# MYASTHENIA GRAVIS:
## A case report and review of the pathophysiology, diagnosis and management.

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Myasthenia gravis is an autoimmune disorder that targets the neuromuscular junction. Symptoms of weakness and fatigue of voluntary muscles characterize the disorder. These two symptoms are known to be the result of an antibody-mediated attack directed against the nicotinic acetylcholine (ACh) receptors at the neuromuscular junctions. The severity of the symptoms and the progression of the disease are related to the reduction of available ACh receptors (2). To better understand myasthenia gravis, an investigation into the clinical features, pathophysiology, diagnosis and medical management of this complex disease is necessary. To begin, this paper presents a case report of myasthenia gravis.

**CASE REPORT**

A 65-year-old male presented to the Balian Eye Center for an initial ocular examination. The patient entered wearing an eye patch over the left eye. His visual symptoms included poor vision in both eyes, restricted ocular movements O.U., and ptosis of the left eye. The patient also complained of occasional floaters and flashing lights in the right eye. Upon questioning, the patient stated the patch was worn to avoid diplopia and confusion. His medical history was significant for long-standing myasthenia gravis. He reported both ocular and systemic symptoms associated with the disease. He claimed difficulties with chewing, talking and swallowing. Also, he stated the fatigue of voluntary muscles has been problematic since his diagnosis in 1969. In 1969, he underwent anticholinesterase testing with prostigmine and single muscle cell fiber analysis. These tests were useful in confirming the myasthenia gravis diagnosis. In an

attempt to remedy the ocular symptoms of the disease, the patient has undergone extra-ocular muscle surgeries in both eyes along with ptosis repair of the right eye. The patient also reported a history of macular degeneration in both eyes. Medications included Levothyroid, Mestinon, and aspirin prn.

Best-corrected visual acuities were 20/30 O.D. and Feinbloom 8/80 O.S. His refraction was plano +1.75 x 166 O.D. and plano O.S. Direct pupillary light responses were normal in the right eye and sluggish in the left. Extra-ocular muscle testing revealed complete external ophthalmoplegia in the left eye with the right eye exhibiting only slight vertical and lateral movement. Slit lamp biomicroscopy revealed grade II corticonuclear cataracts O.U. Corneal pannus was noted in the right eye. Intraocular pressures were measured at 20 and 17 mmHg respectively. Dilated fundus exam revealed cup-to-disk ratios of .8 O.U. The rim tissue appeared healthy but the large cupping was suspicious. The macular region exhibited pigment atrophy in both eyes. Peripheral examination revealed a segmental vein occlusion at 8:00.

The concluding impression was ptosis and external ophthalmoplegia secondary to long-standing myasthenia gravis. In addition, the patient was started on Betoptic S for possible low- tension glaucoma.

Two weeks later, the patient returned for baseline visual fields and an IOP check. At this visit, the patient expressed concern that Betoptic S could potentially worsen his myasthenic symptoms due to the drugs beta-blocking effects; therefore, the patient was switched from Betoptic S to 2% pilocarpine.

Numerous follow-up visits occurred over a two-year period with no significant improvement or progression of myasthenic symptoms. According to the neurologist, the

severely damaged ocular muscles were unresponsive to medications. Due to the compromised ocular status of the patient, the doctor aggressively monitored the low-tension glaucoma. A laser trabeculoplasty was performed in the right eye.

**DISCUSSION**

Myasthenia gravis is a relatively uncommon disorder with a prevalence of 50 to 125 individuals diagnosed per million (2). The onset of the disease has a bimodal pattern that is age and sex dependent. The early peak occurs in the 2nd and 3rd decade with a female predominance, whereas the late peak affects males in their 6th and 7th decade (12).

The onset of myasthenia gravis is generally insidious with progression over weeks to months. A patient will first complain of specific muscle weakness and fatigue that is localized to particular muscle groups. The patient's symptoms of muscle weakness are variable throughout the day with a worsening of symptoms in the evening and with prolonged use of the muscles. In two-thirds of patients, the presentation of ocular motor disturbances, such as diplopia or ptosis, are the primary symptoms (8). The ocular symptoms result from weakness of the extra-ocular or levator palpebrae muscles. The extra-ocular muscles appear to be less resistant to damage from myasthenia gravis. According to Kaminski, some properties of extra-ocular muscles predispose them to damage. First, slight weakness of the ocular muscles leads to misalignment of the visual axes. Misalignment of the visual axes results in a discrepancy in retinal image position. A discrepancy in retinal image position leads to diplopia, blur, vertigo, oscillopsia, and vertical confusion. Extra-ocular muscles also have increased firing frequencies that contribute to fatigability (9). In 15% of the cases, the myasthenic symptoms remain confined to the extra-ocular muscles and are referred to as ocular myasthenia gravis. In

the other 85% of patients, the disease progresses to a more generalized form involving oropharyngeal and limb muscles (7). Oropharyngeal muscle weakness results in difficulty chewing, talking, and swallowing. Mastication difficulties, dysphagia, and dysathria are the initial symptoms in one-sixth of patients, whereas proximal limb weakness is the presenting symptom in 10% of cases (8). Generalized myasthenia gravis that involves the limb muscles, neck muscles, and diaphragm can result in serious consequences. If respiration is adversely affected and mechanical respiration is necessary, the patient is considered in a life-threatening crisis situation.

Respiratory failure, or myasthenic crisis, occurs in 15-20% of patients (17). In a retrospective study performed by Thomas et al., myasthenic crisis was investigated. In this study, researchers reviewed the hospital records of 53 patients admitted for 73 emergency episodes. The median age was 55 with a range of 20-82. Women were affected 2 to 1 over men. Myasthenic crisis usually occurred within eight months from disease onset with 74% of patients experiencing crisis within the first two years. Precipitating factors of crisis were determined to be pneumonia, unknown etiology, and aspiration respectively. Twenty-five percent of patients were removed from mechanical ventilation within seven days, whereas 75% were extubated at 31 days. Four percent of the crisis episodes were fatal; however, this percentage is down from the 80% mortality rate prior to 1955 (17).

Although respiratory failure is possible, the disease course is variable among patients. For some patients spontaneous improvement can occur; however, most patients experience a progressive stage with maximum weakness during the first year in two-thirds of patients (8). After the progressive stage, a stable phase ensues where muscle

strength is largely influenced by outside factors. According to Howard, some factors that worsen myasthenic symptoms are "emotional upset, systemic illness (especially viral respiratory infections), hypothyroid or hyperthyroidism, pregnancy, the menstrual cycle, drugs affecting neuromuscular transmission, and increases in body temperature (8)." After 15-20 years of fluctuating muscular strength, severely affected muscles sustain irreversible damage and undergo atrophy (8). The severity of myasthenia gravis can be graded according to the Osserman scale. Drachman describes the Osserman scale as follows: "grade I involves focal disease (e.g. restricted to ocular muscles); grade II, generalized disease that is either mild (IIA) or moderate (IIB); grade III, severe generalized disease; and grade IV, a crisis with life threatening impairment of respiration (2)."

Understanding the pathophysiology of myasthenia gravis is essential in accurately diagnosing and managing the condition. In a normally functioning neuromuscular junction, ACh is released in response to an action potential. This potential opens calcium ion channels allowing calcium into the pre-synaptic terminal. In turn, these calcium ions cause the synaptic vesicles containing neurotransmitter to bind to the pre-synaptic membrane and release ACh. The ACh diffuses across the synaptic cleft and binds to the nicotinic receptors on the post-synaptic membrane. When a motor nerve is stimulated, ACh depolarizes the muscle end plate resulting in an action potential and subsequent muscle contraction (16). In acquired autoimmune myasthenia gravis, an antibody-mediated attack is directed against the skeletal muscle nicotinic acetylcholine receptors. This attack distorts the post-synaptic membrane and reduces viable ACh receptors due to the binding of abnormal antibodies (3). Therefore, when ACh is released into the

synapse it is unable to bind to post synaptic ACh receptors on the motor end plates. A decreased sensitivity to ACh results in fewer action potentials and subsequently less muscular contractions (8). A group of researchers supported this claim by studying muscle biopsies from myasthenia patients. The myasthenia patients were found to have one-third the ACh receptors of normal controls (15).

The exact mechanism that reduces the ACh receptors remains unclear. Drachman has suggested three possible mechanisms to explain the reduction in ACh receptors. First, he states antibodies such as IgG can cause accelerated endocytosis and degradation of the receptors. Secondly, serum IgG can bind near the receptor sites and block ACh binding by steric hindrance. Thirdly, complement-mediated damage to the post-synaptic membrane can cause morphological changes that inhibit binding (2).

Although the pathophysiology of myasthenia gravis has been well studied, the autoimmune origin of the disease has not. The thymus has been implicated as a possible site of origin for this autoimmune disorder due to 75% of myasthenia patients having thymic abnormalities (2). Thymic abnormalities consist of hyperplasia, or germinal-center formation, and thyoma. Thyomas are well-differentiated tumors that are easily removed and found to be benign 90% of the time (11). In general, two-thirds of patients have hyperplasia and the remaining 15-20% thyomas (11). According to Howard, the hyperplastic areas within the thymic tissue is where B cells interact with T cells to produce the antibodies that bind to the ACh receptors in myasthenia gravis. Howard believes the thymus plays an important role in immunological self-tolerance; therefore, it can be extrapolated thymic abnormalities result in variant antibodies that can attack the ACh receptors. Howard further defends his argument by stating "the thymus contains all

necessary elements for the pathogenesis of myasthenia gravis: myoid cells that express the ACh receptor antigen, antigen presenting cells, and immunocompetent T cells (8)." Drachman links a viral infection to the self-intolerance leading to autoimmune alteration of myoid cells; however, this claim is unsupported by research studies (2). The Wills Eye Manual implicates an underlying thyoma, thyroid disease, or infection as the origin of the disease (1).

The diagnosis of myasthenia gravis relies on evaluating the signs and symptoms elicited through a thorough case history along with a series of laboratory tests. Conditions that mimic the signs and symptoms of the disease must be ruled out to definitively diagnose autoimmune myasthenia gravis. Drachman states congenital and drug-induced myasthenic syndromes, botulism, intracranial mass lesions, Graves' disease, and hyperthyroidism must be ruled out in the differential diagnosis (2). According the Wills Eye Manual, associated conditions that an cause similar muscular weakness of the extra-ocular muscles include: Eaton-Lambert syndrome, drug-induced myasthenia, chronic progressive ophthalmoplegia, Kearns-Sayre syndrome, third-nerve palsy, Horner's syndrome, thyroid eye disease, levator muscle dehiscence or disinsertion, thyroid eye disease, orbital inflammatory pseudotumor, and myotonic dystrophy (1).

A suggested work-up for a suspected myasthenia gravis patient should include a detailed case history questioning the variability and fatigability of the affected muscles. Upon exam, the motor system will be affected without the loss of reflexes or coordination. For generalized myasthenia gravis, forward arm abduction, vital capacity and dynamometry of selected muscles should be performed (2). In the event that a patient presents with ocular involvement, one can evaluate for ptosis or diplopia in

sustained upgaze. Also, asking the patient to hold their eyes closed and attempting to force the patient's eyes open against resistance can test the orbicularis function. The pupillary function should be evaluated because myasthenia patients have normal pupillary responses (1). In addition, the following laboratory tests are essential and should be given in the following order: anticholinesterase tests, repetitive nerve stimulation, serum assay for acetylcholine receptor antibodies, and single fiber electromyography. Thyroid function tests, CT scans, and a blood work-up should be performed to rule out other autoimmune diseases.

The anticholinesterase test allows ACh that is released into the synapse to accumulate due to the inhibition of cholinesterase. Acetylcholine remains in the synapse to repeatedly interact with the nicotinic receptors on the post-synaptic membrane resulting in increased muscle stimulation and contraction. Edrophonium chloride, or Tensilon chloride, is the most commonly used anticholinesterase because of its quick onset and minimal duration (2). An initial dose of 1 to 2 mg of Tensilon is injected and if the weak muscle improves objectively within 10-60 seconds the test is considered positive for myasthenia (4). If the patient is nonresponsive to Tensilon, anticholinesterases with a longer duration of action, such as neostigmine or pyridostigmine, are used (2). Side effects of anticholinesterases include lacrimation, sweating, and fasiculations (4). According to Oh et al., anticholinesterase testing is positive in 90% of myasthenia cases. However, false positive results can be seen in amyotrophic lateral sclerosis, Lambert-Eaton syndrome and patients with intracranial mass lesions (13).

Following the anticholinesterase test, the serum assay of acetylcholine receptor antibody is performed. According to Evoli et al., this is the only test specific for myasthenia gravis with 90% of generalized and 45-65% of ocular myasthenia patients testing positive for serum antibodies (4). Gunji et al. found that the serum antibodies against the acetylcholine receptors were detected in nearly all patients with generalized myasthenia gravis and in one-third of patients with ocular myasthenia (8). Howard argues that "elevated ACh receptor antibody can be found in systemic lupus erythematosus, inflammatory neuropathy, amyotrophic lateral sclerosis, rheumatoid arthritis taking D-penicillamine, thyoma without myasthenia gravis, and in normal relatives of patients with myasthenia gravis;" therefore, he believes the serum assay is not the only important diagnostic tool (8). In conclusion, authors agree to the importance of serum assay testing in the diagnosis but recommend further testing.

Another test is repetitive nerve stimulation (RNS). During this test, three electric shocks per second are delivered to the muscle and the resulting action potentials are recorded. If the amplitude of the evoked potential is rapidly reduced by at least 15%, the test is considered positive (2). RNS testing is performed on limb muscles only because facial testing is uncomfortable. Positive test results occur in 70% of generalized myasthenia gravis, whereas 40% of ocular myasthenia patients test positive (4).

If necessary, the final test is the single fiber electromyopathy (SFEMG). This time-consuming test evaluates the presence of muscular jitter. Increased jitter is observed in weak and normal muscles of myasthenia patients. In 88-92% of myasthenia gravis patients, the test is positive (2). The SFEMG is not specific to myasthenia gravis because jitter only confirms impaired neuromuscular transmission of various etiologies.

Overall, the diagnosis of myasthenia gravis consists of a thorough case history and evaluation of symptoms along with one or all of the previously mentioned laboratory tests. Definitive diagnosis allows for the determination of a treatment plan.

Current treatment for myasthenia gravis consists of four standard therapies. These four therapies include anticholinesterases, thyectomy, immonosuppressive drugs and short-term immunotherapies. Short-term immunotherapies include plasma exchange, or plasmapheresis, and intravenous immune globulin. The therapeutic approach appears to be empirical and varies according to severity of the condition and patient's response to medication. Dosages are variable due to the fluctuation of muscular strength in myasthenia gravis.

Anticholinesterases are the primary line of therapy and appear to improve muscle weakness in most individuals. Unfortunately, the improvement seen with the anticholinesterases may decrease over time requiring different therapeutic approaches (2). Anticholinesterases are rarely effective on extraocular muscles (4). Pyridostigmine bromide, or Mestinon, and neostigmine bromide, or Prostigmine, are the most commonly used anticholinesterases (1).

Surgical removal of the thymus, or thyectomy, is the second line of therapy. Wilkins states "thyectomy is indicated early in the routine management of most patients with generalized myasthenia gravis, as well as those with purely ocular involvement uncontrolled by anticholinesterase medication (18)." He further states that patients should not undergo thyectomy while in respiratory crisis and must be stable prior to surgery even if that requires the use of immunosuppressive agents (18). After removal of the thymus, a favorable response is observed in 2-5 years (8). According to Kanski,

young women with generalized myasthenia gravis benefit the most from thyectomy (10). Patients with thyoma are less likely to benefit than those without thyoma (8).

Immunosuppressive treatment is reserved for patients where anticholinesterases and thyectomy have not alleviated symptoms. Symptoms must be significant to warrant immunosuppressive agents such as corticosteroids, azathioprine and cyclosporine because the side effects of long-term drug therapy are considerable. Patients must be followed closely to avoid complications.

Corticosteroids have their effect by causing immunosuppression. Drachman suggests corticosteroids may actually increase ACh receptors on the post-synaptic membrane and decrease ACh receptor antibodies (2). Corticosteroids allow marked improvement within 6-8 weeks and relief of symptoms in 75% of patients (8). Although the improvement is significant, care must be taken to avoid short-term steroid induced worsening of the disease. Patients with moderate to severe myasthenia gravis are initially hospitalized when beginning steroid therapy. Forty-eight percent of these patients can experience more severe symptoms with steroids (2). The steroid dose must be slowly increased and decreased to find the minimum effective dosage to alleviate or improve symptoms. Corticosteroid side effects include weight gain, cataracts, severe diabetes, hypertension, osteoporosis, and bone fractures (2).

Another immunosuppressant, azathioprine, is used when steroids are contraindicated or ineffective. Azathioprine has a delayed response of 4-8 months (8). Some patients can not tolerate this medication because flu-like symptoms occur with minimal dosages (4). Azathioprine is believed to work on T cells and decrease the production of ACh receptor antibody, which is T cell dependent. In a study performed by

Palace et al., it was stated that "azathioprine as an adjunct to alternate day prednisolone in the treatment of antibody-positive generalized myasthenia gravis reduces the maintenance dose of prednisolone and is associated with fewer treatment failures, longer remission, and fewer side effects (14)."

The final immunosuppressive agent is cyclosporine. Cyclosporine has been shown to improve muscle strength with an onset of action of 1-2 months (8). Side effects include nephrotoxicity and hypertension (4).

The fourth treatment strategy consists of short-term immunotherapies, such as plasma exchange or intravenous immune globulin. These therapies are used to rapidly improve muscle strength for individuals with a sudden deterioration of the myasthenic condition. These are also used prior to surgery and when all other treatment modalities fail.

Plasmapheresis removes variant antibodies from the blood allowing for temporary relief of muscle weakness in 75-80% of patients (4). Five exchange treatments are given over a two-week period. Infusion of high doses of human immunoglobulin interferes with the antibodies directed against the acetylcholine receptors and relieves symptoms for approximating three months (4). Plasmapheresis and immunoglobulin are used to quickly stabilize severely affected patients.

## CONCLUSION

Although many patients with myasthenia gravis are overcoming the condition with the proper diagnosis and management, research must continue to help those who are not successfully managing their disease. Remarkable progress has been made over the past few decades in research concerning myasthenia gravis. The tremendous discovery in

1973 by Fambrough et al. lead to the conclusion that myasthenia gravis was a deficit of the acetylcholine receptors. More specifically, the target antigen was determined to be the nicotinic acetylcholine receptor (5). Since 1973, genetic engineering has allowed the genes for each subunit of the acetylcholine receptor to be cloned and reproduced (2). These significant discoveries have lead to a more thorough understanding of autoimmune disorders. Despite the advances made in the pathophysiology, diagnosis, and management of myasthenia gravis, there are still questions concerning the autoimmune origin of the disease. Strides must be made towards a better understanding of the molecular immunology of the antibody-mediated attack against the acetylcholine receptors. For example, future research must determine what initiates and maintains the autoimmune response? What is the specific mechanism used by the antibodies to decrease the ACh receptors? How do immunological cells interact to produce these variant antibodies? In addition, research must improve on current treatment regimens. Although some treatment is successful, there are patients that can not tolerate the side effects of the anticholinesterases, immunosuppressive agents, and short-term immunotherapies. Overall, the future holds the answers to our complete understanding of myasthenia gravis.

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