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MYASTHENIA GRAVIS: A GRAVE MUSCULAR DISORDER

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Abstract:

Myasthenia Gravis (MG) is a rare, autoimmune neuromuscular junction disorder. Contemporary prevalence rates approach 1/5000, MG presents with painless, fluctuating, fatigable weakness involving specific muscle groups. Ocular weakness with asymmetric ptosis and binocular diplopia is the most typical initial presentation, while early or isolated weakness is less common. The course is variable, and most patients with initial ocular weakness develop bulbar or limb weakness within three years of initial symptoms.MG results from antibody- mediated, T cell-dependent immunologic attack on the endplate region of the postsynaptic membrane.

Key words:
Thymoma, Thymectomy, Mestinon, Prednisone, Azathioprine, Imuran, Mycophenolatemofetil, Pyridostigmine.

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1.Introduction:

What is Myasthenia Gravis :

Myasthenia Gravis is a rare chronic autoimmune disease marked by muscular weakness without atrophy, and caused by a defect in the action of acetylcholine at neuromuscular junctions.

It is an uncommon condition that causes certain muscles to become weak. With treatment, most people can lead a normal life. Myasthenia gravis literally means 'grave muscle weakness'. The condition can affect any muscles that we can control voluntarily. Muscles that we cannot control voluntarily, such as the heart muscles, are not affected. Myasthenia gravis most commonly affects the muscles that control eye and eyelid movement, facial expression, chewing, swallowing and talking, and the muscles in the arms and legs. Less often, the muscles involved in breathing may be affected. The muscle weakness is usually made worse by physical activity and improved by rest.[1]

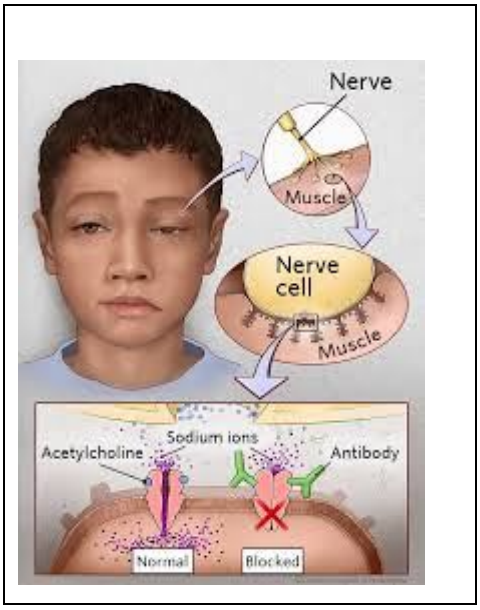

Figure No. 1: Basic mechanism of MG

Demonstrating few effects of Myasthenia gravis:

Figure 2: Effected drooping of eyelids (Ptosis)

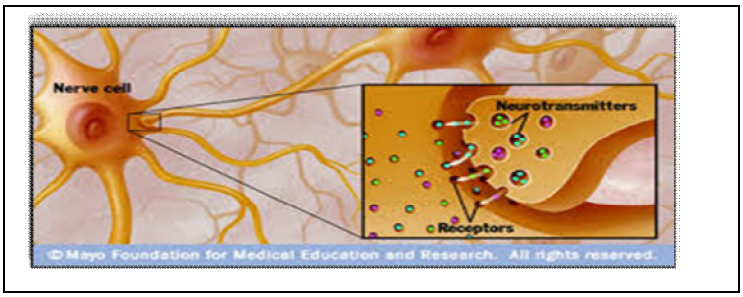

Figure No. 3: Disfunction at the neuromuscular junctions.

Causes of Myasthenia Gravis:

This condition is an autoimmune diseases, which means that it is triggered by the body's own immune system. In normal conditions, in a healthy organism, nerves control the muscle movements by sending messages through neurotransmitters that bind to specific receptors found in the nerve-muscular junctions. In myasthenia gravis, the immune system produces antibodies that prevent these chemicals from reaching the receptors, or destroy the receptor sites. As a result, the signals sent by the brain to muscles are fewer and this leads to a weaker control of muscle reactions. It is not known why the body attacks the neuromuscular junctions, but researchers believe that the thymus gland, which is involved in the production of antibodies,might play a role. Located beneath the breastbone, the thymus gland is part of the immune system and in about 15% of myasthenia gravis patients this gland develops benign tumors called thymomas. These aren't cancerous and can be removed through surgery, leading to

an improvement in MG symptoms and curing the ailment in some people.Even in people who don't undergo surgical procedures for having the thymus gland removed, the available medications and procedures can help in improving the symptoms and controlling them, leading to the temporary or permanent remission of this ailment. This allows patients to lead normal lives and to discontinue medications. In other sufferers, however, the disorder can only be ameliorated but not completely treated. [2]

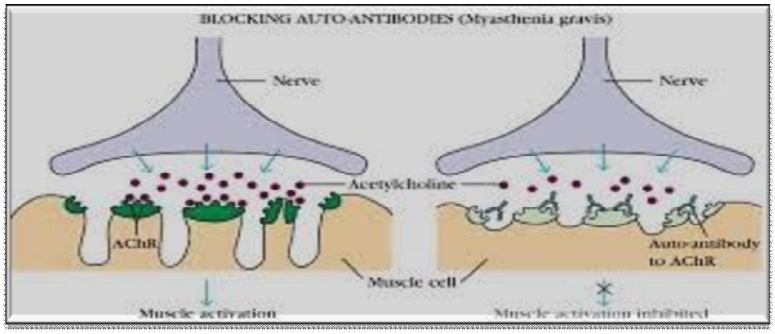

Figure No. 4: Mechanism of blocking neuro-transmitter

1. CLASSIFICATION:

Classification of MG:

Subtypes of MG are broadly classified as follows:

- early-onset MG: age at onset <50 years. Thymic hyperplasia, usually females,
- late-onset MG: age at onset >50 years. Thymic atrophy, mainly males,
- thymoma-associated MG (10%–15%)
- MG with anti-MUSK antibodies,
- ocular MG (oMG): symptoms only affecting extraocular muscles,

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.[3,4]

Table No. 1: Classification of MG in children

CONGENITAL MYASTHENIA GRAVIS	TRANSIENT NEONATAL MYASTHENIA GRAVIS	JUVENILE MYASTHENIA GRAVIS
Very rare non-immune form of MG that is inherited as an autosomal recessive disease.This means that both males and females are equally affected and that two copies of the gene,one inherited from each parent,are necessary to have the condition.Symptoms of congenital MG usually begin in the baby's first year and are life-long.	Between 10 and 20% of babies born to mothers with MG may have a temporary form of MG.This occurs when antibodies common in MG cross the placenta to the developing fetus.Neonatal MG usually lasts only a few weeks, and babies are not at greater risk for developing MG later in life.	This auto-immune disorder develops typically in females adolescents – especially Caucasian females.It is a life-long condition that may go in and out of remission.About 10% of MG cases are juvenile-onset.

Figure No. 5: a) Congenital Myasthenia Gravis.

b) Transient Neonatal Myasthenia Gravis.

c) Juvenile Myasthenia Gravis.

3. WHAT GENES ARE RELATED TO MYASTHENIA GRAVIS:

Several research works show that variations in particular genes may increase the risk of myasthenia gravis, but the identity of these genes is unknown. Many factors likely contribute to the risk of developing this complex disorder. Myasthenia gravis is an autoimmune disorder, which occurs when the immune system malfunctions and attacks the body's own tissues and organs. In myasthenia gravis, the immune system disrupts the transmission of nerve impulses to muscles by producing a protein called an antibody that attaches (binds) to proteins important for nerve signal transmission. Antibodies normally bind to specific foreign particles and germs, marking them for destruction, but the antibody in myasthenia gravis attacks a normal human protein. In most affected individuals, the antibody targets a protein called acetylcholine receptor (AChR); in others, the antibodies attack a related protein called muscle-specific kinase (MuSK). In both cases, the abnormal antibodies lead to a reduction of available AChR. The AChR protein is critical for signaling between nerve and muscle cells, which is necessary for movement. In myasthenia gravis, because of the abnormal immune response, less AChR is present, which reduces signaling between nerve and muscle cells. These signaling abnormalities lead to decreased muscle movement and the muscle weakness characteristic of this condition.[4]

4. SYMPTOMS OF MYASTHENIA GRAVIS:

Affecting mostly women aged 40 and younger, and men older than 60, myasthenia gravis is an autoimmune disorder characterized by weakness of voluntary muscles.

Caused by a disruption in the communication between nerves and the muscles they control, this condition manifests through rapid fatigue of the skeletal muscles, as well as through weakness and fatigue of muscles that control the eye movements, of those located in the face and neck area, and of throat muscles. Although symptoms can vary from one patient to another, there are some common manifestations, and these include the dropping of one or both eyelids, double vision, which usually improves when closing one eye, difficulty swallowing and chewing due to the weakness of throat and face muscles, and altered speaking.

Also common is the loss of control of facial muscles, which results in limited facial expressions, and the weakness of muscles in limbs, which can prevent one from performing daily activities. Fatigue usually improves with rest, and in most patients the symptoms come and go.[5,6]

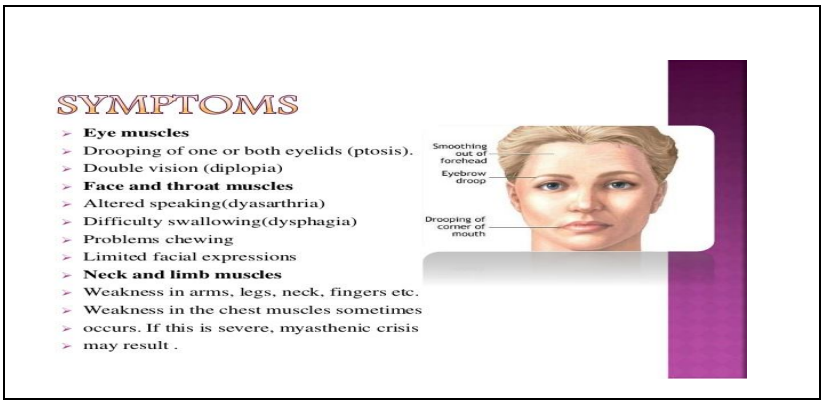

Figure No. 5: Symptoms of Myasthenia Gravis

5. TREATMENT AND DRUGS:

Table No. 2: Types of Drugs

CHOLINESTERASE INHIBITORS:	**CORTICOSTEROIDS:**	**IMMUNOSUPPRESSANTS:**
Medications such as pyridostigmine (Mestinon) enhance communication between nerves and muscles. These medications don't cure the underlying condition, but they may improve muscle contraction and muscle strength. ➢ ***Side effects*** - Possible side effects may	Corticosteroids such as prednisone inhibit the immune system, limiting antibody production**.** ➢ ***Side effects*** - Prolonged use of corticosteroids, however, can lead to serious side effects, such as bone thinning, weight gain, diabetes	Some medications that can alter our immune system, such as azathioprine (Imuran), mycophenolatemofetil (CellCept), cyclosporine (Sandimmune, Neoral) or tacrolimus (Prograf) are also prescribed sometimes. ➢ ***Side effects*** - Side effects of immunosuppressants

include gastrointestinal upset, nausea, and excessive salivation and sweating.	and increased risk of some infections.	can be serious and may include nausea, vomiting, gastrointestinal upset, increased risk of infection, liver damage and kidney damage.

Newer treatment options:

- *Rituximab:*

Rituximab is a humanized monoclonal antibody to CD20 that causes prolonged B-cell depletion approved for treatment of B-cell lymphoma in adults, and has been used in refractory MG. Small series of patients are available, and both MG with and without thymoma have been treated. Rituximab provides promising expectations for the treatment of MG, although no RCTs have been conducted so far.

- *Etanercept:*

Etanercept blocks tumor necrosis factor-α (TNFα) activity and has been shown to suppress ongoing EAMG. Etanercept was used in a prospective pilot trial in corticosteroid-dependent autoimmune MG: 70% of patients who completed the trial improved their muscle strength and lowered corticosteroid requirement. A direct correlation between plasma IL-6, TNF-α, and interferon-γ levels and post-treatment clinical scores of the patients were found. However disease worsening was seen in some patients and MG has been also observed during treatment of rheumatoid arthritis with etanercept through a RCT.[7]

- *Complement inhibitors:*

The role of complement in the pathogenesis of MG is well established; indeed, complement activation by specific autoantibodies is involved in the attack to the NMJ, as demonstrated by localization of C3 activation fragments and membrane attack complex. Recently, administration of a complement inhibitor to experimental MG animals reduced the severity of the disease aswell

as complement deposition at neuromuscular end-plates; these observations are of great interest for a potential application in humans.

SOME COMMON DRUGS:

Acetylcholine esterase (AChE) inhibitors are considered to be the basic treatment of myasthenia gravis (MG). Edrophonium is primarily used as a diagnostic tool owing to its short half-life. Pyridostigmine is used for long-term maintenance.

High doses of corticosteroids commonly are used to suppress autoimmunity. Patients with MG also may be taking other immunosuppressive drugs (eg, azathioprine or cyclosporine). Adverse effects of these medications must be considered in assessment of the clinical picture. Bronchodilators may be useful in overcoming the bronchospasm associated with a cholinergic crisis.[7-9]

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Treatment	Time to Clinical Effect
Pyridostigmine	10–15 minutes
Plasmapheresis	1–14 days
IVIg	1–4 weeks
Prednisone	2–8 weeks
Mycophenolate mofetil	2–6 months
Cyclosporine	2–6 months
Azathioprine	3–18 months

Source: Semin Neurol © 2004 Thieme Medical Publishers

Figure No. 6: Commonly used drugs

6. Thymectomy for Myasthenia Gravis:

Objectives: To assess the change in clinical status of patients with generalized myasthenia gravis treated with thymectomy and to identify prognostic variables that may be of significance in optimizing patient selection.

*Design:*Retrospective review. Mean follow-up period was 41 months.

Setting: Large community hospital.

Patients: Thirty-seven patients (11 male and 26 female) with generalized myasthenia gravis who were referred for thymectomy if they were refractory to medical treatment or had a thymoma. This represents all patients undergoing thymectomy for myasthenia gravis between January 1982 and December 1991.

Interventions: Each patient underwent staging before and after thymectomy using a modified Osserman classification. Medication requirements were also recorded. All patients underwent transsternal thymectomy and complete mediastinal dissection.

Main Outcome Measures: Changes in clinical stage and medication requirement before and after thymectomy; effect of patient age, sex, duration of disease, stage of disease, antibody status, histologic characteristics of the thymus, and duration of follow-up on outcome.

Results: Improvement after thymectomy was noted in all 37 patients. Complete remission was achieved in three patients (8%) and pharmacologic remission in 23 (62%). The remainder improved in stage, medication requirement, or both. Patients in preoperative stages lib and IIc showed the greatest improvement. Age, sex, duration of disease, antibody status, histologic characteristics of the thymus, and duration of follow-up were not significant factors in assessing improvement.[10]

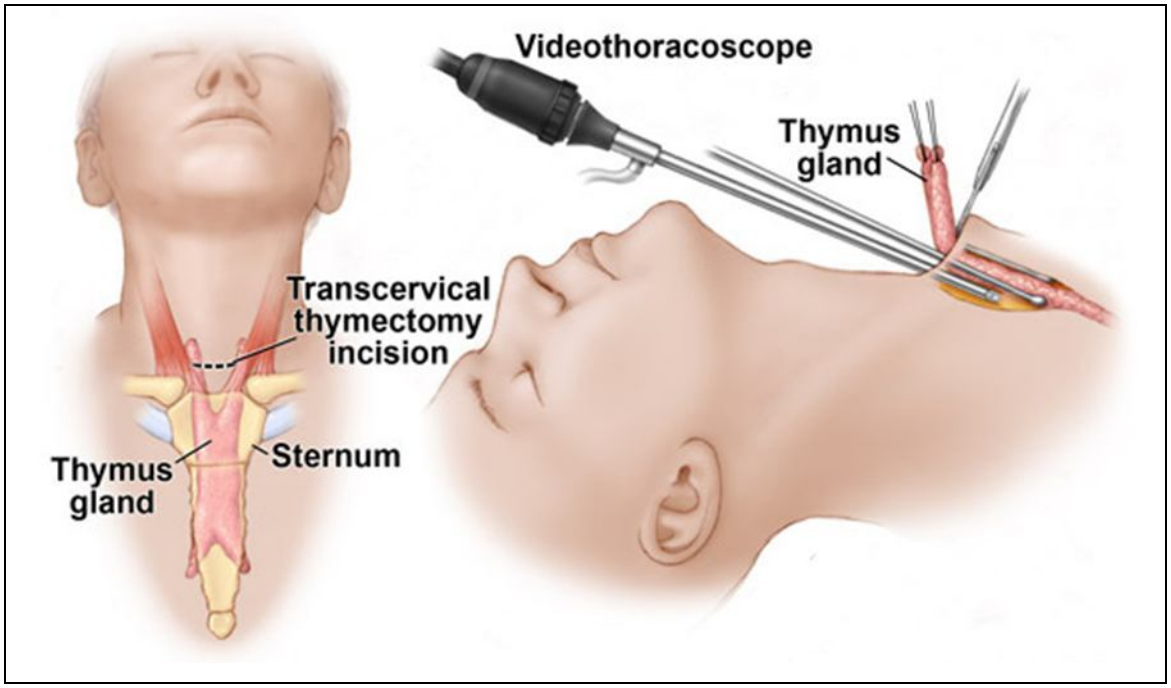

Figure No. 7: Thymectomy for Myasthenia Gravis

7. COMPLICATIONS OF MG:

According to a study of several incidences,the evaluated management of early post-operative complications after thymectomy for myasthenia gravis are:

Methods: During the period between 1987 and 1996, 324 thymectomies were performed through median sternotomy access under general anesthesia. Postoperative management was administered according to a standardized protocol of anticholinesterase medication, which was withdrawn for the 48 hours of obligatory postoperative mechanical ventilation. The mean age of patients was 34 years (range, 8 to 71 years).

Results: One hundred forty-nine patients made an uneventful recovery; 104 patients had only minor complications, whereas 71 patients had major complications. The mortality rate was 0.6% (2 patients). The major surgical complications were recorded as sternal bleeding (1 patient) and sternal disruption (1 patient). The major general complications were recorded as tracheal stenosis (1 patient), pneumonia (3 patients), heart failure (1 patient), gastric hemorrhage (1 patient), and respiratory insufficiency (71 patients). Forty-six reintubations were performed on 40 patients and 19 tracheostomies (6%) were performed postoperatively.[3]

8. PREVENTIVE MEASURES OF MYASTHENIA GRAVIS:

Once the disease has developed, there may be ways to prevent the episodes of worsening symptoms or flare-ups:

- Plenty of rest.
- To avoid strenuous, exhausting activities.
- To avoid excessive heat and cold.
- To avoid emotional stress.
- Whenever possible, exposure to any kind of infection, including colds and influenza (flu) should be avoided.
- Vaccination against common infections, such as influenza.

The patients should work with their doctors to monitor their reactions to prescription medications. Some drugs commonly prescribed for other problems, such as infections, heart disease or hypertension, may make myasthenia gravis worse. The patients must wisely choose the alternative therapies or avoid some medications entirely.

9. Conclusion:

MG has been actively studied since the 1970s, especially following the discovery of anti-AChR autoantibodies. However, recent investigations have improved our understanding of MG and highlighted new questions related to the development of MG. New antigenic targets have been described, and an improved classification system for the different MG subtypes and their distinct pathophysiological mechanisms has been delineated. Recent microarray analyses have revealed a number of mechanisms that are shared between MG and other autoimmune and inflammatory dieases. . The cytokines IFN-g, TNF-a and IL-17 play a central role in these mechanisms.

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