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An Effective Management of Myasthenia Gravis- A Clinical Review

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ABSTRACT:

Myasthenia gravis (MG) is a neuromuscular disorder that arises from autoimmune antibodies. The majority of individuals with MG possess autoantibodies targeting acetylcholine receptors (AChRs), while a smaller portion may test positive for antibodies against muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (Lrp4). The initial symptoms often manifest in the form of uneven, tiresome drooping of the eyelids, which may be accompanied by blurred or double vision. Thymectomy has gained growing acceptance as a treatment for MG. In this review, we provide a brief overview of the underlying treatment categories for MG.

KEYWORDS: Myasthenia Gravis, Autoimmune antibody, Muscle weakness, Treatment, Thymectomy.

INTRODUCTION:

Myasthenia gravis, often abbreviated as MG, is a neuromuscular disorder with a name that reflects its characteristics. "My" refers to muscle, "asthenia" signifies weakness, and "gravis" denotes severity. This condition leads to muscle weakness and fatigue, particularly in the voluntary muscles [(1)]. Myasthenia gravis is a rare, potentially life-threatening, and chronic autoimmune condition. It is characterized by the presence of autoantibodies in the bloodstream that target specific components of the neuromuscular junction within skeletal muscles. The most commonly affected target is the nicotinic acetylcholine receptor (AChR) and the associated proteins found in the postsynaptic membrane. When these autoantibodies interfere, they obstruct neuromuscular transmission, leading to muscle weakness [(1)].

From purely symptoms in the eyes to significant paralysis of the limb, bulbar, and respiratory muscles, the indications might be wide-ranging. Onset of the condition may occur at various ages, with higher prevalence in younger adult women and older men, spanning from childhood to late adulthood [(2)].

The autoimmune disease MG is regarded as a prime example of an antibody-mediated condition. As IgG autoantibodies target both intra and extracellular antigens, resulting in harm to the vital-organs, it can also be seen as an illustration of a class II hypersensitivity reaction [(2)]. The majority of individuals with myasthenia gravis (MG) possess autoantibodies targeting acetylcholine receptors (AChRs), while a smaller portion may test positive for antibodies against muscle-specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (Lrp4).[(2)] Their initial symptoms often manifest in the form of uneven, tiresome drooping of the eyelids, which may be accompanied by blurred or double vision. Neuromuscular dysphagia quickly progresses to total loss of swallowing ability in myasthenic crisis which is the most critical phase of condition and this is often accompanied by weakness in the respiratory muscles and type 2 respiratory failure. The main objective of treatment is to initiate amelioration or modest presentation of the symptoms [(3)].

CLASSIFICATION

Different subgroups of MG can be identified based on the type of clinical characteristics and antibodies involved. Every group has a prognostic value because they react to treatment in different ways:

- Early-onset MG: Thymic hyperplasia with onset age < 50 years
- Late-onset MG: Thymic atrophy and age at onset over 50 years are characteristics.
- Thyroid-related MG
- MG using antibodies against MuSK
- Ocular MG: Periocular muscle-specific symptoms
- MG without discernible MuSK and AChR antibodies

Clinical Classification: Based on clinical characteristics and disease severity, the Myasthenia Gravis Foundation of America (MGFA) separates MG into 5 primary classifications. Every class has a unique prognosis or therapy response [(4)].

- Class I: Consists of any weakness in the ocular muscles, such as the weakness of the eye closure. The remaining muscle groups are all normal.

• Class II: Consists of modest weakness in muscles other than the muscles of the eyes. Any degree of ocular muscle weakness could exist.

• Class IIa: Contains a predominately weak limb, weak axial muscles, or both. To a lesser degree, it might also affect the oropharyngeal muscles.

• Class IIb: Mostly affects the respiratory, oropharyngeal, muscles, or both. It may involve axial muscles, limb muscles, or both to a lesser degree.

Class III: Moderate muscle weakness apart from eye muscles. Any degree of ocular muscle weakness may exist.

Class IIIa: mostly affects the leg, the axial muscles, or both. Less frequently, oropharyngeal muscles may be affected.

Class IIIb: Predominately affects the oropharyngeal, respiratory, or both muscles. Either the axial muscles, the limb, or both may be partially or fully involved.

Class IV: The afflicted muscles have considerable weakness. Any degree of ocular muscle weakness may exist.

Class IVa: Primarily affects the limbs, the axial muscles, or both. Less frequently, oropharyngeal muscles may be affected.

Class IVb: Predominately affects the oropharyngeal, respiratory, or both muscles. Either the axial muscles, the limb, or both may be partially or fully involved. Patients in need of feeding tubes who are not intubated are also included.

Class V: Intubation, either with or without mechanical ventilation, unless it's used for standard postoperative care.

Serum levels of detectable AChR antibodies are nearly always present in MG patients with Thymoma. Additional paraneoplasia-associated antibodies, such as those against voltage-gated K+ and Ca++ channels, anti-Hu, antidihydropyrimidinase-related protein 5, and antiglutamic acid decarboxylase, may also be present in MG associated with thymomas [(5)].

CLINICAL FEATURES

Patients typically exhibit weakness and fatigue, which gets worse with prolonged or repetitive activity and gets better with rest. The symptoms tend to worsen towards the end of the day, and they can change from hour to hour and day to day. Exercise, mental strain, high temperatures, infections, some medications (phenytoin, aminoglycosides, local anaesthetics), menstruation, pregnancy, and surgery are among the variables that exacerbate weakness [(6)].

Most patients will experience ptosis and/or diplopia at some point while their illness is progressing. Furthermore, within two years of the disease beginning, up to 80% of patients with ocular onset will experience the onset of generalised symptoms [(2)].

PATHOGENESIS OF MYATHENIA GRAVIS:

MG occurs because of a decrease in functional skeletal muscle nicotinic acetylcholine receptors (AChR) and structural changes in the neuromuscular endplate caused by various autoantibodies [(7)]. Around 85% of myasthenia gravis (MG) cases stem from acquired antibodies targeting acetylcholine receptors at the postsynaptic side of neuromuscular junctions (NMJs). Ordinarily, a nerve fiber releases acetylcholine, which then binds to acetylcholine receptors on the muscle fiber, triggering muscle contraction [(8)].

The AChR is a five-subunit ligand-gated channel, existing in two distinct forms with specific subunit compositions: the fetal AChR is made up of $\alpha 2\beta\delta\gamma$ subunits, and the adult AChR consists of $\alpha 2\beta\delta\varepsilon$ subunits.

The α-subunit is crucial, containing two essential domains: an extracellular cysteine loop responsible for acetylcholine (ACh) binding, and an extracellular sequence known as the main immunogenic region (MIR), where most AChR autoantibodies bind.

In the process of development and muscle innervation, the γ-subunit in fetal AChR is replaced by the ε -subunit, forming adult AChRs. Functional AChRs, composed of folded subunits, are usually found in skeletal muscle cells and thymic myoid cells exclusively.

Within the normal thymus, non-innervated thymic myoid cells express both adult and fetal AChR, likely aiding in the development of central immunological tolerance towards muscle proteins [(7)].

In MG, autoantibodies not only block acetylcholine receptors but also destroy them through a complement-mediated process, leading to a decrease in available receptors for acetylcholine binding. This results in muscle weakness and fatigue, especially during repeated muscle use, due to the impaired ability of acetylcholine to initiate muscle contractions [(8)].

Furthermore, apart from antibodies targeting acetylcholine receptors, there are other antibodies such as muscle-specific tyrosine kinase and lipoprotein receptor-related protein 4 that have been linked to MG. Autoantibodies targeting AChR, MuSK, and LRP4 are detected in approximately 80%, 1-5%, and 1-33% of myasthenia gravis patients, respectively [(9)].

However, some MG patients do not test positive for these established antibodies. It is believed that there might be unidentified antibodies in these seronegative patients, potentially playing a role in the condition [(8)].

In experimental settings, MuSK IgG4 antibodies impact MuSK's capacity to uphold the correct density of acetylcholine receptors (AChR) at the neuromuscular junction (NMJ). These antibodies also interfere with a compensatory presynaptic mechanism regulating quantal release at the NMJ. Both AChR-MG and MuSK-MG demonstrate high responsiveness to immunomodulatory therapy, meeting the criteria outlined by Witebsky for autoimmune diseases [(9)].

LRP4-MG appears to meet these criteria: immunization with the extracellular domain of LRP4 in mice produced anti-LRP4 antibodies, leading to symptoms associated with myasthenia gravis [(9)].

DIAGNOSIS:

The clinical diagnosis of autoimmune Myasthenia Gravis (MG) is based on the patient's medical history and physical examination, which reveals variable and fatigable muscle weakness within a particular distribution. Aside from helping to identify the type and severity of synaptic disorder, ancillary bedside tests and laboratory methods also help to classify MG based on the antibodies that cause it and objectively evaluate the impact of treatment [(10)].

Tensilon (Edrophonium Chloride) Test: Acetylcholinesterase inhibitors with a short half-life, such as edrophonium chloride, extend the half-life of acetylcholine at the NMJ. After intravenous edrophonium administration, the patient is monitored for objective improvements in muscle strength, specifically in the ptosis of the eyelid and/or extraocular muscle movement. The only conclusive evidence of a successful outcome should be a clear increase in the strength of a sentinel muscle.

Ice Pack Test: When the Edrophonium test is not appropriate for ptosis patients, the non-pharmacological ice pack test may be used. It involves applying an ice pack to the eye for two to five minutes and then determining whether the ptosis has improved.

Electrophysiological Tests: Single fibre electromyography and repetitive nerve stimulation study are the two main electrophysiologic tests used to diagnose MG. Neuromuscular transmission is tested using repetitive nerve stimulation. The nerve is stimulated supramaximally at 2-3 Hz to accomplish the task. An evoked muscle action potential with a 10% decrease between the first and fifth is indicative of MG. In terms of MG diagnostic testing, single-fiber electromyography (SFEMG) is the most sensitive. Action potentials from individual muscle fibres can be identified using a specialised needle electrode. It permits the simultaneous recording of two muscle fibres' action potentials that are innervated by the same motor axon. "Jitter" refers to the variation in the second action potential's time relative to the first. Because there is less safety factor for transmission at the neuromuscular junction in MG, jitter will rise. If the relevant muscles are examined, 95%–99% of MG patients have abnormal jitter on SFEMG [(5)].

MANAGEMENT:

ACHE INGHIBITORS:

AChE inhibitors were one of the earliest remedies for MG, with physostigmine being the initial choice in 1934. Dr. Mary Walker documented a case where subcutaneous physostigmine temporarily restored muscle function in an MG patient.

Later, neostigmine replaced physostigmine due to its safer profile and became the primary treatment until the arrival of pyridostigmine. European guidelines recommend AChE inhibitors as the first-line therapy for MG [(11)].

The initial step in managing mild or moderate symptoms of myasthenia gravis (MG) involves the use of ACE inhibitors, which slow down acetylcholine degradation, prolong its effect at the neuromuscular junction, and alleviate symptoms such as ptosis, dysphagia, and dysarthria. However, responses to ACE inhibitor treatment vary among patients, with some experiencing significant improvement while others may see little or no benefit.

Complete resolution of diplopia rarely occurs with ACE inhibitors alone, often necessitating the addition of immunosuppressive agents for effective MG symptom control. Pyridostigmine is a commonly prescribed medication for MG, with rapid onset and short duration of action.

It can cause muscarinic side effects like nausea and bradycardia, which can be mitigated with concurrent use of specific medications. Cholinergic crises, severe weakness resulting from excessive ACE inhibitor use, are rare due to increased awareness of dosage limitations.

Please note that medical practices evolve, and it's crucial to consult healthcare professionals or the latest guidelines for the most current information on MG treatments [(12)].

In pregnancy, pyridostigmine has not demonstrated teratogenic effects in animal studies, and there are no sufficiently rigorous human trials to confirm its safety. It offers symptomatic relief, similar to non-pregnant myasthenia gravis (MG) patients. The recommended maximum dose for pyridostigmine is below 600 mg/day. It is advisable to refrain from using intravenous cholinesterase inhibitors, as they may induce premature labor [(1)].

SHORT TERM IMMUNOMODULATING THERAPY:

PLASMAPHERESIS:

Immunoadsorption and plasmapheresis Therapeutic plasma exchange (PE) or plasmapheresis is a technique used to remove plasma from the components of corpuscular blood and replace it with a substitute fluid. Therefore, PE is a non-specific treatment method that eliminates all of the plasma. The elimination of pathogenic immune factors in circulation, such as autoantibodies, is the basis for the therapeutic effect. Conversely, immunoadsorption (IA) is a more focused method of eliminating IgG antibodies through binding to a particular matrix (such as tryptophan or protein A) [(8)].

When used by different investigators, plasmapheresis for the treatment of myasthenia gravis has produced inconsistent results due to significant variations in the volume, frequency, and speed of the procedure as well as in the kind and dosage of concurrent immunosuppressive medication therapy. When used as a brief crisis intervention, even in the absence of concurrent medication therapy, plasmapheresis results in a transient improvement in clinical status and a decrease in the antibody titer against the acetylcholine receptor. Most patients can achieve stable improvement with plasmapheresis when used as a long-term primary therapy under ideal circumstances [(14)].

IV. IMMUNOGLOBULIN THERAPY:

The generation of antibodies against AChR appears to be suppressed or the inhibitory processes are generally modulated but the actual mechanism is unclear.

Most patients experience positive changes in their condition, with improvement starts within 1 week and stays for months. Headaches, chills, and fever are among the frequent side effects of IVIG that are correlated with the pace of infusion. By dosing acetaminophen or aspirin plus diphenhydramine prior to every infusion, these responses can be minimised.

Patients implementing IVIG for conditions apart from MG, have documented some catastrophic responses such baldness, aseptic meningitis, leukopenia, and retinal necrosis. It has been documented among IVIG patients who experienced vascular blockage [(15)].

IgG purified immunoglobulin is derived from pooled blood donors, which is used in intravenous immunoglobulin. 2 g/kg (0.4 g/kg/day) over the course of 2 to 5 days is the typical IVIG dose. While IVIG may not be necessary in cases of renal impairment, the presence of cardiac illness may merit it [(16)].

When it comes to reducing the period of mechanical breathing over myasthenic crises, IVIG has been discovered to be just as effective as plasmapheresis and immunoadsorption. Apparently, extended IVIG regimen appears to be beneficial for individuals experiencing drug-resistant myasthenic effects. In the instance of extensive MG prior to surgeries or ahead of implementing a vein-based GCS pulse programme of high dose, IVIG could be ingested for clinical management [(8)].

LONG TERM IMMUNOGLOBULIN THERAPY:

CORTICOSTEROIDS:

The autoimmune nature of the illness and the advantages of this class of medications in other autoimmune diseases provide justification for the use of corticosteroids. There is little knowledge about how corticosteroids work in MG. Impacts on helper T cell activation and B cell proliferation are thought to be involved, as are activated T cells and antigen-presenting cells [(17)]. The primary immunomodulatory therapy used in the long-term management of MG patients is either prednisolone or prednisone. Most will need long-term oral corticosteroid therapy, so it's important to let newly diagnosed patients know that this won't be a quick fix during their initial consultation. It is equally important to explain to patients the extensive list of possible steroid side effects that call for stomach and bone protection. Additionally, patients should have proper monitoring for the onset of hypertension and diabetes mellitus, as well as cautious counselling regarding possible excessive weight gain and any dietary adjustments that may be required in order to prevent and treat these conditions early on. The ceiling dose for prednisolone is typically 50 mg daily, however higher doses have been prescribed in a few specific cases. Initially, we start prednisolone at 5 mg daily and increase every third dose (day) by 5 mg until we achieve stability in MG symptoms and significant improvement [(18)].

IMMUNOSUPPRESIVE AGENTS:

Prednisone and prednisolone are corticosteroids that benefit all forms of MG by increasing muscle strength. Moreover, corticosteroids may stop the disease's progression from ocular to generalized MG. Immunosuppressive drugs such as azathioprine (first-line treatment that can be combined with corticosteroid), cyclosporine, methotrexate, mycophenolate mofetil, or tacrolimus are options for patients who are not responsive to or cannot tolerate corticosteroid [(1)].

AZATHIOPRINE:

Azathioprine is an antimetabolite, disrupts the synthesis of purines resulting in the suppression of DNA and RNA generation, hindering cellular replication, and compromising the function of lymphocytes. Azathioprine is used in cases of generalized myasthenia gravis where symptoms persist despite corticosteroid treatment, as well as for patients with conditions such as hypertension, diabetes mellitus, and osteoporosis that make corticosteroids inadvisable. It is also an option for those who experience severe side effects from corticosteroids [(19)].

Apart from corticosteroids, azathioprine is the predominant choice for prescribed long-term immunosuppression in the management of MG. Typically the treatment begins with the dose of 2-3 mg/kg. To ease treatment commencement, a preliminary test dose of 50 mg per day for one week can be useful. In cases where patients do not respond adequately to steroids, azathioprine becomes the preferred steroid-sparing agent [(20)].

Azathioprine has a gradual onset of action; it may reach its maximum effectiveness within 24 months and it takes about 4 – 12 months to become evident. Treatment tends to be well tolerated, though 10% of patients may encounter unusual flu-like symptoms and GI discomfort during the first few days of the regimen. Xanthine oxidase inhibitors (febuxostat or allopurinol) block the metabolism of azathioprine, concurrent use of these medications should be avoided [21].

METHOTREXATE:

As per the latest EFNS guidelines, if MG patients do not respond to azathioprine, it is advisable to contemplate the use of methotrexate as an appropriate alternative. Methotrexate is initiated at a weekly dosage of 10 mg and is gradually increased to 20 mg per week over two month period. In order to reduce the side effects, it is common practice to prescribe folic acid (5mg weekly) in conjunction with methotrexate. It's advisable to take this on a different day of the week compared to when methotrexate is taken [21].

MYCOPHENOLATE MOFETIL:

Mycophenolate mofetil restrains the growth of T- and B-lymphocytes by inhibiting inosine monophosphate dehydrogenase, an essential enzyme involved in the production of guanosine nucleotides. Patients may experience therapeutic effectiveness as early as five months after commencing therapy, but it might require up to 10 to 12 months for significant progress. The standard regimen involves a daily dose of 2–3 grams of mycophenolate mofetil, divided into two separate doses. After obtaining the desired therapeutic effect, it is advisable to continue this medication for a few years before cautiously reducing the dosage, ensuring that the decrease does not exceed 500 milligrams per day annually. This approach serves as a precaution to prevent the return of MG symptoms or exacerbations. Mycophenolate mofetil is the alternative regimen for patient intolerant to steroids [22].

SURGICAL MANAGEMENT

THYMECTOMY:

Thymectomy is highly advisable for individuals diagnosed with thymoma [5]. For individuals under 45 years old who do not have a thymoma and have positive anti-AChR antibodies, thymectomy is advised. This could lead to a reduction in the need for corticosteroids, stop generalization, and trigger remission [23]. Thymectomy is suggested when the patient's weakness is adequately controlled, enabling them to undergo surgery. Typically, patients about to undergo surgery receive prior treatment with low-dose glucocorticoids and IVIg.[5] Thymectomy has conventionally been executed through the median sternotomy technique. Certainly, minimally invasive methods using transcervical, transthoracic, and subxiphoid approaches are believed to offer several advantages, including reduced chances of respiratory and cardiac complications, lower intraoperative blood loss, decreased need for blood products, reduced inflammatory cytokine response, diminished postoperative discomfort, early removal of chest drains, shorter hospitalization, and improved cosmetic outcomes [23]. Thymectomy might not be a suitable therapeutic option for individuals with anti-MuSK antibody positivity due to the absence of germinal centers and lymphocyte infiltrates, distinguishing their thymi from those of anti-AChR antibody-positive patients. The majority of specialists regard thymectomy as a viable treatment choice for individuals with early-onset gMG who test positive for anti-AChR antibodies and are under the age of 50 [5].

REHABILITATION:

Rehabilitation, as defined by the World Health Organization in the World Report on Disability (Geneva, Switzerland: WHO; 2011), encompasses a series of interventions designed to support individuals with disabilities in achieving and sustaining optimal physical, sensory, intellectual, psychological, and social functioning within their environment.

This process involves a comprehensive and coordinated interdisciplinary care program, offering individualized therapies tailored to the specific needs of each patient. The ultimate goal of rehabilitation is to enhance functional independence and encourage active participation, emphasizing patient education and self-management throughout the process [24].

Patients with MG often report a pervasive sense of fatigue. This fatigue is not specific to particular muscles or movements and isn't correlated with the extent of muscle weakness determined in formal strength assessments.

This generalized lack of energy and tiredness is sometimes referred to as central fatigue, suggesting potential underlying causes beyond antibodies binding to the neuromuscular junction. Typically, this type of fatigue does not respond well to immunosuppressive treatments and tends to discourage patients from engaging in physical activities.

Increasingly, healthcare professionals recommend physical training programs for patients dealing with various physical and psychiatric conditions. Both aerobic exercises and strength training are recommended for individuals with muscular dystrophies and congenital myopathies [25].

Supervised aerobic and resistance training in MG showed that standard physical exercise guidelines could be safely followed by well-regulated MG patients with mild disease. There were no observed exacerbations in MG fatigue or disease activity. The training program was well tolerated, and, in fact, it led to an improvement in muscle function. [26].

CONCLUSION:

Myasthenia gravis (MG) is a disorder of neuromuscular synaptic transmission which arises from autoimmune antibodies. When appropriately treated, individuals with MG can expect to have a life span that is typical, with a combination of medication, thymectomy, and other therapeutic plans often allows many individuals to maintain a high quality of life.

A range of approaches including anticholinesterase agents, immunosuppressive drugs, plasmapheresis are utilized as a sustaining treatment. Thymectomy has gained growing acceptance as a treatment for MG. Typically, individuals who promptly receive accurate diagnoses and effective treatment tend to achieve the best outcomes.

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