Myasthen-i-wha??
The Physiology and Treatment of Myasthenia Gravis

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Physiology:

Myasthenia Gravis is a disease of the neuromuscular junction. The name means “Severe muscle weakness” in Latin. The muscle weakness is due to a lack of Acetylcholine receptors on the muscle side of the neuromuscular junction (NMJ). It occurs only in striated or skeletal muscles like those used for movement. In Myasthenia Gravis (MG), the receptors for the neurotransmitter Acetylcholine (ACh) are damaged, absent or blocked. This means that less ACh is able to attach to the muscle, and therefore less muscle fibers are activated with each nerve impulse. Since muscle strength is dependent on the number of activated muscle fibers in each muscle, animals with myasthenia gravis have increasing weakness with activity.
Presentation:

Myasthenia Gravis typically presents in one of two forms, Congenital or Acquired. The rarer of the two forms is congenital MG, in which an autosomal recessive gene causes a defect in the production of ACh receptors. It is seen in several dog breeds including the Jack Russell terrier, Springer spaniel, Smooth-haired fox terrier, and Miniature Dachshund. These dogs are born with myasthenia, but typically do not start to show symptoms till they are 6-9 weeks old and are beginning to walk. Prognosis of congenital MG is typically grave. While treatment may alleviate symptoms temporarily, the symptoms usually return and progress until the puppy is no longer able to walk. The prognosis of congenital myasthenia is very guarded.

Acquired MG is an auto-immune disorder in which the body makes antibodies to the ACh receptor. These antibodies block or destroy the receptor. It can be seen as a reaction to a thymoma, idiopathic, or as part of a paraneoplastic process (i.e. there is cancer elsewhere in the body causing the immune reaction). While acquired MG may occur at any age, patients generally fall into two age ranges. The first set is in the young adult animals from 3 to 5 years of age and the second set in geriatric animals from 9 to 13 years of age. Geriatric animals are more likely to have a paraneoplastic induction of MG than younger animals. Prognosis of acquired MG is generally poor to grave because of the associated complications of megaesophagus and aspiration pneumonia.

Symptoms of myasthenia gravis include weakness, decreased ability to blink, regurgitation, voice changes (dysphonia) and drooling (ptylism). These animals will tire easily and will usually develop a short and stiff gait before lying down. A brief rest will usually allow the animal to get back up and continue for a while longer. An exercise tolerance test may be needed to trigger the weakness. Some animals will show only focal weakness and not generalized weakness, e.g. ptosis (eyelid droop) or megaesophagus.

Diagnosis:

To diagnose a myasthenic patient, first basic blood work should be done to help rule out other causes of weakness such as neoplasia or infection. Next three-view chest radiographs are needed to look for megaesophagus, aspiration pneumonia and/or thymoma or other cancer, as these findings are often associated with MG. On neurologic examination, MG patients should not be painful. They often have a decreased ability to blink and may have slow to absent palpebral and menace responses. These reflexes, if present, will usually get slower with repeated stimulation as the muscles fatigue. History from the owner may include regurgitation which is often confused with “coughing” and “vomiting” foam.

There are two main tests for MG. Tensilon® (edrophonium, Valeant pharmaceuticals) is a short acting acetylcholinesterase inhibitor. It blocks the enzyme Acetylcholinesterase (AChE) from working to break down ACh in the NMJ. This allows the ACh to remain bound to the receptor longer and allows better transmission of the motor impulse. The patient should be exercised to the point of collapse, and then the edrophonium is given as an IV injection of 0.1mg/kg. In a
positive test the patient returns to normal for 3-5 minutes. Edrophonium does not work in all cases, so a negative test does not rule out MG. Positive test are usually confirmative of congenital and acquired forms of the disease, though myositis can also be helped with edrophonium. Respiratory depression or arrest can occur, though rarely. Other complications include bradycardia, increased secretions on broncoconstriction. Atropine may be given as a pre-medication to help prevent complications.

An acetylcholine receptor antibody test (AChR Ab) is the gold standard for diagnosing acquired MG. This is a serum antibody test done by the Neuromuscular Lab at the University of California, San Diego. It is 98% sensitive for acquired MG. For this test 1-2mL of serum should be shipped on ice to the lab. For more information see http://vetneuromuscular.ucsd.edu/. Test submission is also available through Antech®, Idexx®, and Phoenix Central laboratories. The test is run daily, Monday through Friday, and results are usually available within five to seven working days. Animals with serum AChR antibody concentrations greater than 0.6 nmol/L are considered positive for the disease. There is no correlation between antibody concentrations and severity of the disease. For example, a dog with a titer of 9.6nmol/L may or may not have more severe signs of MG than a dog with a titer of 1.6nmol/L. Ideally the initial sample should be taken before use of corticosteroids, as this may lower the titer results. With time and treatment, the titer results and symptoms of each patient usually decrease, therefore serial AChR Ab testing is recommended to monitor the course of myasthenia gravis.

Other tests for myasthenia include repetitive nerve stimulation and muscle biopsy. These tests are rarely done first as the Tensilon® and Acetylcholine Receptor Antibody tests are usually less invasive. For repetitive nerve stimulation an electromyography or EMG machine is used to stimulate nerves leading to skeletal muscle. The response of the muscle is then recorded. In the case of myasthenia gravis the muscle fatigues and shows decreasing amplitudes on the EMG.

Muscle biopsy may be performed to confirm or rule out MG in patients where diagnosis is inconclusive with other tests, or if they do not respond to treatment. Both nerve stimulation and muscle biopsy require general anesthesia which may cause complications in myasthenic patients.
Treatment:

The main treatment for myasthenia gravis is the use of AChE inhibitors, i.e. anticholinesterases. These chemicals can be found in nature as defense mechanisms in plants such as the daffodil and certain species of mollusk. They have also been manufactured for use as insecticides like Diazinon and as a chemical weapon in Sarin gas. Anticholinesterases work on a wide array of acetylcholine-activated junctions in the eye, heart, brain, bladder, gastrointestinal tract, skeletal muscle and brain. This leads to a number of side effects depending on the substance and administration including bradycardia, hypotension, hypersecretion, bronchoconstriction, GI tract hypermotility, decreased intraocular pressure, prolonged muscle contraction and death. Medicinal uses include treatments for glaucoma, Alzheimer’s and myasthenia gravis, as well as reversal agents for paralytic drugs like atracurium.

There are a few different formulations of AChE inhibitors used for MG. Tensilon®, as already mentioned in the diagnosis section, is a short acting AChE inhibitor that is given IV. Mestinon® (pyridostigmine bromide, Valeant pharmaceuticals), a longer acting AChE inhibitor, is only available as oral formulations. The dose for pyridostigmine is 0.5 to 3 mg/kg by mouth every 8 to 12 hours. Side effects of this medication can include muscle tremors, fatigue, drooling, vomiting and diarrhea. Since these side effects can mirror the symptoms of MG, the dose should be tailored to each patient. If recurrence of symptoms or overdose of medication is suspected, a Tensilon® test may help to differentiate the two. If symptoms are alleviated by Tensilon®, then a dose increase may be in order, while if the symptoms are worsened then a dose decrease may be needed.

If administering medications by mouth is not recommended, due to profound weakness or regurgitation, then neostigmine methylsulfate (generic, multiple manufacturers), another AChE inhibitor, may be given as an intramuscular injection of 0.01 to 0.04mg/kg every six hours as needed for symptom relief until oral medications are indicated. Neostigmine may be used instead of Tensilon® to test
for myasthenia gravis, but this is not generally recommended due to its longer
duration of action and increased side effects over Tensilon®. AChE inhibitors are
the only treatment available for congenital MG, and are sometimes the only
treatment needed for cases of acquired MG. Once the patient responds to
treatment, AChE inhibitors (usually pyridostigmine) should be continued for at least
six to eight months before weaning off the medication, though in some patients
lifetime therapy may be needed to prevent recurrence of symptoms.

Once there is sufficient ACh in the neuro-muscular joint to activate all
receptors on the muscle, the only other way to increase muscle strength and
decrease side effects of the disease is to increase the number of available receptors.
In acquired MG, this is often done with immune-suppressive therapy. With immune-
suppression, the antibodies interfering with or destroying the ACh receptors are
lessened and more receptors are made available for neurotransmission.

The first immune-suppressive agents often used are corticosteroids like
prednisone or dexamethasone. Corticosteroids are generally inexpensive, readily
available and can be given as IV or oral formulations. Side effects are generally well
known to veterinary medical staff and include polyuria, polydipsia, polyphagia, and
gastro-intestinal (GI) upset in the form of vomiting, diarrhea and ulcers. In patients
with myasthenia corticosteroids may worsen weakness when first started. This effect
is transient, but weakness may be significant.

Other immune-suppressants include azathioprine, cyclosporine and a newer
drug, mycophenolate mofetil. All three do not possess the side effects of polyuria,
polydipsia or polyphagia of the corticosteroids, but they all have been associated
with GI upset. Azathioprine is the least expensive of the three and also the slowest
to take effect. It often takes up to three weeks for the effects of azathioprine on the
immune system to be noticed. It can also induce bone marrow suppression, so
regular complete blood counts (CBC) should be done while a patient is on this drug.
Cyclosporine is more expensive, but is readily available at most veterinary practices
in the form of Atopica® (cyclosporine A, Novartis Animal Health). Cyclosporine is
less likely to cause bone marrow suppression as it is more T-cell specific than
azathioprine. Finally mycophenolate mofetil (CellCept®, Roche pharmaceuticals) is
the newest and most expensive immune-suppressant commonly used for MG.
Mycophenolate decreases T and B-cell lymphocytes, but is also less likely to cause
bone marrow suppression. It is available as oral or IV formulations, but is generally
only available at human hospitals or pharmacies.

Immune suppression must be used with caution as the patient may be more
prone to infection while on the treatment. This is especially true in patients with
myasthenia gravis as aspiration pneumonia is a common occurrence in new patients.
Once started immune suppression therapy should be continued until there is a
cessation of signs and a decrease in AChR Ab titer, or until complications develop.

Plasmapheresis is a newly emerging treatment in veterinary medicine and
may be helpful in patients with a large burden of AChR antibodies. Using
plasmapheresis, the patient’s plasma is filtered and specific elements, like antibodies
can be removed. With the use of plasmapheresis the MG symptoms in a severely
affected patient are temporarily relieved. This may help to reduce complications until
the pharmaceutical treatments are effective. Unfortunately this treatment is very expensive and only available at some Universities and a few referral practices at this time.

In patients with a thymoma – cancer of the thymus gland, a thymectomy may help to allieviate symptoms of MG. In human patients thymoma is the leading cause of MG. It is thought that the antigens in the tissue of the thymus may be similar to that of the ACh receptor and that the antibodies produced are meant for the overgrowth of thymic tissue, but also attach to the ACh receptor in the NMJ as well. Incidence of thymoma-induced MG is more common in the feline than the canine patient. Any patient with MG and diagnosed with a thymoma may be a candidate for thymectomy. Since the incidence of thymoma-induced MG is so high in humans, prophylactic thymectomy is sometimes recommended, even without evidence of a thymoma, as it may allieviate the signs of MG. This is not so with veterinary patients, and prophylactic thymectomy is not usually recommended.

**Complications:**

The main complication is megaesophagus. Megaesophagus is a dilation of the esophagus and an inability of the esophagus to properly contract and move food into the stomach. This can occur in canine and feline myasthenic patients as the esophagus is made up of both smooth and striated muscle fibers. As the striated muscle fibers are weakened by MG, megaesophagus develops. As food sits in the esophagus it may be spontaneously ejected from the esophagus into and out of the mouth without contraction of the abdominal wall, this is referred to as regurgitation. A side effect of chronic regurgitation is that the chance of inhaling undigested food is increased. Inhalation of food, water or gastric juices leads to aspiration pneumonia. Consequently it is the aspiration pneumonia that is the most common cause of death in veterinary MG patients. This is not true in human patients, as the esophagus of humans is made of smooth muscle fibers, which are not affected by MG.

Severely affected patients may develop weakness of the intercostal muscles and may suffer respiratory depression or even respiratory arrest. If possible these patients should be placed on a ventilator for respiratory support until the symptoms subside.

Due to the complications of myasthenia gravis, the disease is often fatal in up to 50% of new cases. With early, comprehensive treatment and client education, many of these complications can be reduced or negated. Unfortunately, some patients may succumb to the disease despite all precautions.

**Patient Care:**

To help prevent pneumonia, patients with megaesophagus should be fed so that the esophagus is elevated 30-90 degrees above normal for the feeding and then held in that position for a period of 15 to 30 minutes. This allows gravity to pull food into the stomach without the help of esophageal contraction. Food should be of a liquid or soft consistency to allow the quickest transition into the stomach and should be fed slowly, over 10 to 20 minutes so that the esophagus does not
become overextended. Simply elevating the food bowl may achieve the expected position this, but after feeding the patient will usually revert to a normal stance before the food has been pulled into the stomach.

A device called a “Bailey chair” may help with feedings and post-feeding upright stance. The Bailey Chair is essentially a high chair for dogs. It forces the dog to sit in an upright position, with the esophagus at a 90 degree angle above normal. It was developed for patients with idiopathic megaesophagus, but works well for patients with MG as well. More information about the Bailey Chair can be found at http://www.caninemegaesophagus.org/support.htm. It is also important that patients with megaesophagus drink water and take oral medications in the upright method as well to reduce regurgitation.

Nasogastric (NG) or Percutaneous endoscopic gastric (PEG) tubes may also be placed in patients with severe regurgitation. Bypassing the esophagus allows the patient to be given nutrition without the threat of regurgitation. NG tubes are easily dislodged though, and PEG tubes need to be placed while under general anesthesia. Parenteral nutrition may be indicated if the patient is considered too critical for anesthesia.

For mildly to moderately affected patients, sling-assisted walks allow the patient to get up and about for a short time. Walks should be kept short, and rest breaks to allow the patient to sit or lay down should be given as needed. Patients that are not blinking regularly should have eye lubrication every 4 to 6 hours to prevent corneal ulcers.

For more severely affected patients an extended hospital stay may be warranted. If aspiration pneumonia sets in or if the patient is not ventilating properly, nebulization and/ or oxygen support may be indicated. Oxygen may be delivered through an oxygen cage, nasal oxygen cannula, or by intubation. As mentioned before, assisted ventilation may be needed is the patient becomes too weak. A tracheostomy may be performed to allow the patient to be mechanically ventilated without prolonged anesthesia.

Case Report:

Figaro an 8 year old male neutered domestic shorthair cat presented for acute onset inability to walk and flexion of the neck. On presentation Figaro was only able to take a few steps on his own before lying down. His neck was ventroflexed. He had an otherwise normal neurologic and physical exam. A CBC and blood chemistry was normal, including electrolytes. On thoracic radiographs a mass was seen in the mediastinum. Thoracic ultrasound confirmed a possible thymoma. AChR Ab titers were submitted and returned elevated, confirming myasthenia gravis. Figaro was started on pyridostigmine and prednisolone. He responded very well to treatment and was once again able to run around like his normal self. His owner elected to pursue thymectomy. Figaro returned to the hospital for a thoracotomy and thymectomy surgery. Surgery went well and a large mass was removed from the mediastinal area. Pathology confirmed thymoma. Figaro recovered from surgery well and over the next few months was weaned of the pyridostigmine. His AChR Ab
titers decreased but never returned to normal. Figaro remains on a small amount of prednisolone every other day and has not had a recurrence of symptoms.

References:

