Immune-mediated muscle diseases: myasthenia gravis and inflammatory myopathies

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ACQUIRED MYASTHENIA GRAVIS
Acquired myasthenia gravis (MG) is a neuromuscular disorder characterized by focal or generalized muscle weakness as a result of immune-mediated destruction of acetylcholine receptors at the neuromuscular junction. Acquired MG is probably the most common neuromuscular disorder we can diagnose in the dog. It is not as common in the cat.

Presenting Clinical Signs
Clinical signs are variable and the so-called “classical presentation” of an exercise related weakness is not common
• Generalized weakness
• Regurgitation, dysphagia, dysphonia
• Muscle tremors
• Fatigable or absent palpebral reflexes
• Excessive drooling
• Sleeping with eyes open
• Moist productive cough secondary to aspiration pneumonia
• Tendon reflexes usually normal but may be fatigable
• Cats: Ventroflexion of the neck, decreased palpebral reflexes, and generalized weakness most common

Breeds at High Relative Risk for Acquired MG
• Akita
• Scottish Terrier
• German Shorthaired Pointer
• Chihuahua
• Familial MG identified in Newfoundlands and Great Danes
• Golden Retriever and German Shepherd dogs have highest absolute morbidity
• Cats: Abyssinian and Somali

Age of Onset: A bimodal age of onset in acquired MG has been described with young dogs (4 months-4 years) and older dogs (9-13 years) affected.

Clinical Forms of Acquired MG
• Focal – Regurgitation due to megaesophagus or dysphagia due to pharyngeal weakness (approximately 40% of the cases)
• Mild Generalized – Generalized weakness in the absence of megaesophagus (approximately 10% of the cases)
• Severe Generalized – Generalized weakness and megaesophagus (Approximately 45% of the cases)
• Acute Fulminating – Rapid development and progression of generalized appendicular weakness. May present in lateral recumbency and non-ambulatory. This form of MG may mimic lower motor neuron diseases such as tick paralysis, botulism, and polyradiculoneuritis. Prognosis is poor in these cases as they requiring prompt recognition and intensive care including respiratory support and possibly plasmapheresis (<5% of cases)
• Paraneoplastic MG – Associated with a cranial mediastinal mass or other neoplasias (<5% of cases)
• Cats: Generalized weakness without megaesophagus (30% of cases), generalized weakness with megaesophagus or dysphagia (20% of cases), generalized weakness associated with cranial mediastinal mass (30%), focal MG (15%), drug related MG (methimazole 5% of cases).

MG may be Associated with Other Autoimmune or Neoplastic Diseases
• Hypothyroidism
• Autoimmune hemolytic anemia
• Thrombocytopenia
• Masticatory muscle myositis
• Thymoma
• Cholangiocellular carcinoma
• Osteogenic sarcoma

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Differential diagnosis
• Tick paralysis
• Botulism
• Cholinesterase toxicity
• Acute polyradiculoneuritis
• Polynuropathy
• Polymyopathy

Diagnosis of Acquired Myasthenia Gravis

Presumptive Diagnosis
• Edrophonium chloride challenge (Tensilon Test; 0.1 mg/kg IV). A positive response is a dramatic increase in muscle strength. False positive and negative results may occur with this test. Therefore, do not rely on this test to “make or break” a diagnosis.
• Decrement of the muscle action potential with repetitive nerve stimulation – Needs to be performed by trained people at specialized centers. Requires anesthesia so may be risky in critical patients. Some myasthenic patients will not show a decremental response and other disorders of neuromuscular transmission may decrement so not specific for MG.
• Single fiber EMG – Technically difficult and must be performed at specialized centers. High sensitivity but lower specificity.

Confirmatory Test: The “gold standard” for the diagnosis of acquired MG is demonstration of circulating antibodies against nicotinic acetylcholine receptors (AChRs) by immunoprecipitation radioimmunoassay. This is a sensitive and specific test that confirms the presence of autoantibodies directed against the nicotinic AChR and documents an aberrant immune response. The test is available through the Comparative Neuromuscular Laboratory at the University of California, San Diego (http://medicine.ucsd.edu/vet_neuromuscular)

Ancillary Testing
• Thoracic radiographs - esophageal dilatation and mediastinal masses
• An electrocardiogram should be evaluated if bradycardia is suspected since 3rd degree heart block has been documented in a small number of canine MG patients.
• Laboratory evaluation of thyroid function and testing for other autoimmune diseases

Interpretation of AChR Antibody Titers
• An AChR antibody titer >0.6 nmol/l is diagnostic of acquired MG in dogs and >0.3 nmol/l is diagnostic in cats
• Corticosteroid therapy at immunosuppressive dosages for longer than 7-10 days will lower antibody levels. Collect a pretreatment serum sample to avoid this drug related lowering.
• Unless severe, hemolysis or lipemia do not affect the assay.
• There is no correlation between severity of clinical signs and the degree of elevation of the antibody titer.
• There is a good correlation in an individual animal between the antibody titer and the clinical course of the disease. As dogs go into remission the antibody titer will return to the normal range.

Treatment
• Elevation of food and water
• Fluid support and intensive care including respiratory support if required
• Treatment with antibiotics for aspiration pneumonia (NOTE PRECAUTIONS)
• Gastrostomy tube if unmanageable regurgitation is present
• Anticholinesterase drugs – Cornerstone of therapy for MG
  – Pyridostigmine bromide (Mestinon, 1-3 mg/kg q 8-12 hr PO). Available in tablets, syrup, and time-release forms. If using syrup form dilute 50:50 in water as gastric irritation may result if given straight.
  – For critical animals a constant rate infusion of pyridostigmine bromide (0.01-0.03 mg/kg/h) may be given until oral feedings are resumed or feeding tube is placed.
  – Neostigmine bromide (Prostigmin, 2 mg/kg/d PO in divided doses to effect)
• Immunosuppressive drugs – The role of these drugs in the treatment of canine MG is not yet clear. They may be important in the treatment of feline MG.
  – Low-dose (1 mg/kg) alternate day prednisone if there is not a favorable response to anticholinesterase drugs alone or if the animal has developed a resistance to these drugs. Myasthenic crisis can be precipitated with high doses of daily prednisone worsening the muscle weakness.
  – In severe cases of MG, high-dose pulses of IV methylprednisolone may be of benefit. In one human study, 2 g of methylprednisolone was given IV every 5 days to 15 patients with satisfactory improvement without exacerbation of muscle weakness in 10 of the 15 patients.
  – Other immunosuppressives including azathioprine, mycophenolate? There are no good controlled studies to document any benefit.
  – Consider the benefit: risk ratio, possible degree of benefit, and side effects.
Surgical removal of cranial mediastinal mass
- All animals with a cranial mediastinal mass should be tested for MG prior to surgical removal. If the animal is not weak prior to surgery, weakness may develop following surgery.
- If the mass is completely removed the clinical signs of MG should resolve and the AChR antibody titer returns to the reference range. IF the mass is not completely removed the clinical signs of MG will persist as will the elevated AChR antibody titer.

PRECAUTIONS
Avoid use of drugs that may affect neuromuscular transmission such as ampicillin, aminoglycosides, antiarrhythmic agents, phenothiazines, anesthetics, narcotics, and muscle relaxants. Also, organophosphate dips may result in a cholinergic crisis since they could be additive with pyridostigmine.

Monitoring the Course of Acquired MG: As shown by recent studies, the natural course of canine MG is to go into spontaneous remission. Similar studies have not yet been performed in the cat. In the absence of immunosuppression, determination of serial AChR antibody titers in an individual animal is a good indicator of disease status and should help to determine duration of treatment. As long as AChR antibody titers are positive, treatment should be continued. There has been an excellent correlation between resolution of clinical signs, including megaesophagus, and return of AChR antibody titers to the reference range.

Important dos and don’ts
- Differentiation of vomiting from regurgitation
- Make every attempt to reach a correct diagnosis as soon as possible. Trial and error therapy may result in delays in reaching the correct diagnosis or possibly make obtaining a correct diagnosis difficult
- Know which drugs are contraindicated in myasthenic patients
- Recommend to the owner or breeder not to breed a myasthenic animal
- Spay myasthenic female dogs and cats as soon possible after MG is under control, because pregnancy can exacerbate active MG
- Be careful not to over vaccinate, because vaccinations have been shown to exacerbate active MG

While mortality in canine MG is still unacceptably high, early and accurate diagnosis is a key to a better clinical outcome. In the absence of severe aspiration pneumonia, pharyngeal weakness, or acute fulminating MG, the prognosis should be good. If thymoma is present, prognosis is guarded unless there is complete surgical removal. Concurrent hypothyroidism should be treated if present. Follow up AChR antibody titers should be evaluated every 6-8 weeks since they return to normal range with clinical remission of the disease.

IMMUNE-MEDIATED INFLAMMATORY MYOPATHIES
The immune-mediated inflammatory myopathies including masticatory muscle myositis, polymyositis, and extraocular myositis are among the most commonly recognized neuromuscular diseases in dogs. Inflammatory myopathies are the result of cellular infiltration into striated muscle. A definitive diagnosis and successful therapy is dependent on early recognition of the clinical signs and appropriate diagnostic testing and interpretation. As with most disease processes, the earlier the diagnosis is achieved followed by institution of appropriate therapy, the better the clinical outcome. With inflammatory myopathies, this time factor may translate into either a normal functioning pet or one with a severe permanent disability.

MASTICATORY MUSCLE MYOSITIS (MMM)
Atrophy of the muscles of mastication is a relatively common clinical presentation in the dog and very rarely described in cats. A diagnosis of MMM should not just be assumed based on atrophy of the masticatory muscles as other disorders can also result in similar clinical signs.

Clinical Signs of Masticatory Muscle Myositis
- Atrophy and/or swelling restricted to the muscles of mastication
- Jaw pain
- Exophthalmos in the acute stage and enophthalmos if chronic with marked muscle atrophy
- Abnormalities of jaw movement including trismus
- Rarely inability to close the jaw
- INABILITY TO OPEN THE JAW UNDER ANESTHESIA IS A CLASSICAL FINDING IN MMM

Differential Diagnosis
- Previous corticosteroid therapy. Remember corticosteroids may result in fairly rapid and marked atrophy of the masticatory muscles. Limb muscles affected to a lesser extent.
- Denervation – Atrophy may be unilateral if associated with previous trauma to the side of the head or a neoplasia, or bilateral if associated with a generalized neuropathic disorder
- Temporomandibular (TM) joint disease – May result in disuse atrophy of the masticatory muscles and restricted jaw mobility
- Polymyositis
Extraocular myositis
Retrobulbar abscess - Commonly confused with MMM

Diagnostic Testing
Serum creatine kinase (CK) may be normal or mildly elevated
Electromyographic abnormalities restricted to the muscles of mastication (not necessary for the diagnosis)
Radiographs of TM joints
Probe behind last upper molar for presence of retro orbital abscess
Demonstration of autoantibodies against masticatory muscle type 2M fibers (2M antibody assay) by immunocytochemistry or ELISA is diagnostic of MMM. Corticosteroids will lower antibody levels so best to test a pre-treatment serum sample. This test cannot be used to determine prognosis for return of jaw function or muscle mass
Evaluation of a muscle biopsy specimen is essential for confirming the diagnosis and determining prognosis. The degree of inflammation, amount of fibrosis and myofiber destruction must all be evaluated.
Thyroid evaluation
Testing for AChR antibodies if concurrent clinical signs suggestive of MG
NOTE: One common problem with obtaining a biopsy from the temporalis muscle is that the frontalis muscle is sampled by mistake. The frontalis muscle lies directly under the skin, is not affected in MMM, and will not be diagnostic. This muscle must be incised and retracted to allow exposure of the thick fascia that overlies the temporalis muscle. Incise and retract the fascia and biopsy the temporalis muscle just underneath.

Treatment of MMM: Common causes of a poor clinical outcome in MMM are delay in diagnosis and inappropriate treatment. A delay in diagnosis can make a treatable disease into an untreatable one. Inappropriate therapy may also result in a poor clinical outcome. As a general rule use immunosuppressive dosages to bring the disease under control.
Prednisone – 2 mg/kg/day until jaw function returns to normal and serum CK (if elevated) returns to the normal range. Start at a high dose then slow taper to the lowest alternate day dosage is obtained that will keep the dog free of clinical signs. Maintain this alternate day dosage for 4-6 months.
Other immunosuppressive drugs - Azothiaprine therapy may be added in cases that do not respond optimally to corticosteroids alone or where the side effects of the corticosteroids cannot be tolerated
Inadequate drug dosages and duration of therapy will result in reoccurrence of clinical signs that may be more difficult to manage

Prognosis: In the absence of marked fibrosis and myofiber destruction, the prognosis should be good for return of muscle mass and function. Inflammation and myofiber destruction may be particularly severe in the Rottweiler, Doberman, and Samoyed breeds. Early diagnosis and treatment would be particularly important in these breeds to prevent irreversible myofiber damage.

EXTRAOCULAR MYOSITIS (EOM)
The clinical presentation of EOM may be similar to an acute stage of MMM with bilateral exophthalmos and impaired vision. Golden Retrievers may be particularly susceptible. Serum CK concentration should be normal or only mildly elevated. Immunocytochemical assay for antibodies against type 2M fibers should be negative. An orbital sonogram or MRI may demonstrate swollen extraocular muscles. A biopsy from the masticatory muscles should be normal. Mononuclear cell infiltration in EOM is restricted to the extraocular muscles. Immunosuppressive dosages of corticosteroids as for MMM should result in decreased swelling of extraocular muscles. Prognosis should be favorable if diagnosed correctly and treated adequately. With inadequate therapy and chronic disease, fibrosis of the extraocular muscles may result in strabismus.

POLYMYOSITIS (PM)
Polymyositis occurs less frequently than MMM and can look clinically similar to myasthenia gravis with generalized weakness and esophageal dilatation. Various breeds of dogs may be affected with no obvious age or sex predisposition. Newfoundland and Boxer dogs may be over-represented.

Presenting Clinical Signs
Stiff-stilted gait
Weakness and exercise intolerance
+/- muscle pain
Muscle swelling or atrophy including the muscles of mastication
Regurgitation or dysphagia as a result of pharyngeal or esophageal involvement. May be the presenting clinical sign in some cases with subclinical limb muscle involvement.
If concurrent neoplasia is present, the primary complaint may be related to the location of the neoplasia (ie: dyspnea if cranial mediastinal mass is present)
Differential Diagnosis
- Myasthenia gravis
- Breed associated myopathy
- Polyneuropathy
- Polyarthritis
- Endocrine associated myopathy

Diagnostic Testing
- Serum CK concentration is usually but not always elevated. It is important to remember that an elevated serum CK is supportive but not necessarily diagnostic of PM
- Evaluation of synovial fluid from multiple joints should be performed to eliminate a diagnosis of polyarthritis
- Neurological evaluation should eliminate a diagnosis of polyneuropathy
- EMG evaluation may help determine the distribution of muscle involvement and identify muscles to be biopsied.

**The muscle biopsy is the single most important test to confirm a diagnosis of PM.** Multiple muscles should be sampled as cellular infiltrates may have a focal or multifocal distribution and be missed on a single specimen. Suggested muscles to biopsy include proximal muscles from the forelimb (triceps) and hind limb (vastus lateralis or biceps femoris).
- If muscle biopsies are diagnostic of an inflammatory myopathy, further testing for infectious agents should be performed including antibody titers for protozoal parasites including *Toxoplasma gondii, Neospora caninum, Hepatozoon canis*, *Hepatozoon americanum, Leishmania infantum, Trypanosoma cruzi* and tick-related diseases (Lymes disease, Ehrlichiosis, and Rocky Mountain Spotted fever). In cats, testing for FeLV and FIV should be performed.
- Screening chest and abdominal radiographs for neoplasia
- Thyroid evaluation
- Carefully question owner regarding previous drug therapy or nutriceutical supplements

Treatment of PM
- Specific therapy for an infectious agent if identified
- Specific therapy for neoplasia if identified
- Discontinue any drugs or supplements that could potentially initiate an inflammatory myopathy
- Elevation of food and water or a PEG tube if megaesophagus is present
- Immunosuppressive therapy as for MMM using a similar rationale of high dose prednisone to bring the disease under control followed by a slow taper. Monitor serum CK and use as a guide to therapeutic response
- Azathioprine may also be used for steroid sparing
- Supplementation with L-carnitine (50 mg/kg BID) may be beneficial in improving muscle strength during corticosteroid treatment
- Physical therapy to aid in prevention of steroid related muscle atrophy
- High risk of recurrence if inappropriate treatment

Prognosis: As in MMM, an accurate diagnosis and appropriate therapy are essential to a good clinical outcome. Delay in therapy may result in significant muscle atrophy, extensive myofiber loss, fatty infiltration and fibrosis. It is this author’s impression that PM may be more difficult to treat than MMM. Investigations are currently in progress on canine PM that may provide a more rational approach to therapy.

DERMATOMYOSITIS
Characteristic skin lesions should be present in breeds predisposed to this disorder (Rough coated collies, Shetland sheepdogs, Australian cattle dogs). Concurrent muscle atrophy, pain or abnormal gait may be present similar to PM. Age of onset has been reported to be 3-5 months for familial dermatomyositis. Skin biopsy should be diagnostic. Treatment consists of immunosuppressive therapy as in other immune-mediated muscle disorders. Appropriate breeding programs should be initiated to eliminate this disorder from the line. An autosomal dominant inheritance pattern has been reported in the Rough Coated Collies and Shetland Sheepdogs.

REFERENCES