

# Myasthenia gravis: lessons from the past 10 years

**Over the past 10 years, significant advances have been made in our understanding of acquired myasthenia gravis (MG) in companion animals. The broad spectrum of presenting clinical signs has been defined and an accurate and sensitive diagnostic test is available. Even with these advances, the mortality rate in dogs with acquired MG remains unacceptably high. While an understanding of the genetic basis for susceptibility to autoimmune disease has started to be developed, the trigger for the initiation of this disease is not known and a mechanism for specific suppression of the aberrant immune response against the acetylcholine receptor remains a mystery.**

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## INTRODUCTION

Significant advances have been made in the past 10 years in our understanding of myasthenia gravis (MG) in companion animals. We now have a better understanding of the wide range of clinical presentations, a sensitive and specific diagnostic test that results in a confirmed diagnosis, and specific treatments that can control the clinical signs of MG. The mortality rate, however, still remains unacceptably high. Unlike in human MG where nearly all patients are able to lead full, productive lives (Drachman 1994), MG in dogs remains a 'grave' disease.

Immune-mediated MG is one of the best characterised autoimmune diseases affecting both humans (Lindstrom and others 1988) and companion animals (Shelton and others 1988, 1997). Unlike the case for other autoimmune diseases, the inciting autoantigen is known, there are specific and sensitive diagnostic tests and relatively specific therapies are available. Muscular weakness and excessive fatigability are characteristic of MG and have been shown to be a result of an antibody-mediated autoimmune response directed against nicotinic acetylcholine receptors (AChRs) in skeletal muscle. While recent textbooks of veterinary

medicine still describe this as an uncommon disorder, knowledge gained over the past 10 years has demonstrated that this is not the case. Acquired canine MG may actually be the most common neuromuscular disease that can be diagnosed affecting this species. It has also become apparent that the so-called 'classical' presentation of acquired MG as an exercise-related weakness is not always the case.

## CLINICAL PRESENTATION

Acquired canine MG mimics various other neuromuscular diseases and should be high on the list of differential diagnoses in any dog with focal or generalised muscle weakness. Clinical signs may be focal in nature, associated with regurgitation (megaesophagus) or dysphagia (pharyngeal dysfunction) in the absence of limb muscle weakness (Shelton and others 1990). In a recent study of 1154 dogs with a confirmed diagnosis of acquired MG (Shelton and others 1997), 43 per cent of the dogs did not have clinically detectable limb muscle weakness. Clinical signs consistent with generalised MG were described in the remaining 57 per cent. In the group of dogs with generalised MG, 13 per cent did not have clinical signs of oesophageal or pharyngeal dysfunction and pharyngeal weakness alone was found in only 1 per cent of the cases.

Recently, a severe, acute fulminating form of MG has been described (Dewey and others 1997, King and Vite 1998). These cases are associated with a sudden onset of oesophageal dilatation and rapid progression to quadraparesis and respiratory failure. While the number of cases studied with this form of MG has been small, several of these dogs had concurrent thymoma. In humans, the acute fulminating form of MG is associated with high mortality, myasthenic crisis and with the highest percentage of thymomas (Osserman and Genkins 1971).

## DIAGNOSIS

It is important in cases of MG to establish the diagnosis before initiation of therapy since medical therapies are not without undue risk and side-effects. The history and physical examination provide important clues for the initiation of a correct diagnostic pathway. A history of a recent onset of regurgitation should raise a red flag to the clinician. Dogs with MG usually appear normal at rest and there is an absence of appreciable muscle atrophy. Limb muscle reflexes are usually normal but may be fatigable. The palpebral reflex may be absent or fatigable, and the owner may comment that the dog sleeps with its eyes open. These observations should begin to separate MG from other myopathies and neuropathies.

Once a tentative diagnosis has been established, additional testing, including anticholinesterase challenge and electrodiagnostics, can be performed and further strengthen the tentative diagnosis. Confirmatory laboratory testing involves detection of elevated levels of AChR antibodies in the serum.

A presumptive diagnosis of acquired MG may be made following demonstration of improved muscle strength in a pharmacological trial (edrophonium chloride challenge) or by demonstration of a decremental response by electrical stimulation (repetitive nerve stimulation).

Pharmacological testing involves trial administration of a short-acting anticholinesterase medication and observation of the patient for improved muscle strength. This testing method has been shown to be neither sensitive nor specific (Oh and Cho 1990) as some dogs with MG are not edrophonium-(Tensilon) responsive, and dogs with other neuromuscular disorders, such as myopathies and neuropathies, may show a subjectively positive response. Performance of an edrophonium challenge is still recommended since a dramatic positive response would be consistent with MG and treatment could be initiated while

awaiting results of confirmatory laboratory testing.

A similar lack of specificity and sensitivity may be found with electrical stimulation, which also has the added drawback of the requirement for anaesthesia in a possibly critical patient. Single-fibre electromyography is a sensitive method for detecting delayed or failed neuromuscular transmission and a methodology has been established for the dog (Hopkins and others 1993). Specificity, however, is lacking, with positive findings in other disorders of the nerve, muscle and neuromuscular junction (Oh and others 1992).

The 'gold standard' for the diagnosis of acquired MG remains the demonstration of circulating autoantibodies against the nicotinic AChR by immunoprecipitation radioimmunoassay. This assay is sensitive, specific and demonstrates the presence of autoantibodies against AChR. It involves precipitation of serum immunoglobulin G (IgG) and IgM antibodies that bind to solubilised native AChR complexed with a high-affinity peptide antagonist,  $^{125}\text{I}$ -labelled  $\alpha$ -bungarotoxin. The precipitate's  $\gamma$ -emission reflects the amount of AChR bound to immunoglobulin but it is important that a species-specific assay system is used. Although there is some cross-reactivity in AChR recognition of antibodies between species, the assay is relatively species-specific. Antibody titres in dogs are in general lower than in humans, and low-titre positives may be missed if human AChR is used as antigen.

The AChR binding antibody assay is the first choice for confirming a diagnosis of acquired MG (Lennon 1997). It is not, however, predictive of the degree of weakness. Under the assay conditions of the author's laboratory, sera of healthy dogs bind less than 0.6 nmol of AChR per litre. Results may be negative early in the disease and retesting is suggested if clinical signs are recent in onset. Also, immunosuppressive therapy for longer than seven to 10 days will lower autoantibody titres, so it is advisable that blood collection is performed before corticosteroid therapy and

that the serum is kept refrigerated or frozen until the test can be performed.

While cases of seronegative MG do occur in dogs (Shelton 1989), recent studies have shown that the AChR binding assay detects approximately 98 per cent of the dogs with generalised acquired MG (Shelton 1998). The percentage is not known for focal MG.

In humans, positive results for AChR binding have been described in patients with autoimmune liver disorders; in 13 per cent of patients with autoimmune Lambert Eaton myasthenic syndrome, associated with autoantibodies against the presynaptic voltage sensitive calcium channels; and in 3 per cent of patients with primary lung cancer uncomplicated by neurological autoimmunity (Lennon 1997). To date, the author's group have not detected AChR antibodies in dogs with any disorder other than acquired MG.

While an AChR antibody titre greater than 0.6 nmol/litre is diagnostic of acquired MG, there is poor correlation between the titre and the severity of the disease (Roses and others 1981). This may be in part a result of the large size of the AChR and the detergent extraction process used in the diagnostic assay. Antibodies may be directed against portions of the receptor that are not of functional significance. Alternatively, a low titre of AChR antibodies may be present in which a large proportion of the antibodies are bound to the acetylcholine binding site, resulting in marked weakness. Determination of serial antibody titres in an individual animal, however, is a good indicator of disease status and should guide duration of therapy. Spontaneous remissions are not uncommon in dogs with MG. Clinical signs resolve and the AChR antibody titre is normalised. At that point, treatment may be discontinued.

### Other serological tests

Autoantibodies against several striated muscle proteins have been described in human MG, including myosin, actin and  $\alpha$ -actinin (Williams and Lennon 1986)

and titan (Gautel and others 1993). These have been collectively referred to as striational antibodies (StrAb). Since these antigens are located in the muscle's cytoplasm and are not normally accessible to circulating antibodies, they are believed to be non-pathogenic.

Positive assays for StrAb in humans may support a clinical diagnosis of acquired MG when tests for AChR antibodies are negative (Lennon 1997). StrAb are detected in 80 per cent of human MG patients with thymoma, in approximately 24 per cent of patients having thymoma without clinical signs of MG and in 30 per cent of adult MG patients without thymoma.

While the author has observed StrAb in canine patients with thymoma, the actual incidence has not yet been determined. Studies are currently in progress to address this issue.

Recently, antibodies against the ryanodine receptor (RyR) have been described associated with thymoma (Mygland and others 1992) and late-onset MG in humans (Skeie and others 1995). The presence of autoantibodies against RyR was associated with a severe form of thymoma-associated MG and a higher mortality rate. The RyR is a calcium-release channel in striated muscle involved in muscle contraction and in the mechanism of excitation-contraction coupling. Autoantibodies have also been documented in some dogs with thymoma and late-onset MG (G. D. Shelton, unpublished results). Studies are currently in progress in canine MG correlating the presence of RyR antibodies and clinical severity.

### Differential diagnosis

Other conditions that result in weakness of the cranial and somatic musculature should be considered in the differential diagnosis of MG, particularly those that result in the combination of oesophageal dilatation and limb muscle weakness. Differentials should include other disorders of neuromuscular transmission, including congenital MG, botulism and organo-

phosphate toxicity, polymyositis, hypoadrenocorticism, possibly hypothyroidism, and other myopathies and neuropathies. Since muscle atrophy is not a common feature of MG and reflexes are usually normal although fatigable, determination of the most likely possibilities may begin on physical examination. Age of onset should determine the likelihood of a congenital myasthenic syndrome.

### Identification of associated conditions

Since acquired MG may be associated with other conditions, a thorough laboratory evaluation, including complete blood counts, serum biochemistry panels and endocrine evaluations, should be undertaken in all cases. An optimal response to therapy may not be possible until concurrent abnormalities are identified and treated. MG may be associated with hypothyroidism (Dewey and others 1995), hypoadrenocorticism (G. D. Shelton, unpublished results), thrombocytopenia (G. D. Shelton, unpublished results), and as a paraneoplastic syndrome associated with thymoma (Aronsohn and others 1984, Klehnow 1997), osteogenic sarcoma (Moore and others 1990), cholangiocellular carcinoma (Krotje and others 1990) and anal sac adenocarcinoma (G. D. Shelton, unpublished results). Third-degree heart block has also been found in some dogs with MG, thymoma and polymyositis (Hackett and others 1995).

### TREATMENT

The most important factors for achieving a favourable clinical outcome in most cases of acquired MG are an early and accurate diagnosis and good clinical judgment regarding the choice of appropriate therapies. Dedicated owners are also important as treatment for MG will need to be continued for an average of six to eight months. Differentiation of vomiting from regurgitation and recognition of oesophageal dilatation is critical. Since

clinical signs in MG are heterogeneous and variable, appropriate treatment should be determined by the severity of the disease. Elevation of food and water and maintenance of nutrition and hydration are vitally important in cases with oesophageal dilatation. If regurgitation remains a problem, a feeding tube should be placed restricting liquids and solids by mouth and facilitating delivery of medication into the stomach.

Anticholinesterase agents are the first line of treatment for MG, acting by prolonging the action of acetylcholine at the neuromuscular junction and enhancing neuromuscular transmission. The dosage and schedule of administration must be tailored to the animal's needs.

Immunosuppressive therapy is indicated when weakness is not adequately controlled by anticholinesterase drugs. Prednisone, azathioprine and cyclosporin are agents used for immunosuppression. Steroids are the most commonly used immunosuppressive agents but are also associated with the largest array of potential side-effects.

In humans, patients with moderate to severe generalised weakness are hospitalised for the initiation of steroid therapy because of the risk of transient steroid-induced exacerbation of disease, which may occur during the first weeks of treatment in up to 48 per cent of patients (Johns 1987). Myasthenic crisis may also be precipitated by high doses of daily corticosteroids.

A similar corticosteroid-induced exacerbation of weakness has been observed in dogs with MG, resulting in respiratory arrest (G. D. Shelton, unpublished results). High-dose pulse therapy with intravenous methylprednisolone has been reported to be effective without the initial exacerbation of weakness in some human patients with severe MG (Arsura and others 1985), but this has not been evaluated in dogs.

The use of short-term immunotherapies, including plasma exchange and intravenous immune globulin, are limited in

veterinary medicine due to either equipment requirements or expense. These may be important in the immediate treatment of dogs with acute fulminating MG. Since abnormalities of the thymus other than thymoma have not been fully studied in dogs with MG, thymectomy has only been performed in cases of thymoma.

At a recent international conference on MG, a treatment algorithm for human MG was presented based on disease severity (Keesey 1997). Following confirmation of the diagnosis of MG, general treatment measures, including anticholinesterase drugs, should be initiated. Following determination of disease severity (group I, mild or focal; group II, moderate generalised; group III, severe generalised), three broad therapeutic approaches were discussed with low-dose alternate-day corticosteroid therapy for group I, thymectomy and/or steroids for group II, and plasmapheresis and intravenous gamma globulin for group III. Immunosuppressive therapy, including azathioprine and cyclosporin, were reserved for patients refractory to other treatments.

As a rule of thumb, the greater the degree of weakness that is present, the lower the dose of corticosteroids that should be used. Since canine MG can now be similarly divided into groups, treatment modalities based on severity of disease seems a rational approach in the canine MG population.

### **Predictive factors**

With early accurate diagnosis, appropriate treatment and dedicated owners, the prognosis for a favourable outcome in canine MG may be expected. A poor prognosis should be given if severe aspiration pneumonia is present (particularly if associated with large volumes of aspirated barium), if there is concurrent pharyngeal weakness, in the uncommon cases of acute, fulminating MG, and in critical patients with thymoma. If results of ongoing studies regarding the association of RyR and severity of MG in canine MG are consistent with those in human MG, evaluation of

RyR antibodies may be an important additional test in canine MG to assess disease severity or the early presence of thymoma. Acetylcholine receptor antibodies may also be detected before the radiographic appearance of thymoma.

### **Feline MG**

Compared to canine MG, acquired feline MG is uncommon (Joseph and others 1988). During the time period from 1988 to 1997, 79 cats were diagnosed in the author's laboratory with acquired MG based on demonstration of circulating AChR antibodies. Nine of the cats were of Abyssinian or Somali breeds. While information was not complete in all cases, 15/79 (19 per cent) of the confirmed MG cases were associated with a thymoma. This is in contrast to the canine MG population where 3-4 per cent of the cases were associated with a cranial mediastinal mass (Shelton and others 1997). With the exception of one cat with a steroid-responsive jaw drop, all of the cats had generalised neuromuscular weakness. While clinical information was not complete in all cases, focal MG with regurgitation and oesophageal dilatation has not yet been documented in the cat (G. D. Shelton, unpublished results).

### **FUTURE STUDIES**

While much is currently known about MG, there are two important aspects that still remain a mystery: what initiates and sustains the autoimmune response to AChR and how does one specifically suppress the autoimmune response? Dogs may play an important role in the study of both of these aspects, because the disorder develops spontaneously in dogs, indicating that triggers may be similar to those initiating the disease in humans, and dogs also have spontaneous remissions, indicating that their immune system is able to correct the imbalance that results in clinical disease. Future studies directed at the evaluation of T-lymphocyte activation during

the active phase of the immune response to AChR and during the remission phase may provide some clues. The role of the thymus is also unknown in MG in dogs.

Unequivocal evidence indicates that susceptibility to autoimmune disease is largely genetically determined, and the most clearly established genetic association with autoimmune disease predisposition is related to the major histocompatibility complex class II genes (Compston and others 1980).

In a recent study (Shelton and others 1997), the relative risk of acquired MG for 61 different breeds of dogs was determined and the Akita was found to be at highest relative risk. The Akita, in general, has a higher than expected level of immune-mediated disease compared to a cross-bred population. A significant role for MHC class II genes has also been shown in several animal models of MG (experimental autoimmune MG) with elimination of MHC class II molecules or binding of inhibitory peptide analogues of MHC class II preventing onset of experimental autoimmune MG (Kaul and others 1994). In human MG, significant associations with particular DRB and DBQ alleles are seen in class II genes in early-onset, non-thymoma-associated MG (Vieira and others 1993). A collaborative study is currently in progress with the Veterinary Genetics Laboratory at the University of California, Davis, to determine predisposing or protective MHC alleles associated with MG in the Akita. These studies could later be extended to other breeds.

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## ABSTRACTS

### Coagulation abnormalities in 22 cats with naturally occurring liver disease

Coagulation parameters were assessed in 22 cats with naturally occurring liver disease. All cats had elevated liver enzymes or serum bilirubin on biochemical analysis. Cats that had received treatment with vitamin K were excluded from the study. Prothrombin time, activated partial thromboplastin time, thrombin time, factor VII activity and platelet numbers were evaluated for all cats. Eighty-two per cent of the cats had at least one coagulation abnormality, prolonged prothrombin time being the most common (found in 77 per cent of the cases). Fifty per cent of the cats had coagulation abnormalities consistent with vitamin K deficiency as a result of their liver disease. High serum alkaline phosphatase results were associated with those of abnormal coagulation.

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### Congenital myotonia in two domestic cats

Congenital myotonia was diagnosed in two domestic cats; one male and a female sibling. Presenting clinical signs were noted from four months of age and included stiffness, weakness, falling over and clumsiness. On physical examination, non-painful profound enlargement of the proximal limb muscles was noted. One cat had a very enlarged tongue. In both cats, vocalisation was weak and there were other abnormalities such as prolonged facial distortion after hissing or transient respiratory stridor when stressed on handling. Neurological assessment was normal, as were thyroid and adrenal function tests. Electromyography was abnormal in both cats with similarly increased insertional activity and repetitive spontaneous discharges which waxed and waned and sounded like a 'dive bomber'. A myotonic dimple was evoked in one cat on percussion of the triceps muscle. Light microscopic examination of muscle biopsies from both cats revealed moderate hypertrophy with mild dilatation of transverse tubules on electron microscopy. No aetiology was identified. Neither cat received any treatment and both were no worse at the time of writing. An inherited congenital myotonia is suggested.

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