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Myasthenia Gravis: An Updated Review

Ahmed A and Milind Kothari DO*

Penn State College of Medicine, Hershey Medical Center, Department of Neurology – EC037, 30 Hope Drive, Hershey, PA 17033, USA

***Corresponding author:** Milind Kothari DO, Penn State College of Medicine, Hershey Medical Center, Department of Neurology – EC037, 30 Hope Drive, Hershey, PA 17033, USA

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Abstract

Myasthenia Gravis (MG) is an autoimmune disease caused by autoantibodies directed at the Neuromuscular Junction (NMJ) causing muscle weakness and fatigability. The disease is further characterized by having either a paraneoplastic form (thymoma-associated) or non-paraneoplastic forms and the disorder is immunologically heterogeneous with different antibodies. Currently available management modalities include symptomatic pharmacological treatment, immunomodulatory drugs, thymectomy and supportive therapies. In this review, we summarize the clinical disorder and highlight the different treatment options available to heath care providers caring for patients with MG.

Keywords: Weakness; Fatigue; Neuromuscular junction; Immune modulation

Introduction

Myasthenia gravis results from dysfunction of the neuromuscular junction causing muscle weakness that worsens with muscle use and improves with rest. The majority of the myasthenic disorders result from dysfunction of the postsynaptic component of the NMJ, although involvement of either the synaptic cleft or the presynaptic motor nerve terminal can also produce myasthenia [1].

The prevalence of MG is 150–300 per 1,000,000, with an annual incidence of more than 10 in 1,000,000. Both prevalence and incidence increase with age. Acetylcholine receptor -associated myasthenia gravis has a bimodal age pattern of incidence, with a peak in young adults aged about 30 years and then a steady increase in incidence with increasing age older than 50 years. The incidence peak in young adults is mainly because of the high frequency in women, typical for many autoimmune disorders, although late-onset myasthenia gravis is slightly more frequent in men. MG patients have an increased risk for complicating autoimmune diseases, most commonly autoimmune thyroid disease, systemic lupus erythematosus and rheumatoid arthritis [2-4].

Pathophysiology

The major antigen in MG is the Acetylcholine Receptor (AChR) on the muscle membrane. Some patients without AChR antibodies have autoantibodies against the Muscle Specific Kinase (MuSK) which is a protein that allows AChR clustering at the neuromuscular junction. Less commonly, patients with MG who do not have either AChR or MuSK antibodies have antibodies against low-density lipoprotein receptor-related protein 4 (LRP4), a receptor for neural agrin that relays the signal to MuSK to initiate AChR clustering. Patients without detectable antibodies against any of these three antigens are referred to as seronegative [5-8]. E neural agrin ach of the above mentioned antibody will be discussed in detail:

AChR antibodies

These can be detected with routine assays in 70% of all patients with MG. AChR antibodies bind to extracellular domains of the receptor causing disruption of the signal transduction. AChR antibodies mostly belong to the IgG_1 and IgG_3 subclasses, which activate the complement cascade, leading to destruction of the postsynaptic membrane. This is thought to also contribute by the up regulation of inflammatory cytokines. [9-11]

MUSK antibodies

These are post-synaptic proteins which are critical for the development and maintenance of the NMJ. It is still very unclear how MuSK antibodies cause myasthenia, although recent work suggests that complement activation seems unlikely to play a role. It is thought that inhibition of retrograde signaling may be an important aspect [12,13].

LRP4 antibodies

These bind to block the agrin–LRP4 interaction and thereby also inhibit AChR clustering in the membrane. Interference with the LRP4–MUSK interaction might also be a relevant disease mechanism for this subgroup [14].

Other antibodies

Agrin antibodies have been detected in a few patients with myasthenia gravis and AChR, MUSK, or LRP4 antibodies. Agrin is essential for AChR function, but whether these antibodies contribute to the muscle weakness in this disease is still unclear [15].

Some MG patients have antibodies that bind in a cross-striational pattern to skeletal and heart muscle tissue sections. These antibodies react with epitopes on the muscle proteins titin and ryanodine receptor. The detection of titin and ryanodine receptor antibodies provides more specific clinical information than the immunofluorescent demonstration of striational antibodies [16].

Titin maintains cell structure, whereas the ryanodine receptor is a sarcoplasmic reticulum calcium channel that helps with contraction. These antibodies are present with a high frequency in thymoma-associated myasthenia gravis, with an intermediate frequency in late-onset myasthenia gravis, and very rarely in early-onset and ocular myasthenia gravis. Titin and ryanodine receptor antibodies can be used to diagnose a thymoma in patients younger than 50 years. These antibodies have been proposed as markers for severe myasthenia

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gravis with a need for long-term immunosuppression and no response to thymectomy. Commercial tests with ELISA are available for titin but not for ryanodine receptor antibodies [17,18].

Clinical Presentation

Common complains are diplopia, ptosis, without pupillary abnormalities, bulbar and generalized weakness and fatigability. There can also be respiratory weakness. There are various different forms of MG with classification based often on the combination of certain signs and symptoms and the presence of certain antibodies. They are described below:

Pure ocular presentation

Approximately 15% of MG patients present with only ocular symptoms. Due to the high proportion of patients with initial ocular manifestations in the first year after onset, a minimal delay of two years without generalization is required to classify a patient as having a pure ocular form. One-half of these patients present antibodies not detectable by a classical assay [19].

Generalized form with anti-AChR antibodies

Approximately 85% of the MG population displays this form of the disease. High titers of antibodies are seen in patients with thymic follicular hyperplasia. Thiscan be further classified based on the age of presentation.

Age <50 years

This group has predominantly thymic follicular hyperplasia that is found mainly in women. Other autoimmune diseases can also be associated with MG in these patients.

Age >50 years

This late form is frequently associated with the presence of a thymoma. Other autoantibodies such as the anti-ryanodine antibodies, the anti-titin antibodies or the anti-striated muscle antibodies are frequently found (50%) in those patients, notably in patients with thymoma. Most patients have generalized and severe symptoms such as bulbar involvement [19,20].

Anti-MuSK antibodies

Approximately 5% of the MG population has this antibody type. MuSK positive patients are typically female, and have a severe form of the disease with common muscular atrophy. The facial, bulbar, and respiratory muscles are often affected, whereas ocular symptoms and thymic abnormalities are very uncommon. Interestingly, both presynaptic and postsynaptic components of the NMJ are affected in MuSK-MG disease. There is a clear correlation between the disease severity and the antibody titer [21].

Anti-LRP4 antibodies

Approximately 12–50% of the seronegative population presents antibodies to LRP4. The clinical phenotype of the patients presenting anti-LRP4 antibodies is not well defined [22].

Neonatal MG

In 10–20% of the cases, the newborns of myasthenic mothers will display a Transient Neonatal Myasthenia (TNM) that could last a few days to 3 months. This disease is because of the passive transfer of the antibodies of the mother, especially the anti-AChR antibodies. There is no correlation between the severity of the disease in the mother and the onset and severity of the disease in the infant [23].

Congenital myasthenic syndromes

These are genetic disorders that generally present early in life. The congenital myasthenic syndromes are classified based on the location of the involved protein: presynaptic (eg, voltage-gated sodium channel and choline acetyltransferase), synaptic (cleft) (eg, acetylcholinesterase and β2-laminin), or postsynaptic (eg, ACh receptors, MuSK, DOK7, and rapsyn). These mutations have been identified primarily by DNA sequencing of NMJ genes. [1]

Evaluation

Tensilon test

The diagnosis is supported by unequivocal improvement of strength following administration of an anticholinesterase drug. Intravenous edrophonium (Tensilon) is used usually. The effects of edrophonium are transient, usually less than 10 minutes in duration, but rarely may last longer. Side effects include increased tearing, salivation, muscle fasciculations, and abdominal cramps. Caution should be exercised in patients with cardiac disease because bradycardia and even cardiac arrest can occur.

Electrodiagnostic testing

Routine nerve conduction studies and electromyography usually are not conclusive. The techniques of Repetitive Nerve Stimulation (RNS) studies and Single Fiber Electromyography (SF-EMG) often are necessary for diagnostic purposes Repetitive Nerve Stimulation Studies show a decremental response in MG which denoted the decreased safety factor in NMJ abnormalities. The muscle fiber depolarization is insufficient for the end-plate potential to reach the threshold necessary to generate an action potential. In Single Fiber Electromyography (SF-EMG), action potentials from two or more muscle fibers in the same motor unit are recorded. The time interval between them is variable with consecutive discharges. This variability in synaptic transmission time is due to changes in rise time of the end-plate potentials and is called neuromuscular jitter. When neuromuscular transmission is impaired, with jitter values go up and neuromuscular block may occur as end-plate potentials fail to reach adequate threshold to generate action potentials.

Antibodies

The presence of serum binding antibodies to human AChR is highly specific for the diagnosis of MG. In 74% of patients with myasthenia gravis, serum antibodies to acetylcholine receptor are present. In the remainder suspected cases, the other antibodies discussed in detail above should be tested [24].

Management

This includes symptomatic treatment, immunomodulatory treatment (steroids as well as non steroidal agents), rapidly acting immune therapy and thymectomy [6]. These are discussed below in detail.

Cholinesterase inhibitors

Pyridostigmine bromide is the most common first treatment which causes reduction of acetylcholine breakdown by acetylcholinesterase inhibition. Initial doses of 30 to 60mg of pyridostigmine every 3 to

6 hours are recommended. The maximum effectiveness is seen early in the disease course and over time patients may develop tolerance, which may respond to dose escalation. Single doses greater than 120 to 180mg rarely provide superior benefit and usually only lead to greater side effects. Pyridostigmine continues to have a role in symptomatic management [25]. form can also be used mostly at night time.

Corticosteroids

Prednisone is the first-line immunosuppressant treatment for MG. A dose of 60 to 80 mg daily is usually recommended, but acute worsening of weakness may be observed in first 7 to 14 days after treatment initiation in about half of patients. Because of this, it may be helpful to start with a lower dose and gradually titrate up. Improvement in weakness tends to be seen within 2 weeks, and in upwards of 90% of patients within 1 month with maximum significant improvement observed by 6 to8 weeks [25]. The biggest challenge is the numerous side effects such as hyperglycemia, bone loss, gastric ulcers, weight gain and edema, which makes the long term utility of this form of immune suppressant difficult to use.

Non-steroidal immune suppressants

Use of azathioprine as a steroid-sparing agent is supported by good quality evidence and allows for tapering off of the prednisone. Its mode of action is through purine synthesis inhibition leading to inhibition of the dividing T and B lymphocytes. Azathioprine is usually provided at a dose of 2 to 3 mg/kg divided into two or three doses per day. A treatment response takes over 12 months usually. Adverse effects include a flu-like symptoms, leukopenia, thrombocytopenia, hepatotoxicity, alopecia, and increased risk of neoplasia, primarily lymphoma. Patients with a deficiency of thiopurine S-methyltransferase can manifest enhanced bone marrow toxicity. Red cell thiopurine S-methyltransferase activity can be measured to identify such patients [26,25].

Mycophenolate mofetil inhibits de novo purine synthesis specifically in lymphocytes and is used at a dose of 1000 to 1500 mg twice per day. Retrospective studies with small numbers of patients suggested a corticosteroid-sparing effect and clinical improvement. Two randomized, controlled trials did not demonstrate a therapeutic benefit. These trials have been criticized for their short duration compared with the expected biological effect of mycophenolate on lymphocyte production. Side effects include diarrhea, anemia, leukopenia, infections, and a possible increased risk for lymphoma. Progressive multifocal leukoencephalopathy has also been reported with mycophenolate treatment [25].

Cyclosporine A blocks calcineurin-mediated cytokine signaling and therefore is an inhibitor of T helper cell function. It often is used for patients refractory to or intolerant to treatment with steroids and/or azathioprine. Standard cyclosporine dosage is 5 mg/kg per day in divided doses. The desired serum trough level is 100 to 150 μg/L [27]. Side effects are usually dose dependent and include nephrotoxicity, hypertension, tremor, hirsuitism, gingival hyperplasia, myalgia, flu-like symptoms, and an increased risk of neoplasia. Monitoring of serum creatinine is recommended throughout the course of treatment. Usually clinical improvement is noted in 6 months [25-28]

Tacrolimus (FK506) is a macrolide immunosuppressant and binds to FKBP12 (FK506-binding protein) and, subsequently, by a calcineurin-mediated pathway inhibits T-cell and interleukin-2 production. Tacrolimus has an additional effect on ryanodine receptor-mediated calcium release from the sarcoplasmic reticulum, which theoretically could lead to improvements in muscle strength in patients with myasthenia gravis. A dose of 3 mg/d is used. It can reduce the need to other immune suppressants. Side effects are dose related and include parasthesia, diarrhea, tremor, headache, hypertension, nausea, renal insufficiency, hyperglycemia, hyperkalemia, hypomagnesaemia, and possible risk of malignancy [6,25,29].

Methotrexate is a commonly used alternative to azathioprine. It is an anti-metabolite which has been used for decades in cancer therapy. A recent single-blind study provides evidence that methotrexate is an effective steroid-sparing agent 10 months after treatment initiation in generalized MG. This study suggests that methotrexate has similar efficacy and tolerability to azathioprine. The optimal initiation dosing recommendation is starting at 15 mg weekly. Low doses are well tolerated and side effects include hepatic toxicity, gastrointestinal symptoms and pulmonary fibrosis [30,31].

Cyclophosphamide is a cell-cycle non-specific anti-proliferative agent that exerts its cytotoxic action primarily by unpaired replication of DNA and damage to the DNA structure. Cyclophosphamide is given over 4 to 5 days, however various dosage schedules have been used ranging from a low dose of 2–6 mg/kg to high dose of greater than 1600 mg/m^2 body surface area. Concurrent administration ofondansetron and sodium-2-mercaptoethane sulfonate can decrease vomiting and the risk of hemorrhagic cystitis respectively. IV pulses of cyclophosphamide have been used for maintenance depending on the response, and tolerability. Side effects include included severe vomiting, pancytopenia, sepsis, hemorrhagic cystitis and severe bone marrow suppression. Usually clinical improvement is noted in 6- 12 months [25,32].

Etanerceptis a soluble recombinant tumor necrosis factor α (TNF α) receptor Fc. Bongioanni et al. reported that MG patients have significantly more TNF α receptors in T cells than controls and therefore the enhanced T cell TNF α binding is due to an increased number of TNF α receptors in T-helper lymphocytes. A pilot open-label clinical trial by Rowin et al. was conducted to assess the safety and potential efficacy of etanercept in a group of corticosteroid-dependent patients with MG. It showed improvement after 5 months of treatment. The small numbers and open-label design of the study questioned the definitive assessment of efficacy [33,34].

The use of monoclonal antibodies is gaining attention. A commonly used agent is rituximab. This is a genetically engineered chimeric mouse/human monoclonal antibody. It is approved for the treatment of some lymphoma types and of severe active rheumatoid arthritis. Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. It is considered to provide better clinical in anti-MuSK than in anti-AChR MG patients. The standard dose is 375 mg/m^2 every week for 4 consecutive weeks and then monthly for the next 2 months. Adverse effects are fever, chills, bronchospasm, neutropenia, thrombocytopenia, and a risk of progressive multifocal leukoencephalopathy [25,35].

Plasmapheresis works by removal of autoantibodies and factors such as complement proteins. It is used in patients regardless of whether patients have detectable autoantibodies. Plasmapheresis treatment consists of 4 to 6 exchanges, each removing 3–5 L of plasma, performed daily or every other day. Plasma exchange is an important and effective short-term treatment for myasthenic exacerbations or crisis. The improvement is seen within 48 h of the first or second exchange. Commons concerns include involvement of invasive procedure such as placing an intravenous catheter and associated risk of infection and thromboembolism. Other side effects include paresthesia from citrate-induced hypocalcemia, hypotension, and risk of bleeding due to thrombocytopenia [25,31].

Intravenous Immunoglobulin (IVIG) is a concentrated immunoglobulin solution, primarily composed of IgG. The mode of action includes cytokine inhibition, competition with autoantibodies, complement inhibition, interference with Fc receptor binding, and interference with antigen recognition by sensitized T cells. Infusion of 2 g/kg divided over 5 days is the standard dose. Clinical improvement can be seen in14 days after treatment among patients with an exacerbation, with a treatment effect present 28 days after infusion. Complications include headache, aseptic meningitis, and flu-like symptom. Anaphylactic reaction occurs in patients with IgA deficiency. Thrombotic complications, including stroke and myocardial infarction can also occur. The ease of administration of IVIG via peripheral venous access is a significant advantage over Plasmapheresis. [36,25]

IVIG has comparable efficacy to plasma exchange in the treatment of patients with moderate to severe MG. Both treatments are well-tolerated, and the duration of effect is comparable. Either treatment may be offered to patients depending on availability of resources [37].

Thymectomy

10–20% of MG patients have a thymoma and about 30% of thymoma patients have thymoma-associated MG. Inflammatory, neoplastic and age-related thymicvariations are involved in the initiation of the various MG subtypes that are due to autoantibodies against the acetylcholine receptor. A role of the thymus in the pathogenesis of MuSK MG is considered unlikely given the normal histology of thymectomy specimens and failure of thymectomy to improve MuSK MG. The relationship between the thymus and LRP4 MG and "triple sero-negative MG" is currently unknown [38]. Thymectomy is indicated in patients with neoplastic thymoma due to the risk of extension of the tumor into adjacent structures in the mediastinum. Removal of the tumor does not lead to remission. Local irradiation may be needed. Some thymomas follow a malignant course with metastases and aggressive recurrence for which chemotherapy is required.

Uncertainty exists regarding several issues related to thymectomy. It is thought that the age of the patients should be < 65 years due to the commonly expected a trophy of thymus in elderly. Thymectomy is usually recommended within the first 3 years of diagnosis. Numerous approaches to thymus removal are in use, but limited evidence exists to promote one procedure over another. It is thought that the procedure that offers the greatest removal of thymic tissue would be superior to others. Despite a lack of expert consensus thymectomy is frequently performed for patients younger than 65 years who have generalized MG within the first 3 years of diagnosis [25,39].

Summary

With time, we are realizing the hetrogenicity of the immune mediated process responsible for acquired MG. Therefore, the mainstay of the treatment is immune modulation. We have now more medications in this category. However, the choice of the medication remains dependent on multiple factors such as co-morbidities, the associated antibodies present as well as the socio-economical status.

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