaptic cleft by nerve stimulus requires calcium and the process is called stimulus-secretion coupling. Calcium influx occurs through the voltage gated calcium channels that are situated near the release sites. In Lambert-Eaton myasthenic syndrome, autoantibodies against these voltage gated channels produce muscle weakness by interfering with the acetylcholine release. The entry of calcium triggers the fusion of the vesicle with the presynaptic nerve cell membrane.26 Subsequently, the contents of the vesicles are released into the synaptic cleft by the process of exocytosis. A number of proteins are involved in this process. Destruction of any of these proteins (for example, by various serotypes of botulinum toxin) can interfere with the quantal release of acetylcholine to cause paralysis. Once acetylcholine is released, the presynaptic membrane is recaptured by pinocytosis, and the vesicles are remade and repleted with acetylcholine. It is worth noting that the acetylcholine release sites are located opposite to the peaks of the folds in the postsynaptic membrane where AChRs are clustered at high concentrations.

Synaptic clefts

Synaptic clefts are divided into primary and secondary synaptic clefts. The primary cleft is the space that separates presynaptic nerve membrane from the postsynaptic membrane muscle membrane. It is approximately 70 nm wide and its length is equal to the presynaptic membrane. It has no lateral boundaries and, therefore, it communicates with the extracellular space. Acetylcholine is released into this space before it acts on the AChR. The secondary clefts are the spaces between the junctional folds of the postsynaptic membrane and they communicate with the primary cleft. Acetylcholinesterase is most highly concentrated in the secondary clefts. It hydrolyses acetylcholine to terminate

neuromuscular transmission so that muscle fibre can be stimulated again. The acetylcholinesterase inhibitors are used in the treatment of myasthenia gravis. By inhibiting acetylcholinesterase, they increase the availability of acetylcholine to react with the AChR and, therefore, improve transmission at the neuromuscular junction. However, an excess of acetylcholine can desensitise receptors and may worsen the weakness, the so-called cholinergic crisis. Acetylcholinesterase can be irreversibly blocked by the organophosphorous compounds. The genetic defects leading to acetylcholinesterase deficiency at the motor endplate may produce muscle weakness manifesting in infancy or childhood.

Postsynaptic

The surface of a muscle cell membrane opposite to the nerve cell terminal at the neuromuscular junction is thrown into folds (junctional folds). The normal junctional fold has a slender stalk and a terminal expansion ("peak"). AChRs are mostly concentrated in the peaks of these folds. Acetylcholinesterases are primarily located in the secondary clefts and they hydrolyse acetylcholine as described above. The structure, function, and the molecular biology of the AChR are now well understood. This has led to a better understanding of myasthenia gravis, congenital myasthenic syndromes, and the effects of several drugs and toxins that work through the neuromuscular junction.

The AChR is a glycoprotein comprising five subunits arranged around a central channel (fig 2). In an innervated muscle, these subunits are two α subunits, one β subunit, one δ subunit, and one ε subunit. In an immature or denervated muscle, the ε subunit is replacedby a γ subunit. In the resting state, ion channel of the AChR is closed. When both the α subunit binding sites are occupied, the AChR molecule twists slightly like a Chinese purse, opening the channel and allowing the entry of sodium ions into the interior of the muscle cell, which results in partial depolarisation of the postsynaptic membrane and generation of an excitatory postsynaptic potential. If the number of open sodium channels reaches threshold, a self propagating muscle action potential is generated in the postsynaptic membrane. Some of the congenital myasthenic syndromes (for example, slow channel syndrome and fast channel syndrome) are caused by the abnormalities of the AChR channels. Genes for all the subunits of the AChR have been cloned,andit is possible to produce these subunits by genetic engineering.

As mentioned above, AChRs are mostly concentrated in the peaks of these folds. This clustering of AChRs involves an interaction of several proteins including a MuSK—the protein now found to be a target for antibodies in seronegative myasthenia gravis. There is a constant turnover and renewal of the AChRs at the neuromuscular junction allowing a near complete recovery in myasthenia gravis after the autoimmune attack is brought under control.

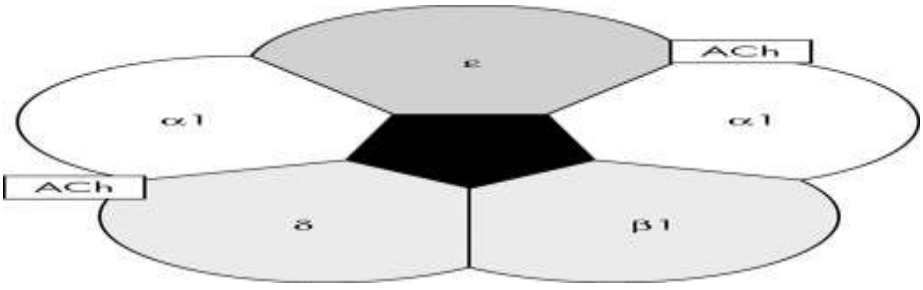


Fig.6 Ach Receptors

Anatomy and physiology of the neuromuscular junction in myasthenia gravis:

The major abnormalities of the neuromusculaer junction in myasthenia gravis include:

(a) reduced number of the AChRs leading to reduced length of the postsynaptic membrane.

(b) shortening of the synaptic folds due to destruction of the terminal expansions.

(c) widening of the synaptic clefts caused by the shortening of the junctional folds.

These changes are brought about by autoimmune attack on the postsynaptic membrane. It is worth noting that the abnormalities in myasthenia gravis are postsynaptic in location (in contrast to presynaptic abnormality in Lambert-Eaton syndrome). The consequence of these abnormalities is a reduced safety factor. As previously discussed, reduction in safety factor coupled with a normal "synaptic rundown" leads to progressive reduction in amplitude of the EPP. This leads to myasthenic weakness characterised by fatigue on exertion.

Fig.7 Neuromuscular Junction In Mg

DIAGNOSIS OF MYASTHENIA GRAVIS

In patients with a characteristic history it may be easy to make a diagnosis on clinical grounds alone. However, it is important to confirm diagnosis of myasthenia gravis before committing patients to long term treatment. It should be emphasised that the diagnosis of myasthenia gravis is mostly based on the results of the test for the antibody against AChR and the neurophysiological tests. The Tensilon test should only be used where the diagnosis is required urgently and the facilities for full resuscitation are available.

Diagnostic evaluation

- **History**
- **Physical Examination**
- **Edrophonium(tensilon) Test**
- **Blood analysis**
- **Repetitive nerve stimulation**
- **Single_ fiber electromyograohy(EMG)**
- **Imaging scans**

Physical Examination

- Muscle strength and tone
- Coordination

- Sense of touch
- Impairment of eye movement

Anticholinestarase Test

- Edrophonium chloride(tensilon) is injected intravenously, 2 mg at a time to a total of 10 mg. 30 sec after injection,facial muscle weakness and ptopis should reslove for about 5 mins.
- This immediate improvement in muscle strength after administration of this agent represent a positive test and usually confirms the diagnosis.

Blood Analsyis

- Elevated levels of acetyl choline receptor antibodies
- Anti MuSK(Muscle specific kinase) antibody.

Repetitive Nerve Stimulation

- Repetitive nerve stimulation, which repeatedly stimulates person's nerves with small pulses of electricity to tire specific muscles.
- Muscle fibers do not respond as well to repeated electrical stimulation.

Single- Fiber Electromyography(Emg)

- It consider the most sensitive test for myasthenia gravis detects impaired nerve- to- muscle transmission.

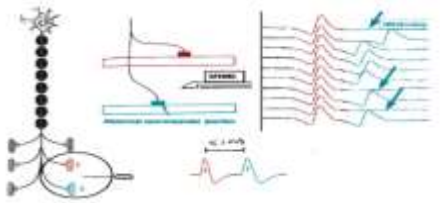


FIG.8 Single Fiber Electromyography

Imaging Scans

- CT or MRI: it's shows thymus enlargement. [32]

MANAGEMENT OF MYASTHENIA GRAVIS

Management of MG should be individualized according to patient characteristics and the severity of the disease. There are two approaches for management of MG based on the pathophysiology of the disease. The first is by increasing the amount of Acetylcholine that is available to bind with the postsynaptic receptor using an acetylcholinesterase inhibitor agent, and the second is by using immunosuppressive medications that decrease the binding of acetylcholine receptors by antibodies.

There are four basic therapies used to treat MG:

(i)symptomatic treatment with acetylcholinesterase inhibitors.

(ii)rapid short-term immunomodulating treatment with plasmapheresis and intravenous immunoglobulin,

(iii)chronic long-term immunomodulating treatment with glucocorticoids and other immunosuppressive drugs,

(iv)surgical treatment.

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors are the first-line treatment in patients with MG. Response to treatment varies from marked improvement in some patients to little or no improvement in others. Acetylcholinesterase inhibitors are used as a symptomatic therapy and act by increasing the amount of available acetylcholine at the NMJ.They do not alter disease progression or outcome. Pyridostigmine is the most commonly used drug.[34] It has a rapid onset of action within 15 to 30 minutes reaching peak activity in about two hours. The effect lasts for about three to four hours. The initial oral dose is 15–30 mg every 4–6 hours and is titrated upwards depending on the patient's response. Adverse side effects of Pyridostigmine are mostly due to the cholinergic properties of the drug such as abdominal cramping, diarrhea, increased salivation and bronchial secretions, nausea, sweating, and bradycardia. Nicotinic side effects are also frequent and include muscle fasciculation and cramping. High doses of pyridostigmine exceeding 450 mg daily, administered to patients with renal failure, have been reported to cause worsening of muscle weakness.

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.

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 .

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,[35] 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 with immunoadsorption techniques.

IVIg is considered to be safe but rare cases of complications do occur such as thrombosis due to increased blood viscosity and other complications related to large volumes of the infused preparation.

Compared to plasma exchange, IVIg is similar in terms of efficacy, mortality, and complications.However, plasma exchange (PLEX) has considerable cost advantages over IVIg with a cost benefit ratio of 2 : 1 for treatment of myasthenia gravis.

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.

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.

Nonsteroidal Immunosuppressive Agents

Azathioprine, a purine analog, reduces nucleic acid synthesis, thereby interfering with T-and B-cell proliferation. It has been utilized as an immunosuppressant agent in MG since the 1970s and is effective in 70%–90% of patients with MG.It usually takes up to 15 months to detect clinical response. When used in combination with prednisone, it might be more effective and better tolerated than prednisone alone Adverse side effects include hepatotoxicity and leukopenia.

Mycophenolate mofetil selectively blocks purine synthesis, thereby suppressing both T-cell and B-cell proliferation. Widely used in the treatment of MG, its efficacy in MG was actually suggested by a few non-randomized clinical trials.

The standard dose used in MG is 1000 mg twice daily, but doses up to 3000 mg daily can be used. Higher doses are associated with myelosuppression, and complete blood counts should be monitored at least once monthly. The drug is contraindicated in pregnancy and should be used with caution in renal diseases, GI diseases, bone marrow suppression, and elderly patients.

Cyclophosphamide administered intravenously and orally is an effective treatment for MG.More than half of the patients become asymptomatic within 1 year of treatment. Undesirable side effects include hair loss, nausea, vomiting, anorexia, and skin discoloration, which limit its use to the management of patients who do not respond to other immunosuppressive treatments.

Cyclosporine blocks the synthesis of IL-2 cytokine receptors and other proteins critical to the function of CD4+ T cells. Cyclosporin is used mainly in patients who do not tolerate or respond to azathioprine. Large retrospective studies have supported its use as a steroid-sparing agent

Tacrolimus has been used successfully to treat MG at low doses. It has the theoretical advantage of less nephrotoxicity than cyclosporine. However, there are more controlled trial data supporting the use of cyclosporine. Like other immunosuppressive agents, Tacrolimus also has the potential for severe side effects.

Surgical Management

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.[37] This supports a different pathologic mechanism in anti-MuSK Ab-positive and anti-AChR Ab-positive MG.Most experts consider thymectomy to be a therapeutic option in anti-AChR Ab-positive gMG with disease onset before the age of 50 years. [38]

FIG.9 Surgical Management

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.

CONCLUSION

Myasthenia gravis is an autoimmune disorder characterised by the weakness and fatigability of the voluntary muscles that is caused by autoantibodies against the nicotinic AChR on the postsynaptic membrane at the neuromuscular junction. Our understanding of the pathogenesis, immunology, and molecular biology of myasthenia gravis has greatly improved in the last three decades. It is almost always possible to establish the diagnosis of myasthenia gravis with the current tests. Modern treatment is highly successful and mortality of treated disease is practically zero. However, there are still important gaps in our knowledge of the origin of myasthenia gravis, the factors that contribute to chronic disease, and the way to cure the disease.[30]

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