BRIEF REPORT

Myasthenia Gravis

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KEYWORDS:

Acetylocholine

Lipoprotein receptor-related protein

Muscle Specific Kinase

Myasthenia Crisis

Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder affecting 36,000 – 60,000 Americans. This article reviews the incidence, presentation, immune system markers and various treatment options for this illness. Family physicians must be aware of this disorder as they may be the first health professional contact for patients experiencing symptoms.

INTRODUCTION

Myasthenia Gravis (MG) is a neuromuscular autoimmune disorder characterized by muscle weakness and fatigability. It often presents with the ocular manifestations of ptosis and diplopia, however, it can include difficulty swallowing, generalized muscle fatigability, and respiratory muscle weakness. The disorder is caused by autoantibodies that target the neuromuscular junction, specifically at the acetylcholine receptor or related molecules described below. The prevalence of MG is 14 – 20 per 100,000 population in the US with approximately 36,000 – 60,000 total cases at any given time. Formerly it occurred twice as often in women, in whom the peak onset is during childbearing years. Men have a peak onset at age 70 and with the increase in late onset MG, men are now affected more often, usually after age 50. The symptoms can range from ocular weakness, to mild generalized symptoms and to severe symptoms leading to respiratory failure requiring intubation and mechanical ventilation *(Myasthenia Crisis)*.[1]

In 2010, Carr et al estimated an annual incidence of 9.4 cases per million person years from a variety of international studies.[2] The current incidence in the United states in not available in the literature. The antibody most commonly present in MG targets the acetylcholine receptor (anti-AChR) which approaches 100% specificity for the disease and occurs in 80% of MG patients.[3] Antibodies to muscle specific kinase (MuSK) are present in 4% of patients– including 40% of those with generalized MG. Another 2% have antibodies to lipoprotein receptor-related protein 4 (LRP4).[4] Most authors consider patients without AChR antibody seronegative, while others refer to patients without antibodies to AChr, Musk or LRP4 as seronegative. Patients with generalized Myasthenia Gravis are more likely to have MuSK or AChR. Some patients may have other less common antibodies (titin, agrin, striated muscle).[5,6,7] Positive antibody tests in patients with symptoms of MG are diagnostic. This variation in antibodies creates a dilemma in diagnosis and prognosis, given the additional variability in presentation and outcomes. Presently studies are being undertaken to discover if treatment should be tailored to the identified antibody type.

Myasthenia Crisis is a severe form of the illness in which respiratory muscles are affected, leading to periods of decompensation requiring respiratory support including intubation and mechanical ventilation or noninvasive ventilatory support to avoid intubation.[8] Myasthenia Crisis usually occurs in patients with generalized MG within the first two years following diagnosis. Patients with Myasthenia Crisis may have frequent admissions to the intensive care unit and have a poorer quality of life (QOL) score.[10,11,12]

The Myasthenia Gravis Foundation of America MGFA clinical classification for MG identifies patient characteristics as follows:

DIAGNOSIS

Myasthenia Gravis most often presents with symptoms of diplopia, from extraocular muscle weakness, and ptosis. Therefore, the physician must have a level of familiarity with the disease and clinical suspicion to diagnose the patient. Patients with these ocular findings without other causes should raise the suspicion of MG. Many patients complain only of muscle fatigue, a complaint with which physicians are commonly confronted. Finding an etiology becomes more difficult in the MG patient due to the intermittent nature of symptoms and findings, making a detailed patient history the most important aspect of the encounter. The hallmark of the disease is patient reports of intermittent weakness and fatigue of voluntary muscles, which become worse with activity. Periods

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TABLE 1:

MGFA Clinical Classifications[13,14]

Class I	– Any ocular weakness – May have weakness of eye closure – All other muscle strength is normal
Class II	– Mild weakness affecting other than ocular muscles – May also have ocular muscle weakness of any severity
Class IIa	– Mild weakness predominantly affecting limb, axial muscles, or both – May also have lesser involvement of oropharyngeal weakness
Class IIb	– Mild weakness predominantly affecting oropharyngeal respiratory, muscles or both – May also have lesser or equal involvement of limb, axial muscles or both
Class III	– Moderate weakness affecting other than ocular muscles – May also have ocular muscle weakness of any severity
Class IIIa	– Moderate weakness predominantly affecting limb, axial muscles, or both – May also have lesser involvement of oropharyngeal muscles
Class IIIb	– Moderate weakness predominantly affecting oropharyngeal, respiratory muscle or both – May also have lesser or equal involvement of limb, axial muscle or both
Class IV	– Severe weakness affecting other than ocular muscles – May also have ocular muscle weakness of any severity
Class IVa	– Severe weakness predominantly affecting limb and/or axial muscles
Class IVb	– Severe weakness predominantly affecting oropharyngeal, respiratory muscles or both – May also have lesser or equal involvement of limb, axial muscles or both
Class V	– Defined by intubation, with or without mechanical ventilation, except when employed during routine post-operative management. The use of a feeding tube without intubation places the patient in class IVb

of exacerbation followed by remissions are common. Additional symptoms, although less common, may include facial paresis, dysphonia, and neck weakness. The weakness is not associated with sensory abnormalities, resulting in a normal sensory exam. Patients with more advanced disease can have bulbar symptoms (difficulty swallowing, dysarthria, slurred speech) or generalized symptoms (extremity and respiratory muscle weakness) on presentation. A patient with findings of fatigability and any of these symptoms should be tested for MG.[15,16] The differential diagnosis in patients presenting with these findings includes amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and myasthenic syndromes; Lambert-Eaton Syndrome and toxic and drug induced myasthenic syndromes from botulism, Penicillamine, chloroquine, hydroxychloroquine.[17]

Although, not studied in a large cohort, case reports suggest the "ice pack test" may help with the diagnosis. This test is easily performed in the office and is accomplished by placing an ice pack over an affected eye for 2 minutes.[18] Improvement in the ptosis suggests a diagnosis of myasthenia gravis. This test has limited utility in diagnosing MG, since patients may not have ptosis at the office visit.

Laboratory testing is the primary method of diagnosing MG. Over 80% of MG patients have antibodies to the Acetylcholine receptor at the neuromuscular junction and a positive AChR Binding Antibody test. Additionally, 30% of generalized MG patients and 95% of MG patients with thymoma test positive for muscle specific tyrosine kinase antibodies (MuSK).[19] Finding these antibodies in the presence of symptoms of fatigability provides a diagnosis. Patients without AChR or MuSK antibodies (double seronegative) create a more difficult diagnostic challenge. Recently Lipoprotein receptor – related protein 4 (LRP4) was shown to be positive in a subset of seronegative patients.[20] Single-fiber Electromyography (SFEM) and Repetitive Nerve Stimulation (RNS) provide additional diagnostic options.[21] Clinically, the use of edrophonium hydrochloride, the "Tensilon Test", through its ability to briefly alleviate symptoms in patients with MG can lead to the diagnosis. Patients with antibodies to Acetylcholine receptors should be screened for thymoma, although there is a recent case report of thymoma occurring in a patient without this antibody. *Figure 1* represents the diagnostic workup for MG.

TREATMENT

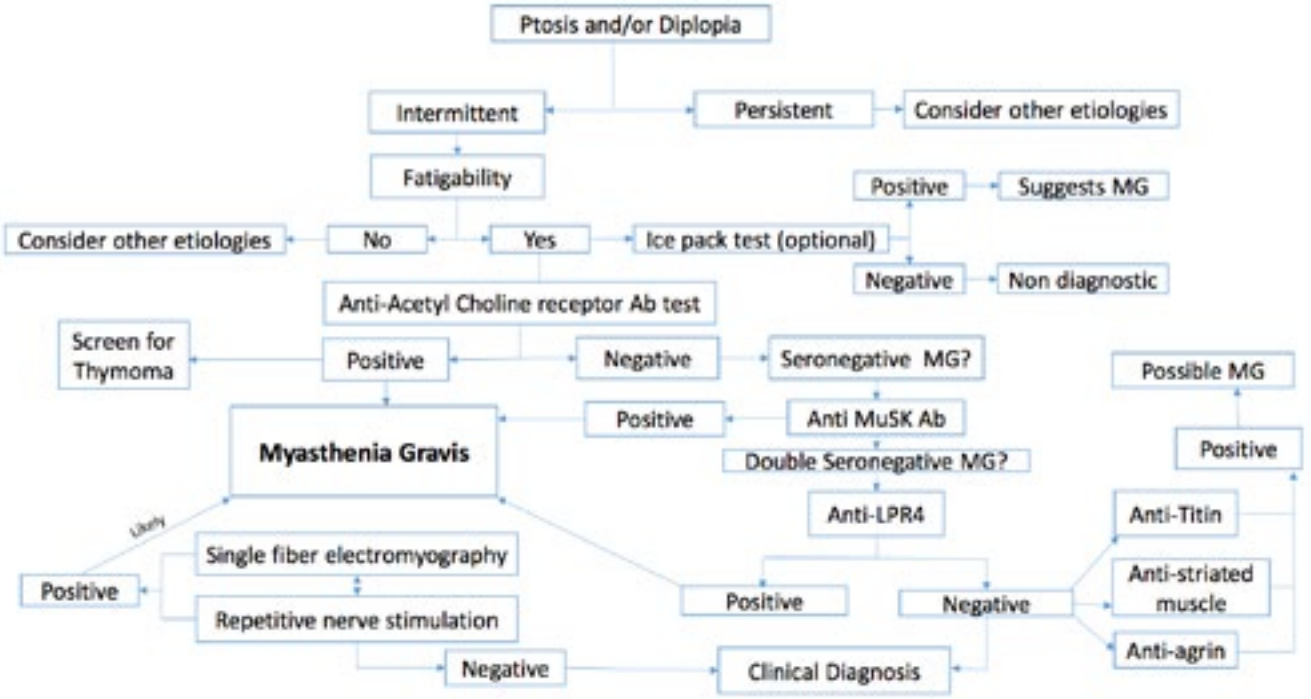
Once diagnosed, treatment depends on severity of symptoms and response to standard regimens. Most patients are initially started on acetylcholinesterase inhibitors, and /or corticosteroids to control symptoms.[23] Patients with persistent debilitating symptoms require long-term immunosuppressive agents, such as azathioprine, cyclosporine,[24,25] tacrolimus,[26,27] Methotrexate,[28] or mycophenolate mofetil,[29] all of which have been investigated with varying results. Still others with generalized refractory MG, particularly those with Myasthenia Crisis, may require cyclophosphamide,[30] rituximab,[31] and eculizumab,[32] and intravenous IVIg or plasma exchange (PLEX) for maintenance or crisis.[33,34] Select patients may also undergo thymectomy.[35,36] More recently, the use of autologous stem cell transplantation has been reported with some success, although the precise mechanism by which this alters the course of MG is unknown.[37,38,39,40] Various treatments for MG are listed in *Table 2*.

CONCLUSION

Because of the low prevalence of MG, large double blind studies of these treatments are lacking. Additionally, criteria for positive outcomes are variable.[41] Much of the guideline information is the result of studies with small cohorts and is based on expert opinion. Therefore, the treatment of the patient with myasthenia gravis requires the input of experts in the field. Often, the family physician will be the first contact for the patient and can play an integral role in the initial diagnostic workup for this disease. This is of importance since these patients often have a delay in diagnosis.

FIGURE 1:

Diagnosis of Myasthenia Gravis



The specialty centers available to patients, particularly helpful for those with generalized and refractory myasthenia gravis, are often far from the patient's home. Frequent exacerbations can be physically and emotionally debilitating for the patient and require expedited office and hospital care. The family physician should participate in team-based care of these patients, which often includes input from neurology, pulmonology, respiratory therapy, physical therapy, and behavioral health. As the patient's primary provider of health care, the family physician can be a source of emotional support and provide prompt treatment of acute events resulting from MG. Additionally, the family physician must ensure that, like other major diagnoses, an MG diagnosis does not result in neglect of routine and preventive medical care.

AUTHOR DISCLOSURES:

No relevant financial affiliations

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TABLE 2:

TREATMENT	USE	MECHANISM	ONSET OF ACTION	ADMINISTRATION
CORTICOSTEROIDS				
Pyridostigmine Bromide	Acute and chronic treatment of Ocular and generalized MG	Increases acetylcholine at the synaptic cleft by inhibiting acetylcholinesterase	Minutes	Oral tablet, syrup IM injection
Intranasal Neostigmine			Minutes	Intranasal Spray
CORTICOSTEROIDS				
Prednisone	Initial and chronic treatment of ocular and generalized MG	Unclear mechanism in MG. Reduces leukocyte activity (recruitment, migration) and production of cytokines.	Weeks. Possible exacerbation in first 14 days	Oral
Prednisolone/ Methylpredinsolone				oral, IV
IMMUNOSUPPRESSANTS (LONG TERM)				
Azathioprine	Long term immunosuppression for generalized and refractory MG	Blocks purine synthesis in lymphocytes	3 months	Oral
Cyclosporine		Calcineurin Inhibitor	12 months	Oral
Tacrolimus		Calcineurin Inhibitor, T-cell supression	52 weeks	Oral
Mycophenolate Mofetil		Inhibits inosine monophosphate dehydrogenase in activated lymphocytes	Not superior to Placebo	Oral
Cyclophosphamide		Alkylating agent for guanine base of DNA	3 weeks to 3 months	Oral, intravenous
PLASMA EXCHANGE (PLEX)				
Plasma exchange	Generalized, severe and Myasthenia Crisis	Clears plasma of auto-antibodies	Hours to days	Procedure
INTRAVENOUS IMMUNOGLOBULIN (IVIG)				
IVIg	Generalized, severe MG and Myasthenia Crisis	Catabolizes IgG, suppresses antibody production	Hours to days	infusion
MONOCLONAL ANTIBODY				
Eculizumab (Solaris®)	Generalized refractory MG	Blocks activation of complement by binding to C5 preventing cleavage to C5a and C5b	16 weeks	IV infusion
Rituximab (Rituxan®)		Depletion of B lymphocytes	2 weeks	
THYMECTOMY				
Thymectomy	MG patients with thymus hyperplasia or suspected thymoma	Incompletely understood, but may relate to anti AChR B-Cell lymphocyte persistence in thymus	Months to years	Surgical
Stem Cell Transplant	Severe MG refractory to other treatments	Unknown	Unknown	IV Infusion

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