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REVIEW ARTICLE

DIAGNOSIS AND TREATMENT METHODS OF AUTOIMMUNE MYASTHENIA GRAVIS: A SYSTEMATIC REVIEW

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Abstract

Myasthenia Gravis (MG), which is an autoimmune disorder, causes abnormalities in the neuromuscular junction and has a prevalence of 15-20 per 100,000 people. Although skeletal and extraocular muscles are commonly affected by the disease, approximately 10% of patients have severe involvement in the muscles necessary for respiration. A myasthenic crisis may cause life-threatening consequences. The prevalence and incidence of autoimmune MG increase with age. Women's disease incidence peaks between the ages of 30 and 40, while men's incidence peaks between the ages of 60 and 80. The existence of autoantibodies against postsynaptic membrane proteins is the most crucial indicator of MG. Anti-AChR (acetylcholine receptor antibody) positive is a distinct feature of MG (% 80). While anti-MuSK (muscle-specific kinase antibody) positivity is detected in 1-10% of all patients, LRP4 (low density lipoprotein receptor related protein 4) antibody positivity is seen in 3-25% of MG patients without AChR and MuSK antibodies (anti-LRP4). Despite many methods used in the diagnosis of MG, it is not possible to make the diagnosis in some patients because of conditions that may vary from patient to patient, such as fluctuation in symptoms and clinical findings. Rapid diagnosis is crucial in patients with MG, because effective treatment must begin as early as possible to prevent potentially fatal complications. Moreover, rapid diagnosis of patients and determination of the patient's subtype is an important step in the treatment process. Therefore, the aim of this study is to summarize the techniques used in the diagnosis and treatment of MG which is one of the rare diseases.

Keywords: Myasthenia Gravis; Diagnosis Methods; Treatment Methods; Rare Diseases; Neuromuscular Disorders; Autoimmune Disorders

1. INTRODUCTION

MG is an autoimmune disease that causes a postsynaptic neuromuscular conduction abnormality that can be caused by a variety of factors including toxicity, immunology, or genetics (Sieb, 2014). The immune system can distinguish between the body's cells and tissues and does not produce antibodies against its antigens. However, autoimmune diseases, such as MG, are caused by the body's inability to tolerate its cells and tissues. The body's immune response is compromised and it begins to produce autoantibodies against its antigens. As a result, the body's cells and tissues, which are the target of the immune response, are damaged (Lleo et al., 2010; Ngo et al., 2014). MG develops in individuals who are genetically predisposed and subjected to trigger conditions, just like autoimmune diseases. Infections, surgery, drugs and immunization can all be triggering factors. Muscle weakness is a symptom of this condition. The production of autoantibodies against postsynaptic membrane proteins results in a reduction in the transmission of electrical impulses at the neuromuscular junction, resulting in muscle weakness (Beloor Suresh and Asuncion, 2022).

MG can lead to a whole slew of complications. The most serious of these is respiratory muscle involvement, which is known as myasthenic crisis and necessitates immediate medical attention. It commonly affects ocular, bulbar, oculobulbar, limbs and respiration muscles. Long-term medication therapy can cause adverse events such as opportunistic infections and lymphoproliferative cancers (Beloor Suresh and Asuncion, 2022). The commencement of MG is marked by ocular muscle weakness, which is apparent in the majority of patients. Diplopia and ptosis develop as the condition worsens. Oropharyngeal weakness causes difficulties in chewing, articulation and swallowing. MG is categorized based on symptoms, onset age and treatment requirements (Sieb, 2014).

2. DIAGNOSIS OF MG

Clinical symptoms of patients are an important indicator in the diagnosis of MG. The clinical symptoms are double vision, drooping eyelids and weakness/fatigue in the bulbar, extremity and cervical muscles (Yavuz, 2019). Moreover, other symptoms may be a coexistence of droopy eyelids, facial paralysis greater effort to make a sound, exhaustion and weakness in neck muscles. Additionally, unexplained muscle weakness and symptoms that worsen with exercise may be seen. Furthermore, there are variable symptoms such as increased nighttime fatigue or symptoms that exacerbate the menstrual period and a cyclical increase in symptoms that occurs every few months or weeks.

Several tests are performed on patients who present with the suspicion of MG with these symptoms, both to diagnose and to determine the MG subgroup, which has a substantial impact on the treatment method.

The initial step to be applied to the patient is a serological test. First, anti-AChR and anti-MuSK are examined. If the test results are positive, additional testing may not be required (Gilhus and Verschuuren, 2015; Gilhus et al., 2019). Thymus and thyroid tests, on the other hand, may be performed to rule out other disorders. Nevertheless, many competent sources show a high false-positive rate for MG (Shelly et al., 2020; Pasnoor et al., 2018).

Electrophysiological examinations are the next step for seronegative patients who do not have anti-AChR or anti-MuSK. Because it is more accessible, repetitive nerve stimulation (RNS) is utilized first. It is quite specific, though less sensitive. When RNS yields a negative result, single fiber electromyography (SFEMG) is conducted. It would be wise to include as many muscles as possible in the tests (Meriggioli and Sanders, 2004). Instead of electrophysiological tests, the edrophonium test might be utilized as a secondary diagnostic step. However, it is difficult to access. The ice pack test is also advised, particularly for ocular-MG (Rousseff, 2021). Despite numerous diagnostic procedures, it is difficult to detect and distinguish the disease at its onset from other disorders.

2. 1. Serological Test

A specific diagnostic approach for MG is determining the anti-AChR levels in serum and additional testing may not be required. It can also be used to identify disease subgroups (Rousseff, 2021; Vincent et al., 2018). However, it does not provide information about the severity or course of the disease. This approach is 85 percent sensitive in individuals with generalized MG and 50 percent sensitive in people with ocular MG (Lennon, 1997; Vincent and Newsom-Davis, 1985). The probability of false positives is less than five percent in patients with Lambert-Eaton myasthenic syndrome (LEMS), three or five percent in patients with motor neurons and less than one percent in patients with polymyositis (Dincer, 2015). The radioimmunoprecipitation (RIP) is the most commonly used anti-AChR test (Lazaridis and Tzartos, 2020). Normal reference values vary per laboratory but are usually between 0.03 and 0.5 nmol/L (Yavuz, 2019) Anti-MuSK testing should be performed on suspected patients who test negative for anti-AChR. These tests are known as radioimmunoprecipitation (RIP) or enzyme-linked immunosorbent assays (ELISA). Anti-MuSK antibodies are detected in 6-8% of cases (Rousseff, 2021).

Anti-LRP4 testing should be performed on MG patients who are anti-AChR and anti-MuSK negative. The prevalence of anti-LRP4 in patients ranges from 2 to 50%. Anti-LRP4 positivity has also been observed in patients with amyotrophic lateral sclerosis (ALS), various neuroimmune disorders, including MuSK-MG. As a result, anti-LRP4 is not a particular MG diagnostic technique (Frykman et al., 2020; Zhang et al., 2012).

The presence of antibodies against actin, titin, -actinin, myosin and ryanodine receptors in the serum of MG patients may raise the possibility of thymoma. The presence of these antibodies in EO-MG patients raises the risk of developing thymoma. They are not, however, specific for MG because these antibodies

are also present in individuals who do not have thymoma or in people who have thymoma but do not have MG. Furthermore, titin and ryanodine antibodies are a predictor of the severity of the disease in LO-MG individuals who develop MG after the age of 40 (Dincer, 2015; Yavuz, 2019).

2. 2. Electrophysiological Tests

Diagnosis with this method can be effective in seronegative MG patients or in situations where rapid results are required. It not only determines the neuromuscular disorder but also can make a differential diagnosis from other neuromuscular disorders. It has two different methods: (1) repetitive nerve stimulation (RNS) and (2) single fiber electromyography (SFEMG) (Meriggioli and Sanders, 2004)

2. 2. 1. Repetitive Nerve Stimulation (RNS):

The goal of this test method is to determine the factor of safety and a muscle is successively stimulated with frequencies of 2Hz or 5Hz. If the first and fifth impulse muscle action potentials decline by 10% (decremental response), this is indicative of MG. When patients who were unable to be diagnosed the first time get weary after 1 minute of activity, the test is repeated and a secondary decrement is sought. Significant results are found in 75% of generalized MG patients and 50% of ocular MG patients (Dincer, 2015; Oh et al., 1992).

2. 2. 2. Single Fiber Electromyography (SFEMG):

It is the most sensitive approach to diagnosing MG, which determines a single muscle fiber's action potential. The action potentials of two muscle fibers stimulated by the same axon are monitored and the temporal fluctuation between them is referred to as "jitter." The jitter response increases as the NMJ safety response decreases in MG. The test is diagnostic in 90 to 95 percent of MG patients when conducted appropriately. Abnormal jitter is present in 50% of ocular-MG patients and 85% of generalized MG patients. For differential diagnosis from other NMJ patients, routine needle electromyography EMG should be conducted (Dincer, 2015; Gwathmey and Burns, 2015; Yavuz, 2019).

2. 3. Edrophonium Test

Edrophonium chloride, which is an acetylcholinesterase inhibitor, is only effective for a short period and is reversible. The patient is given 10 mg of edrophonium intravenously. By inhibiting the acetylcholinesterase enzyme, it amplifies the action of acetylcholine in NMJ. As a result, it improves extraocular muscle signs such as ptosis. The sensitivity for MG ranges from 71% to 95%. The test is not advised since it may yield negative results in anti-MuSK-MG patients. As an alternative to edrophonium, neostigmine can be used by injecting intramuscularly. It may take five to ten minutes for the healing effect and be recommended for diagnosis in young children (Evoli and Padua, 2013; Pasnoor et al., 2018).

2. 4. Ice Pack Test

For 2-5 minutes, an ice pack is administered to the eye with drooping eyelids. The acetylcholinesterase

enzyme is suppressed by cold action. This slows acetylcholine breakdown, resulting in a transient improvement in NMJ signal transduction. A positive test is indicated by an improvement of more than 2 mm in the eyelid. It is specific for 80-90 percent MG (Rousseff, 2021).

2. 5. Imaging

Radiological investigations for thymus pathology should be conducted in MG patients. These tests may include computed tomography (CT) and magnetic resonance imaging (MRI). CT scans have a sensitivity of more than 90% for thymoma and 30-60% for thymic hyperplasia. Patients with anti-AChR MG who were not thymectomized should have their thymus examined every five years (Berrih-Aknin et al., 2014; Sieb, 2013).

3. TREATMENT OF MG

The therapeutic strategy used for MG is patient-specific. It is calculated by taking into account the patient's age, the severity and the symptoms of the condition. As a result, it necessitates continual monitoring and attentive follow-up. There are four fundamental therapeutic methods (Dincer, 2015). These are: (1) Symptomatic therapy (acetylcholinesterase inhibitors), (2) Immunosuppressive therapy, (3) Immunomodulatory therapy (IVIg and Plasmapheresis), (4) Surgical intervention (thymectomy)

3. 1. Acetylcholinesterase Inhibitor

These medications are used to treat symptoms without impacting the disease's immunological system. It stops AChE from destroying acetylcholine in the NMJ, allowing it to persist in the synaptic cleft for a longer period. This ensures that neuromuscular conduction is accurate. Mestinon (pyridostigmine bromide) is the most often used acetylcholinesterase inhibitor. Other inhibitors that can be employed include pyridostigmine (neostigmine bromide) and mytelase (ambenonium chloride). These acetylcholinesterase inhibitors are given when symptoms develop and expecting to fade or lessen within 1-2 hours (Pascuzzi, 2003).

Acetylcholinesterase inhibitor medicines are not recommended in anti-MuSK positive patients since they can have negative side effects. On the other hand, while some patients show significant improvement, which may be adequate treatment, some patients have little or no effect (Gwathmey and Burns, 2015).

In patients without thymoma, patients with regional improvement following thymectomy and individuals with only ocular-MG, acetylcholinesterase inhibitors are the only therapy options (Dincer, 2015).

3. 2. Immunosuppressive Therapies

Several drugs are used in immunosuppressive therapies, which have different effective mechanisms. These drugs and their mechanisms are detailed in Table 1.

Table 1. Immunosuppressive medications used to treat MG and their mechanisms of action [Jayam Trouth et al., 2012; Melzer et al., 2016; Yavuz, 2019]

Drug	Effect mechanism
Corticosteroids	It causes T cell death, lowers cytokine gene transcription, and impairs dendritic cell maturation.
Azathioprine	It reduces serum anti-AChR levels. It functions as a purine analog. It inhibits nucleic acid synthesis. It inhibits the proliferation of T and B cells.
Mycophenolate mofetil	It limits T and B cell proliferation and briefly inhibits purine synthesis. It inhibits the production of antibodies that are involved in complement-dependent degradation. It suppresses cytotoxicity.
Methotrexate	It is an antimetabolite, an analog of folic acid. It inhibits the enzyme dihydrofolate reductase as well as lymphocyte proliferation.
Cyclophosphamide	It is nitrogen mustard that acts as an alkylating agent. It creates DNA crosslinks by introducing an alkyl group into the DNA. It affects DNA replication.
Cyclosporine	It inhibits the synthesis of proteins required for the function of IL-2 cytokine receptors and CD4+ T cells.
Tacrolimus	It functions as a calcineurin inhibitor. It suppresses the activation and development of antigen-specific lymphocytes. It also prevents lymphocytes from performing efficient activities.
Rituximab	It is a monoclonal IgG1 antibody that targets the CD20 antigen. CD20 B cell surface activation promotes differentiation and growth.
Eculizumab	It is an IgG 2/4k human monoclonal antibody. It interacts with the C5 complement protein, blocking the activation of endpoint complement.

3. 2. Immunomodulatory Therapy

Plasma exchange (plasmapheresis) or intravenous immunoglobulin (IVIg) therapy may be considered in patients who have an aggravation of symptoms. It is utilized as a therapeutic approach in patients with severe MG who have not responded to previous immunosuppressive or symptomatic treatments. The therapy approach used is determined by the patient's characteristics. Plasmapheresis is not an option for patients with sepsis and IVIg is not an option for individuals with renal failure. Because the treatment effect is only temporary, it should be used in conjunction with immunosuppressive therapy. It can be repeated as the treatment's effectiveness fades.

3. 2. Intravenous immunoglobulin (IVIg):
Immunoglobulins are separated from human plasma collected from hundreds of donors using ethanol cryoprecipitation and given to patients at a dose of 0.4 g/kg/day for 5 days. Within a week, healing begins and the impact lasts for several months. IVIg has several therapeutic effects. It prevents cytokines from competing with autoantibodies, T cells from recognizing antigens, the synthesis of anti-AChR and complement-dependent degradation. It also affects the expression and activity of Fc receptors on macrophages. Moreover, it inhibits the binding of Ig receptors on the surface of B cells (Jayam Trouth et al., 2012; Samuelsson et al., 2001).

Plasmapheresis is frequently advised as IVIg therapy is less successful in anti-MuSK positive individuals. However, IVIg therapy is a more acceptable treatment because it has fewer adverse effects. Recovery is seen in 50-100 percent of patients (Yavuz, 2019).

3. 3. 2. Plasma Exchange (Plasmapheresis):
It entails exchanging two or three liters of plasma three times per week. Healing usually begins after the second and third iteration and treatment continues for about 5-6 replacements until it stabilizes. Plasmapheresis can be applied intermittently to patients with severe exacerbation of symptoms, before surgical interventions such as thymectomy, patients who are resistant to all treatments and generally to patients with respiratory involvement (Conti-Fine et al., 2006; Yavuz, 2019).

3. 4. Surgical Intervention
The thymus plays a significant part in the pathogenesis of MG by inducing anti-AChR production (Marx et al., 2013). Thymic pathology occurs in 80-90% of MG patients and is most subtle in seronegative MG. Thymic hyperplasia occurs 60-70% of anti-AChR-positive MG patients while thymoma occurs10-15% patients. Because of these cases, thymectomy is a surgical procedure performed in patients with MG. Patients with MG who develop thymoma benefit from thymectomy, which removes the thymus. However, it has been suggested that in EO-MG patients, total thymectomy would be advantageous without waiting for the development of thymoma. In numerous studies, patients who applied thymectomy showed greater improvement than patients who received other treatments (Gronseth and Barohn, 2000). In MG patients, thymectomy results in 54-94% improvement and 13-46% remission (Murai et al., 2006). The remission rate is roughly 35% if the operation is performed within the first two years of the disease, but it lowers if the operation is delayed. The effect of thymectomy is long-lasting and begins within a few months. Antibody levels drop or eliminate in people who recover. Thymectomy is not recommended in patients who have anti-MuSK and anti-LRP4 antibodies or negative for all MG-specific antibodies (Yavuz, 2019).

Remes Troch et al. (2002) recommends thymectomy to be performed in Generalized MG patients between the ages of 15-60, in patients with stable moderate or severe MG despite medical treatment, in patients with resistant Ocular-MG, in patients with suspected thymoma and patients over 60 years

of age who do not respond to medical treatment or react to therapeutic drugs such as corticosteroids (Remes Troch et al., 2002).

Using IVIg or Plasmapheresis before surgery minimizes the risk of problems and allows for a speedier recovery. Even in critically patients, the mortality rate with thymectomy is less than 1% (Gronseth and Barohn, 2000). Myasthenic crisis (6%), infection (11%) and phrenic nerve injury (2%) are all possible complications the following thymectomy (Yavuz, 2019).
Finally, MG patients should avoid taking certain drugs that may affect the NMJ. These drugs are showed in Table 2.

Table 2. Drugs that are contraindicated for use in MG [Dincer, 2015]

Antibiotics	Antiarrhythmic agents	Others
Aminoglycoside antibiotics, especially gentamicin, kanamycin, neomycin, and streptomycin	Beta-blockers (pindolol, propranolol, timolol)	Some antiepileptics (Diphenylhydantoin)
		Lithium
macrolides	Calcium channel blockers (verapamil, diltiazem, nifedipine)	Morphine and other narcotic analgesics
		Tranchylazanes and barbiturates
fluoroquinolones	Quinidine	Some antidepressants (tricyclics)
		Muscle relaxants
Tetracyclines	Lidocaine	Levothyroxine
Sulfonamides	Procainamide	Adrenocorticotropic hormone (ACTH)
Penicillin (high dose)	Trimethaphan	Magnesium salts
		Iodized contrast agents
		Succinylcholine, D-tubocurarine or other neuromuscular blocking agents
		D-Penicillamine (never use)
		Estrogen-containing preparations
		Calcium channel blockers

4. CONCLUSION

The biomarkers employed in the subgrouping of MG and the patient-specific clinical character of the disease are assessed when deciding on the therapeutic approach to be used. The existence of autoantibodies against proteins in the post-synaptic membrane is the most crucial marker in the diagnosis of MG and patients are classified based on the presence of these antibodies. Serological confirmation or exclusion of the diagnosis is required in MG, especially when clinical and electrophysiological investigations fail to indicate neuromuscular junction dysfunction (Vincent et al., 2003). When anti-AChR or anti-MuSK cannot be confirmed serologically, treatment may be delayed. Clarifying the pathogenesis of MG is critical for accurate and early diagnosis, as well as the development of innovative diagnostic and treatment techniques (Skeie et al., 2010)

Despite many methods used in the diagnosis of MG, the diagnosis is not possible for some patients. Conditions that may vary from patient to patient, such as fluctuation in symptoms and clinical findings, delay diagnosis in 13 percent of patients for more than 5 years and causes non-deterministic diagnoses in 26 percent (Gilhus et al., 2016). Chewing difficulty, droopy eyes, speech difficulties and muscle exhaustion in elderly persons, on the other hand, can be misinterpreted as age-related, hindering the diagnosis. Moreover, there are cases in which elderly patients with MG symptoms are diagnosed with Parkinson's disease, stroke and motor neuron disease (Montero-Odasso, 2006). Meanwhile, normal electrophysiology in seronegative patients is another circumstance that complicates diagnosis (Vincent et al., 2003).

Rapid and early diagnosis is critical in MG patients. Because proper therapy must be initiated as soon as possible to avoid life-threatening consequences. At the same time, because it is an autoimmune disease, patients may require long-term immunosuppressive therapy. This circumstance may expose the person to unneeded treatments, as well as being a burden in terms of time and money in the case of an incorrect diagnosis.

As a result, new techniques for the most accurate and rapid diagnosis of MG are necessary. Furthermore, research into the molecular mechanism of MG is continuing (Guo et al., 2019; Ingelfinger et al., 2021; Lushchekina et al., 2015). These investigations will contribute to the development of new therapeutic medications, thus, successful treatment approaches.

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Conflict of Interest

Authors declare no conflict of interest.

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