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Myasthenia Gravis: A Systematic Review

Chetana Gulabrao Nikam and Diya Anil Patil
Smt. S.S. Patil College of Pharmacy, Chopda (425107)

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***Corresponding Author Email:** cgnikam198@gmail.com

Abstract
An autoimmune neurological condition called myasthenia gravis (MG) is typified by impaired neuromuscular junction communication. Between 4.1 and 30 cases per million person-years are the disease's incidence. And between 150 and 200 cases per million is the prevalence rate. MG is Regarded as a quintessential illustration of antibody-mediated autoimmune Illness. The majority of MG patients develop autoantibodies against the Receptors for acetylcholine (AChRs). Less frequently recognized Among the autoantibodies directed against muscle-specific kinase (MuSK), Agrin, as well as low-density lipoprotein receptor-related protein 4 (Lrp4). Cholinergic communication between nerve cells is disrupted by these autoantibodies. Muscle fibres and terminals resulting in downregulation, damage, AChRs can be functionally blocked, or their clustering in the Membrane between synapses. The primary clinical sign of MG is Weakness in fatigable muscles that can impact the eyes, brain.

Keywords
Acetylcholine, Autoantibody, B cell, Cytokinase, Neuromuscular junction.

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INTRODUCTION
The most prevalent autoimmune condition affecting the neuromuscular junction is myasthenia gravis (MG). Although MG is mostly curable, it can cause serious morbidity and even death. Typically, this can be avoided with prompt diagnosis and suitable illness management. From an aetiology and phenotypic perspective, MG is a diverse illness. The range of symptoms includes significant weakening of the respiratory, bulbar, and limb muscles as well as exclusively ocular signs. The condition peaks in younger adult women and older men, and the onset age varies from childhood to late adulthood.[1]
MG is regarded as a quintessential illustration of antibody-mediated autoimmune disease. MG is regarded as a quintessential illustration of antibody-mediated autoimmune disease. Illness. Another way to look at it is as an illustration of class II hypersensitivity. Response, as autoantibodies of IgG respond to external or intracellular antigens, Causing harm to the end organs. Autoantibodies are seen in the majority of MG patients. Against the AChRs (acetylcholine receptors) [2,3], and a small percentage Have antibodies against muscle-specific kinase (MuSK) that are seropositive. Protein 4 that is related to the low-density coptein receptor (Lrp4). Additionally, these antibodies Serve as the foundation for classifying illness subtypes and aid in establishing Variations in phenotype. Within a subgroup [4,5]

EPIDEMIOLOGY
MG is a rare neurological disease, and pediatric MG is even rarer. Both incidence and prevalence show significant geographic variation, but the incidence of MG is thought to have increased worldwide over the past seven decades. The prevalence of MG was estimated at 1 in 200,000 from 1915 to 1934, then increased to 1 in 20,000 after the introduction of anticholinesterases in 1934 and to 1 in 17,000 after the discovery of AChR antibodies from 1969 to 200 million cases and has increased steadily over the past 50 years, at least in part due to improvements in recognition, diagnosis and treatment, as well as a

general increase in life expectancy.[6] More recent studies on incidence rates have been conducted in Europe and show a wide range variation ranging from 4.1 to 30 cases per million person-years[7,8]. The annual fee is lower in studies from North America and Japan, with an incidence ranging from 3 to 9.1 cases per million. Lower incidence and prevalence rates have been reported in a large number of studies conducted in China, 0.155-0.366 per million and 2.19-11.07 per 100,000, respectively Population-based studies conducted in Korea showed a prevalence of 9.67-10.42 per 100,000 people in 2010, which rose to 12.99 per 100,000 in 2014. On the other hand, a smaller study using data from a health organization. Based on a hospital estimated the incidence of MG at 38.8 per 1,000,000 person-years for the Argentine population. Different study methodologies, including diagnostic criteria, and other sources of bias, such as the small size of the study population and underreporting of patients with milder disease, are likely to play a role in the considerable variability in incidence over time and across different geographic regions. The incidence rate has a bimodal distribution in women, with peaks around the ages of 30 and 50 years. In men, the incidence increases steadily with age, and the highest rates are between the ages of 60 and 89. Women are more commonly affected before the age of 40 years, with a female: male ratio of 3:1 for first MG. During the fifth decade of life, women and men are equally affected, while men have a higher proportion after the age of 50, with a male: female ratio of 3:2. Approximately 10% of cases are paediatric, defined as onset before the age of 18 years. English MG can affect people of all races and ethnicities and is slightly more common in patients of African descent. [9,10] Furthermore, the phenotype of MG may vary by ethnicity. In a retrospective study from South Africa, black patients were more likely to have treatment-resistant ophthalmoplegia and ptosis than whites, while whites were more likely to develop treatment-refractory generalized MG. Age at diagnosis was 17 years higher among Caucasians than among non-Caucasians in another group of patients with ocular MG. In an American study, Oh et al. Found that MG had an earlier onset and a more severe phenotype in African Americans than in Caucasians. HIV-negative African Americans had a higher proportion of MuSK seropositivity in this study (50% versus 17% in whites) [11]. On the other hand, patients of Asian descent had higher levels of Musk antibodies compared with Caucasians and people of African descent. MG-related Musk is also more prevalent in people living at latitudes closer to the equator [12,13]. The mortality rate of MG has decreased significantly since the early 20th century following the availability of acetyl cholinesterase inhibitors, immunosuppressants, intravenous immunoglobulin, and advanced respiratory care. However, the mortality rate of the disease remains between 5 and 9%, slightly higher in men than in women. Use the database In the United States National Hospital Sample (NIS) for the years 2000 to 2005, the overall hospital mortality rate was estimated at 2.2%, but higher among people with MG crisis (4.7%), the main predictors of death are advanced age and the presence of respiratory failure.[14]

CLASSIFICATION OF MG

(1) Early GD: age at onset is 50 years. Thymus hyperplasia, usually women,
(2) Late GD: age at onset and 50 years. Thymic atrophy, especially men,
(3) MG associated with thymoma (10%-15%)
(4) MG with anti-MUSK antibodies,
(5) Ocular MG (OMG): symptoms affecting only the muscles outside the eye,
(6) MG without detectable AChR and without tyrosine kinase (MuSK)-specific antibodies.

MG patients with thymomas almost always have detectable serum AChR antibodies. Thymoma-associated MG may also have additional antibodies associated with paraneoplasia (eg, voltage-gated K and Cat channels, anti-Hu, dihydropyrimidinase-related protein 5, and anti-acid decarboxylase, glutamic acid antibodies). About 15% of patients with generalized MG do not have anti-AChR antibodies on current laboratory tests. In 40% of patients of this subgroup, antibodies against MuSK and another protein of the postsynaptic neuromuscular junction (NMI) are found. They present with atypical clinical features such as selective weakness of the facial, bulbar, neck, or respiratory muscles with occasional marked muscle atrophy and relative involvement of the eye muscles. Respiratory crises are more common when muscle groups such as the paraspinal and upper esophageal muscles are affected. Increased sensitivity, lack of response or even clinical deterioration to anticholinesterase drugs have also been reported. The onset of the disease is early with a female predominance and the histology of the thymus is usually normal. Seronegative GPs do not have anti-AChR antibodies or anti-MuSK antibodies and form a clinically heterogeneous group with purely ocular, mild generalized or severe generalized disease. Some patients may have low-affinity anti-AChR antibodies, undetectable by current tests. They are essentially indistinguishable from patients with

anti-AChR antibodies in terms of clinical features, response to pharmacological treatment, and possibly thymic abnormalities. Thymomas are often associated with autoimmunity. Neoplastic epithelial cells of thymomas express several autoimmune antigens, including AChR-like, titin-like, and ryanodine receptor-like epitopes. These antibodies react with epitopes of muscle proteins, the titin and ryanodine receptor, and are mainly found in association with thymoma and late myasthenia gravis and may be related to the severity of myasthenia gravis. These band antibodies are mainly detected only in the sera of MG patients and are rarely found in MG without AChR antibodies. The frequency of striatal antibodies in patients with thymoma-associated MG is elevated. Anti-titin antibodies are detected in 49-95% of thymoma-associated MG cases, anti-ryanodine receptor antibodies in 70-80% of cases, and anti-KV1.4 antibodies (VGKC) in 40-70%. Cases Since the presence of striatal autoantibodies is associated with more severe disease in all MG subgroups, these antibodies can be used as prognostic determinants in MG patients. [15,16]

CLINICAL CLASSIFICATION:

The clinical classification of the Myasthenia Gravis Foundation of America (MGFA) divides MG into 5 main classes and several subclasses [17]. It is designed to identify subgroups of patients with MG who share distinct clinical features or disease severity that may indicate different prognoses or responses to treatment. It should not be used to measure results and that's it.

Class I MG is characterized by the following:

1. Any weakness of the eye muscles.
2. May present with weakness in closing the eyes.
3. All other muscle strength is normal.

Class II MG is characterized by the following:

1. Mild weakness affecting muscles other than the eye muscles,
2. May also occur with eye muscle weakness of any severity.

Class IIa MG is characterized by the following:

1. Predominantly affecting the limbs, axial muscles, or both
2. There may also be less involvement of the oropharyngeal muscles.

Class IIb MG is characterized by the following:

1. It mainly affects the oropharyngeal muscles, the respiratory muscles or both
2. There may also be less or equal involvement of the muscles of the limbs, the axial muscles, or both.

Class III MG is characterized by the following:

1. Moderate weakness affecting muscles other than eye muscles,
2. It may also occur with eye muscle weakness of any severity.

Class IIIa MG is characterized by the following:

1. It primarily affects the limbs, axial muscles, or both,
2. There may also be less involvement of the oropharyngeal muscles.

Class IIIb MG is characterized by the following:

1. It mainly affects the oropharyngeal muscles, the respiratory muscles or both.
2. There may also be less or equal involvement of the limbs, the axial muscles, or both.

Class IV MG is characterized by the following:

1. Severe weakness affecting muscles other than eye muscles.
2. There can also be weakness of the eye muscles of any severity.

MG Class Iva is characterized by the following:

1. Mainly affecting the limbs, axial muscles or both,
2. There may also be less involvement of the oropharyngeal muscles.

Class IVB MG is characterized by the following:

1. Mainly affects oropharyngeal muscles, respiratory muscles or both,
2. There may also be less or equal involvement of the limbs, axial muscles or from both.

MG Class V is characterized by the following:

1. Intubation with or without mechanical ventilation, unless used as part of routine postoperative management,
2. Using a feeding tube without intubation puts the patient in class IVb,

PATHOPHYSIOLOGY:

1. Physiology and organization of the neuromuscular junction.

The neuromuscular junction is the site of transmission of impulses between nerve endings and muscle fibers. This process requires the release of presynaptic acetylcholine (Ach) and its subsequent binding to a postsynaptic Ach receptor. Synaptic vesicles containing Ach are released from the presynaptic membrane after an action potential activates voltage-gated calcium channels, allowing an influx of calcium into the nerve terminal [18]. The diffusion time of Ach across the synaptic cleft is very short and is modulated by the enzyme Ach esterase (AChE), which promotes the degradation of Ach. The spontaneous release of synaptic vesicles generates the miniature endplate potential (MEPP), while upon stimulation/depolarization of nerve fibers, a synchronous release of several synaptic vesicles causes a significant depolarization of the endplate membrane, generating an endplate evoked potential (EPP). This in turn causes an action potential in the myofiber, which eventually leads to its contraction. The amount of Ach released at the synapse is generally greater than that required to generate an action potential, allowing for reliable transmission. The binding of Ach to its receptors on the postsynaptic membrane opens the specific Ach cation channel, resulting in localized depolarization and activation of voltage-gated sodium channels. This allows the chemical reaction to be translated into an electrical signal, which is the action potential of the muscle fiber. Therefore, the role of AChE in the hydrolysis of Ach is crucial, as it prevents a single Ach molecule from repeatedly activating AChR. The efficiency of neuromuscular junction transmission is also determined by the amount of Ach released from the nerve terminal, the density of Ach receptors in the postsynaptic membrane, and the density of voltage-gated sodium channels in the plate. The latter depends on the presence of wrinkles in the postsynaptic membrane. These wrinkles determine the density of voltage-gated sodium channels in the postsynaptic membrane and therefore increase the effective coupling of localized EPP to the myofiber action potential [18,19]. Neuromuscular junction disorders such as MG disrupt the cascade of events that lead to reliable muscle contraction. In addition, we observed a reduction in the number of AChRs and voltage-gated sodium channels due to complement damage to the postsynaptic membrane. MG. The resulting inefficient neuromuscular transmission is reflected in a reduced amplitude response of the compound muscle action potential (CMAP) during repetitive nerve stimulation (RNS) and abnormal excitability or block in single fiber EMG. [19,20]

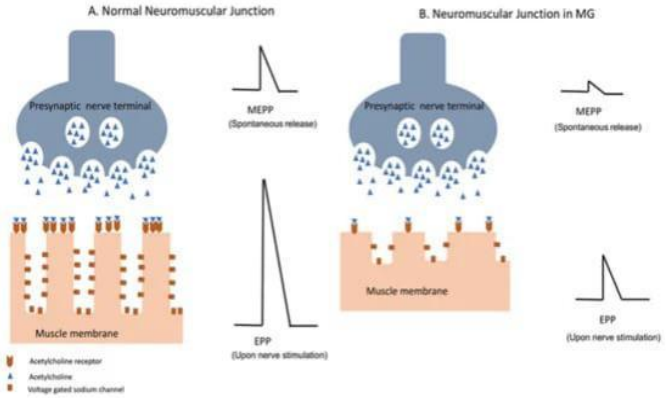

Figure 1. Neuromuscular transmission in normal individuals (A) and in patients with MG (B). Decreased density of the AChR and complement-mediated damage to the postsynaptic membrane in MG patients result in decrease in miniature end Plate potential (MEPP), which occurs with spontaneous release of AChR vesicles, as well as endplate potential (EPP) in Response to nerve action potential of the presynaptic membrane. Diminished amplitude of EPP in MG results in impaired Neuromuscular transmission.

2.Immune dysregulation in MG

B cell tolerance is mediated by clonal deletion or receptor modification in newly generated B cell clones in the bone marrow after reaching the immature B cell stage. A second checkpoint occurs for newly migrated/transient B cells before they enter the mature naïve B cell division. Lee et al. Found that the frequency of newly migrating/transient B cells and mature B cells expressing polyreactive and autoreactive B cell receptors (BCR) is higher in ACHR-MG and MuSK-MG, supporting the concept that the patients with MG present defects in the center. And peripheral B cell tolerance. Therefore, these patients are also at greater risk of developing other autoimmune

diseases such as systemic lupus erythematosus, rheumatoid arthritis and thyroiditis. [21,22]

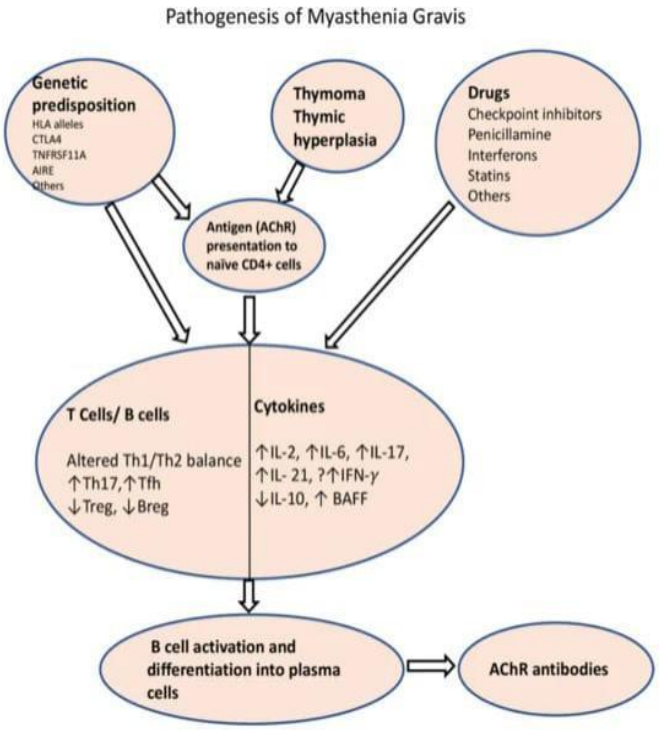

Figure 2. Schematic diagram of pathogenesis of AChR-MG.

3.Generation of autoantibodies

Autoantibodies disrupt neuromuscular transmission by targeting structural elements of the neuromuscular junction. The most common proteins targeted by pathogenic autoantibodies in MG are lipoprotein 4 protein (LRP4), muscle-specific kinases, and nicotinic acetylcholine receptors. Immunoglobulin G1 and immunoglobulin G3 antibodies against the acetylcholine receptor are the most common cause of these cases. Acetylcholine receptor turnover is accelerated, and complement-mediated damage is induced, resulting in the loss of its acetylcholine receptors from the postsynaptic membrane. In addition, antibodies against muscle-specific kinase or related proteins such as agrin and LRP4 are detected. Muscle-specific kinase antibodies, mainly of the IgG4 type, interfere with the physiological role of muscle-specific kinase in the maintenance of synapses and adaptability, leading to disruption of the pathogen.

4.Role of cytokines and T cells:

Pathogenic autoantibodies are produced, and inflammation is induced at the neuromuscular junction by activated cytokines, T cells, B cells, and plasma cells. Each of these processes is important. Several potential factors may exacerbate the pathogenesis of MG. These include chronic inflammation mediated by T helper type 17 (Th17) cells, follicular Th (Tfh) cells that stimulate B cells and plasma cells to produce autoantibodies, and dysfunction of T cells (Treg) that drive the immune system. Higher proportions of Th1 and Th17 cells worsen the pathophysiology of MG, although higher proportions of Th2 and Treg cells slow disease progression.[23]

5.Abnormalities of the thymus

The pathophysiology of the disease undoubtedly involves the thymus. Autoantibody production appears to be concentrated in the thymus. Most patients with anti-acetylcholine receptor antibodies have germinal centers, which house the B cells that generate these antibodies. The MG thymus is considered an archetype of tertiary lymphoid neogenesis due to its altered form and function, which provides perfect conditions for lymphocytes and antigen-presenting cells to interact, and an immune response is initiated. About 75% of MG patients have thymus function. Thymic tumors, or thymomas, affect 10% of individuals, but the thymus is “hyperplastic” in about 65% of cases and has active germinal centers.

6. Genetics

Around 35% of monozygotic MG twins are concordant, which suggests Environmental factors are primarily responsible for the disease's etiology. Nevertheless, MG is not subject to Mendelian inheritance. Family members of people with MG are approximately 1000 times more likely to have the Illness than people in general individuals suffering from MG have varied Symp- toms, and their level of muscle weakness fluctuates daily. Without treatment, symptoms typically worsen over time.

SPECIFICATIONS FOR DIAGNOSIS

Serological test:

1. Acetylcholine receptor antibodies:

These are the most common and best antibodies characterized by MG. By binding and activating complement, which destroys the post-synaptic membrane, by binding to acetylcholine receptors, which accelerates its endocytosis and degradation and directly block the acetylcholine receptor binding sites, these antibodies disrupt transmission at the NMJ.[24]

2.Anti-muscle specific kinase antibodies:

It is rare for patients have antibodies against the muscle acetylcholine receptor, most have antibodies against muscle-specific kinase. In seropositive MG, specific anti-muscle kinase antibodies are absent. These antibodies are related to a more pronounced bulbar and cervical weakness increased respiratory distress in patients with MG [25].

Pharmacological test:

1. **Edrophonium test (tensilon test):** Acetylcholine levels in the NMJ are Raised by the reversible acetyl- cholinesterase inhibitor edrophonium. It has A quick start and a brief duration of action. MG patients' skeletal and Muscular strength temporarily improved due to the elevated acetylcholine levels in the NMJ. Edrophonium testing is rarely used but effective in cases of detectable ptosis. Testing with edrophonium was superior in patients with ocular MG [26]
2. **Neostigmine Test:** This is a pharmacological test that shows that patients with MG have clinical improvement. Treatment with intravenous neostigmine is a rapid method, accurate and safe to treat MG with ocular involvement in cases difficult to diagnose. To avoid false negative results, Eyelid posture and strabismus are assessed quantitatively during the administration of neostigmine test in MG patients with ocular involvement [27].
3. **Ice pack test:** This is a quick and easy method to diagnose MG. This is a technique relatively simple, affordable and safe that the doctor can perform directly at the patient's bedside. The ice pack test also has no side effects and does not require expensive equipment or medication. It involves applying an ice pack to the patient's affected eye for three to five minutes. When the diplopia or ptosis improves, the response is favorable [28]

ELECTRODIAGNOSIS:

1. **Repetitive nerve stimulation test (RNS):** For diseases of the neuromuscular junction, including MG, the repetitive nerve stimulation test is a useful and often used neurophysiological test. Presynaptic nerve endings that receive repeated electrical stimulation from a motor nerve gradually lose their ability to release synaptic vesicles. As a result, the endplate potential of people with MG can fall below the cutoff point needed to produce action potentials in the muscle. Since confirmatory antibody test results often take some time to return, rapid confirmation of the diagnosis of MG can be facilitated by in-hospital RNS [29].
2. **Single fiber electromyogram (SFEMG):** The evaluation of individual muscle fiber action potentials (MFAP) is possible through a highly selective technique called single fiber electromyography. SFEMG can reveal coupled excitability by stimulating motor nerve branches to specific endplates, either

voluntarily or by axonal stimulation. The most accurate clinical neurophysiological test is single-fiber electromyography.[30]

TREATMENT:

MG cannot be cured; however, its symptoms can be managed the activity of the immune system may be limited. The immune system can be Managed with immunosuppressants and corticosteroids. These drugs help to reduce the aberrant immune response seen in MG. It is also possible to use cholinesterase inhibitors, such as pyridostigmine, which can also be used to improve the transmission of signals between muscles and nerves.[31]

- Pyridostigmine bromide Most people with MG are advised to start treatment with Acetylcholinesterase inhibitors, such as pyridostigmine. Acetylcholinesterase inhibitors were first widely recognized as a treatment for MG by Dr. Mary Broadfoot Walker in 1934. Pyridostigmine helps improve transmission of nerve impulses at the neuromuscular junction by preventing the enzyme acetylcholinesterase from breaking down acetylcholine.
- Corticosteroids One of the most popular immunosuppressive medications for immune-mediated diseases such as MG are corticosteroids. Reducing cytokine production, the inflammatory and endothelial adhesion of leukocytes has a significant antagonistic influence on the immune response.
- Azathioprine The most common immunosuppressive drug used to treat MG is azathioprine. Azathioprine inhibits DNA synthesis, which reduces the number of new cells produced. Azathioprine mainly prevents the development of white blood cells. Reduces the production of harmful autoantibodies stop the growth of white blood cells, which are responsible for the production of antibodies. Azathioprine is a stable substitute for corticosteroids in some myasthenic patients who require immunosuppression.
- Mycophenolate mofetil (MMF) If conventional treatment regimens cannot treat MG, mycophenolate mofetil may be a useful alternative. Its application is simple and general well tolerated. The activity of adhesion molecules and glycosylation are inhibited by it, which reduces the recruitment of lymphocytes and monocytes to inflammatory areas.
- Cyclosporine Cyclosporine is an immunosuppressive drug approved for MG patients with a poor response to corticosteroids after thymectomy. Cyclosporine prevents the loss of acetylcholine at the neuromuscular junction and nearly inhibits the antibody response against acetylcholine receptors.
- Cyclophosphamide It is a DNA alkylating agent that significantly inhibits DNA transcription and replication activity and is effective in refractory MG The use of immunoablative doses of cyclophosphamide for treatment resulted in significant and sustained improvements in MG symptoms. Patients with extremely resistant disease may benefit from high doses of cyclophosphamide.
- Methotrexate (MTX) Methotrexate, a potent immunosuppressive drug for autoimmune disorders, selectively inhibits dihydrofolate reductase and lymphocyte proliferation. MTX is taken up by cells, where the glutamate moiety is added and retained as methotrexate polyglutamate (MTXPG)
- Intravenous (IV) therapy. Plasmapheresis Patients with acutely worsening MG respond very well to plasmapheresis treatment. Therapeutic plasma exchange, a form of extracorporeal blood purification, involves removing plasma from the blood and using plasma or albumin from a healthy donor instead. Immune complexes, pathogenic autoantibodies, toxins, and cryoglobulins are among the high molecular weight materials often extracted from plasma by this process. Its efficacy in MG is attributed to the elimination of biologically active autoimmune protein antibodies, particularly antibodies against the acetylcholine receptor, which significantly benefit motor efficiency, muscle endurance, and neuromuscular junction transmission.
- Intravenous immunoglobulin (IVIg) Immunoglobulins collected from thousands of donors constitutes this pool. IVIg is a substitute for many immunosuppressants [42]. O Popular type of treatment for some autoimmune neuromuscular diseases is an immunoglobulin therapy. It has been used for the acute and long-term treatment of patients with MG.
- Monoclonal antibody Monoclonal antibody therapies for MG inhibit the complement effect mechanism and the ability of the receptor for neonatal crystallized fragments (FcRn) to lower antibody levels. The synthesis of autoantibodies was reduced with use antibodies against differentiation groups (CD20) and signaling pathways that promote lymphocyte activity.

CONCLUSION:

Myasthenia gravis is a relatively rare disease that destroys communication between the nervous system and the muscles. Absence of specific essential molecules because the organism causes this disease. When a person has, he gets tired. This disease can appear at any age, even during childhood, but men over 60 years and young women under 40 are more at risk. A person may need specific physical examinations and other tests to confirm the exact origin of the disease, depending on the symptoms, infectious diseases and medical history varied. MG is a challenging disease that can vary in severity and affects all aspects of life. MG has no treatment options and is managed with medication, plasmapheresis, thymus removal, intravenous immunoglobulin and rest to reduce muscle weakness.

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