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Review Article

Myasthenia gravis: A Review

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Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. A number of molecules, including ion channels and other proteins at the neuromuscular junction, may be targeted by auto-antibodies leading to abnormal neuromuscular transmission. In approximately 85% of patients, auto-antibodies directed against the postsynaptic nicotinic acetylcholine receptor can be detected in the serum and confirm the diagnosis, but in general, do not precisely predict the degree of weakness or response to the therapy. Antibodies to the muscle-specific tyrosine kinase are detected in approximately 50% of generalized myasthenia gravis patients who are seronegative for anti acetylcholine receptor antibodies, and levels of anti muscle-specific tyrosine kinase antibodies do appear to correlate with disease severity and treatment response. Antibodies to other muscle antigens may be found in the subsets of myasthenia gravis patients, potentially providing clinically useful diagnostic information, but their utility as relevant biomarkers (measures of disease state or response to treatment) is currently unclear.

Key words: Acetylcholine receptors, autoimmune disease, myasthenia gravis, neuromuscular junction, biomarkers, Musk.

INTRODUCTION

Myasthenia gravis (MG) is the prototypical neurological autoimmune disorder that affects the neuromuscular junction (NMJ) at the postsynaptic level. It can be categorized into autoimmune and congenital myasthenia syndromes. It is a neuromuscular disease that leads to fluctuating muscle (under voluntary control) weakness and fatigue. In the most common cases, muscle weakness is caused by circulating antibodies that blockacetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors at neuromuscular junctions. Alternatively, in a much rarer form, muscle weakness is caused by a genetic defect in some portion of the neuromuscular junction that is inherited at birth as opposed to developing through passive transmission from the mother's immune system at birth or through autoimmunity later in life.[1]

In general, detecting circulating anti-AChR and Muscle specific kinase (MuSK) antibodies and anti-striated muscle antibodies, single fiber electromyogram, tensilon testing and thymic imaging in MG provides an important means to confirm the clinical diagnosis in patients with suspected disease, allowing specific treatment.Myasthenia is treated with medications such as acetyl cholinesterase - inhibitors or immunosuppressants, and, in selected cases, thymectomy(surgical removal of the thymus gland). The disease is diagnosed in 3 to 30 people per million per year.[2] Diagnosis is becoming more common due to increased awareness.[2]

Thomas Willis and Samuel Wilksfirst described the malady in 1672, but it was not until 1895 that Jolly

used the name, Myasthenia gravis pseudo-paralytica. In about two-thirds of patients, the extrinsic ocular muscles (EOMs) present the initial symptoms. The symptoms usually progress to the other bulbar muscles and limb muscles, resulting in generalized MG (gMG). In about 10% of MG patients, symptoms remain limited to the EOM, and this condition is termed ocular MG (oMG). MG fulfills the strict criteria of an Ab mediated autoimmune disorder:

a. Abs is present at the site of pathology, the neuromuscular junction (NMJ);
b. Ig from MG patients or anti-AChR Abs from experimental animals causes MG symptoms when injected into rodents;
c. Immunization of animals with AChR reproduces the disease;
d. Therapies that remove Abs decrease the severity of MG symptoms.

Epidemiology

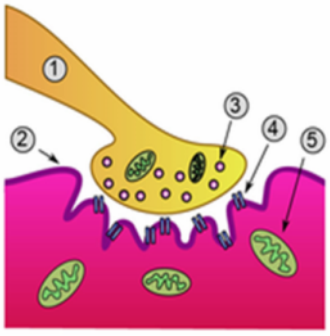
Myasthenia gravis occurs in all ethnic groups and both sexes. It most commonly affects women under 40 and people from 50 to 70 years old of either sex, but it has been known to occur at any age. Younger patients rarely have thymoma. In India, MG is reported more common in males than in females. Onset occurs at an earlier age in women (mean age 28 years) than in men (mean age 42 years).

Structure and function of neuromuscular junction

Neuromuscular junctions (NMJs) (myoneural junction) are a chemical synapse formed by the contact between a motor neuron and muscle fiber. It is at the neuromuscular junction that a motor neuron is able to transmit a signal to the muscle fiber causing muscle contraction.

Synaptic transmission at the neuromuscular junction begins when an action potential reaches the presynaptic terminal of a motor neuron, which activates voltage dependent calcium channels to allow calcium ions to enter the neuron. Calcium ions bind to sensor proteins (synaptotagmin) on synaptic vesicles, triggering vesicles fusion with the cell membrane and subsequent neurotransmitter release from the motor neuron into the synaptic cleft.

In vertebrates, motor neurons release acetylcholine (ACh), a small molecule neurotransmitter, which diffuses across the synaptic cleft and binds to nicotinic acetylcholine receptors (nAChRs) on the cell membrane of the muscle fiber, also known as the sarcolemma. nAChRs are ionotropic receptors, meaning they serve as ligand-gated ion channels. The binding of ACh to the receptor can depolarize the muscle fiber, causing a cascade that eventually results in muscle contraction. The neuromuscular junction differs from chemical synapses between neurons . Presynaptic motor axons stop 30



Detailed view of a neuromuscular junction:
1. Presynaptic terminal
2. Sarcolemma
3. Synaptic vesicle
4. Nicotinic acetylcholine receptor
5. Mitochondrion

nanometers from the sarcolemma, the cell membrane of a muscle cell. This 30-nanometer space forms the synaptic cleft through which signaling molecules are released. The sarcolemma has invaginations called postjunctional folds, which increase the surface area of the membrane exposed to the synaptic cleft.[2] These postjunctional folds form what is referred to as the motor endplate, which possessnicotinic acetylcholine receptors (nAChRs) at a density of 10,000 receptors/micrometer^2 in skeletal muscle.[3] The presynaptic axons form bulges called terminal buttons (or presynaptic terminals) that project into the postjunctional folds of the sarcolemma. The presynaptic terminals have active zones that contain vesicles, also called quanta, full of acetylcholine molecules. These vesicles can fuse with the presynaptic membrane and release ACh molecules into the synaptic cleft via exocytosis after depolarization.[2] AChRs are localized opposite the presynaptic terminals by protein scaffolds at the postjunctional folds of the sarcolemma. Dystrophin, a structural protein, connects the sarcomere, sarcolemma, and extracellular matrix components. Rapsyn is another protein that docks AChRs and structural proteins to the cytoskeleton. Also present is the receptor tyrosine kinase protein MuSK, a signaling protein involved in the development of the neuromuscular junction, which is also held in place by rapsyn.[2]

Signs and Symptoms

The initial, main symptom in MG is painless weakness of specific muscles, not fatigue.[3] The muscle weakness becomes progressively worse during periods of physical activity, and improves after periods of rest. Typically, the weakness and fatigue are worse towards the end of the day.[4] MG generally starts with ocular (eye) weakness; it might then progress to a more severe generalized form, characterized by weakness in the extremities or while performing basic life functions.[5]

Eyes

In about two-thirds of individuals, the initial symptom of MG is related to the muscles around the eye.[3] There may be eyelid drooping (ptosis due to weakness of levator palpebrae superioris)[6] and double vision (diplopia,[3] due to weakness of the extraocular muscles).[4] Eye symptoms tend to get worse when watching television, reading or driving, particularly in bright conditions.[3] Consequently, some affected individuals choose to wear sunglasses.[3] The term "ocular myasthenia gravis" describes a subtype of MG where muscle weakness is confined to the eyes, i.e. extra ocular muscles, levator palpebrae superioris and orbicularis oculi.[6] Typically, this subtype evolves into generalized MG, usually after a few years.[6]

Eating

Weakness of the muscles involved in swallowing may lead to swallowing difficulty (dysphagia). Typically, this means that some food may be left in the mouth after an attempt to swallow,[7] or food and liquids may regurgitate into the nose rather than go down the throat (velopharyngeal insufficiency).[4] Weakness of the muscles that move the jaw (muscles of mastication) may cause difficulty chewing. In

individuals with MG, chewing tends to become more tiring when chewing tough, fibrous foods.[3] Difficulty in swallowing, chewing and speaking is the first symptom in about one-sixth of individuals.[3]

Voice

Weakness of the muscles involved in speaking may lead to dysarthria and hypophonia.[3] Speech may be slow and slurred,[8] or have a nasal quality.[4] In some cases a singing hobby or profession must be abandoned.[7]

Head and neck

Due to weakness of the muscles of facial expression and muscles of mastication, there may be facial weakness, manifesting as inability to hold the mouth closed[3] (the "hanging jaw sign"), and a snarling appearance when attempting to smile.[4] Together with drooping eyelids, facial weakness may make the individual appear sleepy or sad.[3] There may be difficulty in holding the head upright.[8]

Other

The muscles that control breathing (dyspnea) and limb movements can also be affected, but rarely do these present as the first symptoms of MG, and they develop over months to years.[9] In a myasthenic crisis, a paralysis of the respiratory muscles occurs, necessitating assisted ventilation to sustain life.[10] Crises may be triggered by various biological stressors such as infection, fever, an adverse reaction to medication, or emotional stress.[10]

Pathophysiology

Myasthenia gravis is believed to be caused by variations in certain genes. The disorder occurs when the immune system malfunctions and attacks the body's tissues. The antibody in myasthenia gravis attacks normal human protein, targeting a protein called an acetylcholine receptor, or a related protein called a muscle-specific kinase.[12]

Human leukocyte antigens have been associated with MG susceptibility. Many of these genes are present among other autoimmune diseases. Relatives of MG patients have a higher percentage of other immune disorders.[13]

The thymus gland cells form part of the body's immune system. In those with myasthenia gravis, the thymus gland is large and abnormal. It sometimes contains clusters of immune cells which indicate lymphoid hyperplasia, and it is believed the thymus gland may give wrong instructions to immune cells.[14]

Extraocular muscles (EOMs) are more commonly affected as twitch fibers in EOMs develop tension faster and have a higher frequency of synaptic firing than limb muscles. This makes them more susceptible to fatigue.

Diagnosis

MG can be difficult to diagnose, as the symptoms can be subtle and hard to distinguish from both normal variants and other neurological disorders.[21]

Three types of myasthenic symptoms in children can be distinguished: [22]

1. Transient Neonatal: occurs in 10 to 15% of babies born to mothers afflicted with the disorder, and disappears after a few weeks.
2. Congenital: the rarest form; genes are present in both parents.

3. Juvenile myasthenia gravis: most common in females

Congenital myasthenias cause muscle weakness and fatigability similar to those of MG. The signs of congenital myasthenia usually are present in the first years of childhood although they may not be recognized until adulthood.[23]

Classification

When diagnosed with MG, a person is assessed for his or her neurological status and the level of illness is established. This is usually done using the accepted Myasthenia Gravis Foundation of America Clinical Classification scale, which is as follows:

CLASS	DESCRIPTION
I	Any eye muscle weakness, possible ptosis, no other evidence of muscle weakness elsewhere
II	Eye muscle weakness of any severity, mild weakness of other muscles
IIa	Predominantly limb or axial muscles
IIb	Predominantly bulbar and/or respiratory muscles
III	Eye muscle weakness of any severity, moderate weakness of other muscles
IIIa	Predominantly limb or axial muscles
IIIb	Predominantly bulbar and/or respiratory muscles
IV	Eye muscle weakness of any severity, severe weakness of other muscles
IVa	Predominantly limb or axial muscles
IVb	Predominantly bulbar and/or respiratory muscles
V	Intubation needed to maintain airway

Physical examination

During a physical examination to check for MG, a doctor might ask the potentially affected person to look at a fixed point for 30 seconds and to relax the muscles of their forehead. This is done because a person with MG and ptosis of their eyes might be involuntarily using their forehead muscles to compensate for the weakness in their eyelids.[21] The clinical examiner might also try to elicit the "curtain sign" in a patient by holding one of the person's eyes open, which in the case of MG will lead the other eye to close.[21]

Blood tests

If the diagnosis is suspected, serology can be performed:

- One test is for antibodies against the

acetylcholine receptor,[21] the test has a reasonable sensitivity of 80–96%, but in ocular myasthenia, the sensitivity falls to 50%.

- A proportion of the patients without antibodies against the acetylcholine receptor have antibodies against the MuSK protein.[25]

Electrodiagnostics

Muscle fibers of patients with MG are easily fatigued, and a test called the repetitive nerve stimulation test can be performed. In single-fiber electromyography, which is considered to be the most sensitive (although not the most specific) test for MG,[21] a thin needle electrode is inserted into different areas of a particular muscle to record the action potentials from several samplings of different individual muscle fibers. Two muscle fibers belonging to the same motor unit are identified, and the temporal variability in their firing patterns is measured. Frequency and proportion of particular abnormal action potential patterns, called "jitter" and "blocking", are diagnostic. Jitter refers to the abnormal variation in the time interval between action potentials of adjacent muscle fibers in the same motor unit. Blocking refers to the failure of nerve impulses to elicit action potentials in adjacent muscle fibers of the same motor unit.[27]

Ice test

Applying ice for two to five minutes (for ophthalmoparesis) to the patient's closed eyelids reportedly has sensitivity and specificity of 76.9% and 98.3%, respectively, for the identification of MG. Acetylcholinesterase is thought to be inhibited at the lower temperature, and this is the basis for this diagnostic test. This generally is performed on the eyelids when a ptosis is present and is deemed positive if there is a ≥2mm raise in the eyelid after the ice is removed.[28]

Edrophonium test

This test requires the intravenous administration of edrophonium chloride or neostigmine, drugs that block the breakdown of acetylcholine by cholinesterase (acetylcholinesterase inhibitors)[29]

This test is no longer typically performed as its use can lead to life-threatening bradycardia (slow heart rate) which requires immediate emergency attention.[30] Production of edrophonium was discontinued in 2008.[10]

Imaging

A chest X-ray may identify widening of the mediastinum suggestive of thymoma, but computed tomography or magnetic resonance imaging (MRI) are more sensitive ways to identify thymomas and are generally done for this reason.[31] MRI of the cranium and orbits may also be performed to exclude compressive and inflammatory lesions of the cranial nerves and ocular muscles.[32]

Pulmonary function test

The forced vital capacity may be monitored at intervals to detect increasing muscular weakness. Acutely, negative inspiratory force may be used to determine adequacy of ventilation; it is performed on those individuals with MG.[33][34]

Management

There are many effective treatments for myasthenia gravis. Spontaneous improvement and even remission (although uncommon) may occur without

Diagnostic test for MG

TEST	SENSTIVITY	COMMENTS
Clinical tests		
Edrophonium	Detectable in 80%–90% of MG patients	Edrophonium testing is safe. However, because of known adverse effects, alternative nonpharmaological tests have been developed
Sleep	Criteria poorly defined	
Ice-pack test	Criteria poorly defined	
Assays of serum Abs		
Anti-AChR	Detectable in approximately 80%–90% of gMG patients and 30%–50% of oMG patients	May also be observed in patients with Lambert-Eaton syndrome and motor neuron disease, thymoma patients without MG, and relatives of MG patients.
Anti-MuSK	Detectable in approximately 30%–40% of anti-AChRAb–negative gMG patients and rarely in oMG patients	
Anti-striational protein	Detectable in 80% of thymomatous MG patients and 30% of nonthymomatous MG patients	More common in older patients. First autoantibody detected in MG. However, poor specificity makes this test nondiagnostic.
Electrodiagnostic tests		
Repetitive stimulation of peripheral nerves	Positive in approximately 90% of gMG patients and 30%–60% of oMG patients	
Single-fiber electromyography	Positive in 95%–99% of MG patients	Despite its sensitivity, single-fiber electromyography is not the test of choice because it is dependent on operator skills and patient cooperation. Also, results are abnormal in neuropathies and motor neuron and muscle diseases.

specific therapy.Treatment is by medication and/or surgery. Medication consists mainly of acetylcholine esterase inhibitors to directly improve muscle function and immunosuppressant drugs to reduce the autoimmune process.[35] Thymectomy is a surgical method to treat MG.[36]

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors can serve to increase the duration of action of the neurotransmitter. These provide symptomatic benefit, without modifying the long term immunologic disease activity.[37] While they might not fully remove all symptoms of MG, they still

may allow a person the ability to perform normal daily activities.[37] Usually, acetylcholinesterase inhibitors are started at a low dose and increased until the desired result is achieved. If taken 30 minutes before a meal, symptoms will be mild during eating, which is helpful for those who have difficulty swallowing due to their illness. Another medication used for MG is atropine, which can reduce the muscarinic side effects of acetylcholinesterase inhibitors.[38] Pyridostigmine is a short-lived drug its onset of action ranges from 30-45 mins after ingestion and lasts for up to 6 hrs.,with relatively few side effects.[39] In tablet form (30 mg), it is usually, administered 2-4 times a day, up to a maximum of 1500mg/day. Generally, it is discontinued in those who are being mechanically ventilated as it is known to increase the amount of salivary secretions.[39] Possible side effects may include GIT upset, nausea and excessive salivation and sweating. An increased incidence of hypotension and bradycardia has been reported when co-administered with beta blockers or opiates. Other contraindications include asthma and cardiac arrhythmias.

Neostigmine is an alternative drug of the same class. These are poorly absorbed orally; oral dose is 20-30 times higher than the parental dose. They do not effectively penetrate cornea or cross blood-brain barrier. They are partially hydrolyzed and partially

excreted unchanged in urine.

Corticosteroids

Corticosteroids are the most widely used immune modulating agents in patient with MG. They chiefly act through their anti-inflammatory properties, additionally causing a reduction in cytokine expression, lymphocyte differentiation and proliferation, and also increase muscle AChR synthesis.

Treatment usually starts at a dose of 20mg per day of orally administered prednisolone. Doseoptimization requires uptitration over several weeks, generally to a level of mg/kg/day. This may be maintained for 6-12 weeks and then tapered slowly over months. Initiating oral prednisolone therapy with high dose can result in a worsening of symptoms and even lead to myasthenic crisis in up to 15% of patients, hence, patients on corticosteroids should be evaluated monthly.[39] Corticosteroids produce favorable response in OMG in 65-85% of patients. However, patients rarely go into complete remission with oral corticosteroids alone. Steroids in the course of early OMG may reduce the likelihood of progression to GMG. Prednisolone may also delay generalization. Without prednisolone, GMG develops in 50% of OMG patients, typically within 1 year.[39]

Common side effects of corticosteroid therapy include acne, obesity, hypertension, diabetes, osteoporosis, and steroid-induced myopathy. The risk of opportunistic infections is omnipresent, and tuberculosis needs to be ruled out before initiating therapy.

Immunosuppressants

Doctor may also prescribe other medications that alter the immune system, such as azathioprine (imuran),mycophenolatemofetil (cellcept), cyclo-

sporine (sandimmmune, neoral) or tacrolimus (prograf). Azathioprine is a purine antagonist which inhibits DNA and RNA synthesis in fast dividing T and B cells. Azathioprine can be used both as monotherapy (for example, in steroid-resistant patients) as well as in conjunction with oral corticosteroids. The clinical response to azathioprine alone is, usually, delayed (>6 months), and is accompanied by a progressive fall in AChR-Ab titers. The full effect is seen after 2-3 years of continuous administration.

In view of potential hepatotoxicity and bone marrow toxicity, blood count and liver function tests should be done bi-weekly for the first 2 months after initiating treatment and monthly thereafter. Treatment should be discontinued if the white blood cells count falls below 3000/mm^3.Dose reduction may be considered if it is below 3500/mm^3. Azathioprine is potentially teratogenic. Cyclosporine A inhibits calcineurin, which decreases the antigen-stimulated interleukin-2 production in T-cells.It is a third line drug and may be of particular use in patients who are dependent or intolerant of steroids and/or azathioprine. Treatment is initiated at a dose of 5 mg/kg/day in two to three divided doses and is subsequently modified is on the basis of serum creatinine levels and clinical response. Improvement in muscle strength and a reduction in AChR-Abs titers have been reported with cyclosporine. Mycophenolatemofetil (MMF) selectively inhibits T- and B-lymphocytes proliferation by blocking purine synthesis exclusively in lymphocytes. It is a relatively new drug in the treatment of MG and has been used both as a steroid-sparing agent as well as monotherapy. MMF is administered orally in a dose between 1000 and 1500 mg twice a day. Clinical response is, usually, observed only 2 months after initiation of treatment. Treatment with MMF may reduce the rate of generalization of ocular disease. A dose of 1.0 g/day was safe and tolerable as a long term immunosupressant for OMG. MMF with prednisone has not been found to be seropositive GMG patients. Side effects of immunosuppressants can be serious and may include nausea, vomiting, GIT upset, increased risk of infection, liver damage and kidney damage.

Plasmapheresis and IVIG

If myasthenia is serious (myasthenic crisis), plasmapheresis can be used to remove the putative antibodies from circulation. The process of plasmapheresis uses a filtering process similar to dialysis. The blood is routed through a machine that removes the antibodies that block transmission of signals from the nerve endings to the muscles' receptor sites. The patient's plasma is separated from whole blood and replaced with saline, albumin, or plasma protein fraction, thereby reducing serum AChR-Ab levels. However, the beneficial effects usually last only a few weeks. After repeated treatments, it may be difficult for doctors to gain access to the vein. They may need to implant a long, flexible tube (catheter) into the chest to conduct the procedure.Other risks associated with plasmapheresis include a drop in BP, bleeding, heart rhythm problems or muscle cramps. Some people may also develop an allergic reaction to the solutions

used to replace the plasma.

Also, intravenous immunoglobulins (IVIGs) can be used to bind the circulating antibodies. This therapy provides the body with normal antibodies, which alters the immune system response. IVIG accelerates the catabolism of IgG in addition to suppressing antibody production and inhibiting complement activation and Fc receptor function. IVIG may take about a week to start working and the benefits usually last no more than three to six weeks. Side effects are usually mild, may include chills, dizziness, headache and fluid retention.

Both of these treatments have relatively short-lived benefits, typically measured in weeks, and often are associated with high costs which make them prohibitive; they are generally reserved for when MG requires hospitalization.[39][41]

Surgery

As thymomas are seen in 10% of all people with the MG, patients are often given a chest X-ray and CT scan to evaluate their need for surgical removal of their thymus and any cancerous tissue that may be present.[10][30] Even if surgery is performed to remove a thymoma, it generally does not lead to the remission of MG.[39] Surgery in the case of MG involves the removal of the thymus although there is no clear consensus that it would be beneficial except in the presence of a thymoma. However, thymectomy should not be done in ocular myasthenia.[42] Currently, there is no literature that gives meaningful conclusions in regard to the benefit of thymectomy in affected individuals. Some observational studies indicate that thymectomy could be prudent in MG.[42]

Physical measures

Patients with MG should be educated regarding the fluctuating nature of their symptoms, including weakness and exercise-induced fatigue. Exercise participation should be encouraged with frequent rest.[43] In people with generalized MG, some evidence indicates a partial home program including training in diaphragmatic breathing, pursed lip breathing, and interval-based muscle therapy may improve respiratory muscle strength, chest wall mobility, respiratory pattern, and respiratory endurance.[44]

Notable cases

- Indian actor Amitabh Bachchan was diagnosed with it in 1983.
- Brandon Cox, starting Auburn quarterback from 2005-2007, finished with a record of 29-9.[52]
- Henrique Mecking, Brazilian chess grandmaster
- Christopher Robin Milne, the son of A. A. Milne, author of the *Winnie-the-Pooh* books and the person on whom Christopher Robin was based, lived with myasthenia gravis for several years before his death in 1996.[53]
- Aristotle Onassis (1906-1975), Greek shipping magnate and businessman, suffered from the disease during the last years of his life.
- Actor Roger Smith, husband of Ann-Margret, was diagnosed in 1980.[54]
- *Days Of Our Lives* actress Suzanne Rogers has the condition and so does the character she plays, Maggie Horton
- *Powhatan* chief Opchanacanough (Uncle of *Pocahontas*) was thought to have the condition.

- Stephen Garrett, also known as Static Major. He made up half of the R&B group "Playa".
- Anselmo Ralph, Angolan singer.

Summary

MG most commonly is an acquired autoimmune disease that is exemplified by production of AChR antibodies. Decreased AChR numbers at the NMJ are manifested as decreased amplitude of the endplate potential, which is represented clinically as muscle weakness. The AChR antibodies are present in 80% - 90% of cases and are produced by B cells in a cell dependent manner, and a pathologic thymus is implicated to have an important role in MG genesis and progression. IgG and complement components are deposited on the postsynaptic membrane, and destructive mechanisms may consist of increased degradation of AChRs, cross linking of AChRs, and blockage of AChRs. Since the NMJ involves the site of action of many commonly used anesthetic drugs, anaesthesia providers must understand the pathophysiology of MG, be cognizant of the many drugs interactions that can be detrimental to the myasthenic patient, and administer anesthetics that would most benefit the patient with MG.

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