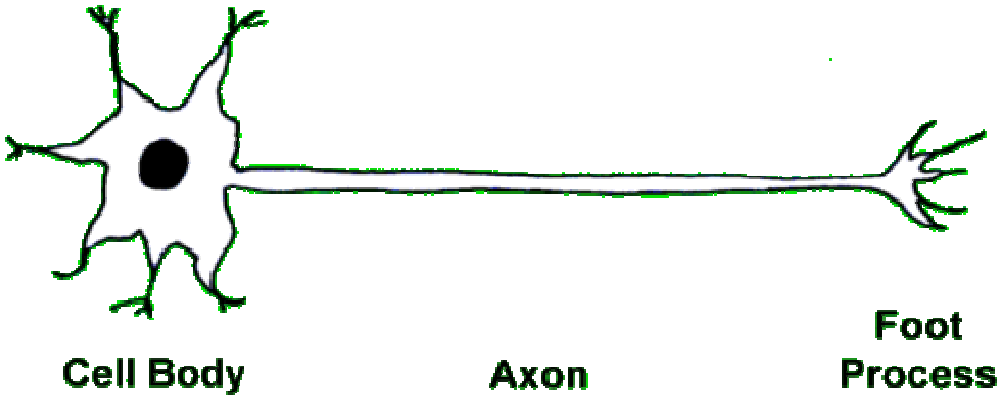
Myasthenia gravis

What You Need to Know to Understand this Disease

Myasthenia gravis is a disease that interrupts the way nerves communicate with muscles. In order to understand this disease, you must have some understanding of how things work in the normal situation.



Beginner's Terminology

A neuron is a cell. It has a head called a cell body at one end, a long strand called an axon, and a foot piece with small branching fingers called foot processes. The neurons that myasthenia gravis involve have their cell bodies (their heads) in the spinal cord and their foot processes (their feet) in the voluntary muscles that we use to move our bodies (our skeletal muscles.) The spinal cord sends a message to move a certain muscle. The neuron receives this message and carries it to that muscle.

A nerve is a group of axons. The white fibrous structures we call nerves are actually groups of axons bundled together similar to the way electrical wires in your home are bundled inside an insulating cord.

Neurotransmitters are chemicals. In order for a message to be transferred between neurons, a chemical is released from the foot processes of the first neuron and is taken up by one of the branches of the receiving neuron's head (or by the muscle.) After the chemical message has been successfully transferred, an enzyme destroys the neurotransmitter molecule in order to prevent on-going stimulation. The neurotransmitter we are concerned with in myasthenia gravis is called acetylcholine and the enzyme that degrades it is called acetylcholinesterase.

The neuromuscular junction is the area where neuron and muscle interface. There are three types of muscle: heart muscle; smooth (or involuntary) muscle, the kind that moves food through your intestine or constricts your pupils); and striated (or voluntary) muscle, with which you use to walk, type, sing, and control facial expression. It is the neuromuscular junction on the striated muscle that is stricken in myasthenia gravis.

MYASTHENIA GRAVIS

Myasthenia gravis is the condition where the neuromuscular junctions are diseased. The acetylcholine message from the nerve trying to stimulate the muscle is quickly blunted. There are several forms of myasthenia gravis.

Congenital Myasthenia Gravis
In this condition, the patient is born without normal neuromuscular junctions to striated muscles. There is no effective treatment. Myasthenia gravis has been described as a recessive genetic disease in Jack Russell terriers, Springer Spaniels, and Smooth Fox Terriers. The miniature dachshund gets a congenital form that actually resolves with age.

Acquired Myasthenia Gravis
This is a so-called autoimmune disease, meaning that the immune system is destroying neuromuscular junctions as if they were foreign invaders. What muscles are affected depend on which junctions have been destroyed. Therapy centers on stopping this immune reaction and prolonging what acetylcholine activity is still present. This is done with a combination of immunosuppressive agents and medications to inhibit breakdown of neurotransmitters.

Acquired myasthenia gravis can be further divided into four subtypes:

1. Focal - only one body part, usually the esophagus, is involved
2. Generalized - all skeletal muscles involved
3. Fulminating - rapidly progressive and usually fatal
4. Paraneoplastic – caused by cancer, most often thymoma.

Clinical Signs

Symptoms center on muscle weakness affecting the eyes, muscles of facial expression, throat, esophagus, and limbs. This translates into fatigue and muscle weakness brought on quickly by exercise (in about 60% of patients); megaesophagus (flaccid esophagus); voice change; laryngeal (voice box) paralysis; or difficulty swallowing. Generally, symptoms come on relatively suddenly over days to weeks and can be fairly broad spectrum. The classic exercise-induced weakness may not be seen at all and sometimes megaesophagus is the only sign (as in the focal form of myasthenia gravis).

Because swallowing difficulties and regurgitation often are included in the clinical picture, pneumonia resulting from accidental inhalation of saliva, food, or vomit into the lungs can occur, complicating the picture and creating a more serious situation. This complication is called aspiration pneumonia and substantially worsens prognosis.

Unlike humans with myasthenia gravis, most animal patients will cure spontaneously and prognosis is good if they survive the initial month when weakness is most severe and the risk of aspiration pneumonia is greatest. The owner should be prepared to treat the patient long term (i.e. a year or more) though treatment periods of only a few months are not unusual. Cats tend to require indefinite therapy while dogs tend to spontaneously cure.

The paraneoplastic form of myasthenia gravis is associated with thymoma, a tumor of the thymus gland located in the chest, and should be identified as early as possible as surgery to remove the tumor is important. This form of myasthenia is not going to resolve spontaneously.

Because myasthenia gravis is unfortunately common, any dog with general muscle weakness, difficulty swallowing, or megaesophagus should be tested for myasthenia gravis.

Testing

Blood Testing
Nowadays, a simple (though not inexpensive) blood test can be done to check for antibodies against acetylcholine receptors. It is called an AChR test. This blood test is able to detect 98% of pets with myasthenia gravis. When antibodies drop to less than 0.6 nmol/L in dogs and 0.3 nmol/L in cats, clinical signs generally resolve. The disadvantage of this test is that it is only run only at one laboratory, located at University of California San Diego, and results take as long as a couple of weeks.

There is a window during which a patient who has myasthenia gravis will not have a high enough antibody level to be considered positive. In pets that test negative, a second test should be performed after a couple of months before considering myasthenia gravis to be ruled out.

The Tensilon Test
This test involves giving an injection of edrophonium chloride (brand name Tensilon®) intravenously to a patient suspected of having myasthenia gravis. Edrophonium chloride is a short-acting anticholinesterase. This allows acetylcholine to accumulate in the neuromuscular junction, strengthening the message from nerve to muscle. The response can be dramatic. This allows for a tentative diagnosis to be made quickly rather than waiting for the blood test results. Unfortunately, right now, Tensilon® is not on the market.

It is important to recognize some disadvantages of the Tensilon test, however:
- Results may not be as dramatic, lending some subjectivity to interpretation.
- A negative test does not rule out myasthenia gravis.
- Edrophonium chloride can cause an airway spasm, leading to the need to intubate the patient and deliver oxygen on an emergency basis.
- Edrophonium chloride has potential to drop heart rate, which could be dangerous for a patient with a pre-existing heart problem. (Note: this issue is not a problem with oral anticholinesterases.)
- Many other diseases that cause weakness may appear to improve with the Tensilon injection.
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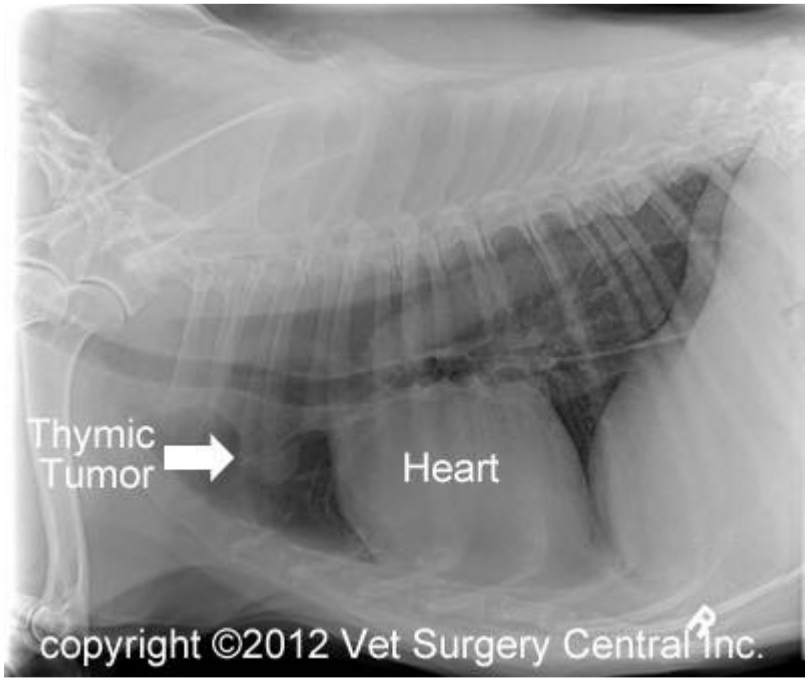
Tissue Biopsy
Historically, testing was more complicated. Muscles were biopsied and tissue samples stained for antibodies. Obviously, harvesting a strip of muscle is somewhat invasive compared to the above tests and now that blood testing is available, it is not commonly done any longer.

Chest Radiographs (x-rays)
A chest radiograph set should be taken to check for thymoma. Surgery to remove the tumor is recommended for patients who have thymic masses so it is important to identify these patients. In cats with myasthenia gravis, one in four can be expected to have a mass in the chest in the area of the thymus gland so it is extra important to screen feline patients. In dogs, only around 3-4% of patients will fit in this category.

The other reason to take a chest radiograph is to look for megaesophagus and aspiration pneumonia, which us potentially life threatening and must be treated immediately.



Radiograph of a dog's chest shows a thymic mass. (Graphic courtesy of Vet Surgery Central Inc.)

Treatment

With early detection and proper treatment, treatment can be expected to yield a positive response with normal life quality and normal life expectancy, if the animal does not die of aspiration pneumonia during the short term.

Anticholinesterases
Pyridostigmine (Mestinon®) is the typical medication used to prolong the action of acetylcholine. By inactivating the enzyme acetylcholinesterase, the receptors that have not yet been destroyed by the immune system can bind acetylcholine longer. It is typically given orally 2 to 3 times daily and may be associated with some nausea, cramping, and possibly diarrhea. This can be dealt with by diluting the medication or by giving medication on a full stomach. Other side effects can be excess tearing of the eyes, and drooling. Pyridostigmine could be thought of as a longer-acting version of edrophonium chloride.

Neostigmine bromide (brand name Prostigmin®) is also an anticholinesterase that could be used; however, pyridostigmine generally has fewer side effects.

Because most pets resolve their myasthenia gravis spontaneously, the goal of therapy is to control symptoms until that happens. Many canine patients will require no further treatment beyond one of these medications. Cats generally do better if immune suppression is included in their regimen.

Immune-Suppression
Corticosteroids, such as prednisone and similar drugs, can suppress the production of the antibodies that are destroying the neuromuscular junctions. In general these medications are avoided unless the anticholinesterase therapy does not yield acceptable results. Other

stronger immune suppressive drugs such as azathioprine (Imuran®), cyclosporine (Atopica®, Sandimmune®, Neoral®) or cyclophosphamide (Cytoxan®), are only used if there are reasons that corticosteroids (prednisone, dexamethasone, etc.) cannot be used for some reason, or if the myasthenia is severe. Often canine patients get weaker when steroid therapy is initiated so frequently a lower starting dose is used, gradually working up to an immune-suppressive dose. Feline patients generally start with higher doses right away.

Megaesophagus
In megaesophagus, the esophagus (the tube that connects the throat and stomach and transports food) becomes flaccid and useless. Patients with this condition regurgitate their food because they cannot effectively move food into their stomachs. They lose weight because they cannot retain food. They are also highly predisposed to aspirating (inhaling) food and saliva and developing especially intractable pneumonia as a result. Special management of these patients is required to avoid pneumonia and maintain nutrition.

It is important that this condition be recognized quickly so as to prevent debilitating weight loss and pneumonia.

Removing the thymus gland?
The thymus gland, located in the chest, generally shrivels up after childhood/puppyhood/kittenhood. It is involved in the maturation of the immune system. In humans, tumors and excessive growths of the thymus frequently accompany the development of myasthenia gravis. Thymectomy (removal of the thymus gland) is a well-accepted part of treatment for myasthenia gravis in humans but in dogs and cats it would only be done if they have a thymic tumor.

Removing a thymic tumor is a highly invasive chest surgery. If the tumor can be completely removed, the myasthenia gravis should resolve, and the blood test for antibodies can be used to determine if complete removal has been achieved. If the tumor cannot be fully removed, then continuing treatment will be needed.

Vaccination should be postponed in patients with this problem, as it has been shown to exacerbate active myasthenia gravis.

Myasthenia gravis has been reported as a drug reaction in hyperthyroid cats in the first few months of treatment with methimazole. Another form of treatment for hyperthyroidism should be utilized in these patients. In this unique situation, disease resolves with discontinuation of the drug.

References:

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