

# Risk factors for acquired myasthenia gravis in cats: 105 cases (1986–1998)

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**Objective**—To determine prevalence of initial clinical signs and risk factors for acquired myasthenia gravis (MG) in cats.

**Design**—Retrospective case-control study.

**Animals**—105 cats from the United States, Canada, and the United Kingdom with a confirmed diagnosis of acquired MG and 510 cats with other neuromuscular disorders, including generalized weakness, megaesophagus, and dysphagia (control group).

**Procedures**—Records were retrieved from a database containing results of serum samples tested for acetylcholine receptor antibodies. Signalment, including breed, age, and state or country of origin, month of onset, and initial clinical signs were obtained. An acetylcholine receptor antibody titer > 0.3 nmol/L was diagnostic for acquired MG. Unconditional logistic regression was used for statistical analysis.

**Results**—Compared with mixed-breed cats, the breed with the highest relative risk of acquired MG was the Abyssinian (including Somali). Significant differences between sexes were not detected. There was no compelling evidence for a difference in risk of developing MG between states or countries. Relative risk increased after 3 years of age. The most common clinical signs were generalized weakness without megaesophagus and weakness associated with a cranial mediastinal mass. Focal signs, including megaesophagus and dysphagia without signs of generalized weakness, were also evident.

**Conclusions and Clinical Relevance**—A breed predisposition for acquired MG in Abyssinians (and related Somalis) was observed. Clinical signs were variable and included generalized weakness, megaesophagus, and dysphagia. A cranial mediastinal mass was commonly associated with MG in cats. (*J Am Vet Med Assoc* 2000;216:55–57)

Acquired myasthenia gravis (MG) has been described as an uncommon neuromuscular disorder affecting cats, and there are few published case reports regarding this disorder.<sup>1-6</sup> Episodic weakness, including ventroflexion of the neck, lack of palpebral reflexes, and, less commonly, regurgitation, change in vocalization, and cranial mediastinal masses have been described. A predisposition to acquired feline MG has been suggested for Abyssinians and related Somali cats, because 6 of the 9 reported cases involved cats of these breeds.

During the years 1986 to 1998, 615 feline serum samples were submitted by veterinarians throughout the United States, Canada, and the United Kingdom to

the Comparative Neuromuscular Laboratory at the University of California-San Diego and tested for acetylcholine receptor (AChR) antibodies by use of immunoprecipitation radioimmunoassay. Detection of serum antibodies against muscle AChR has been the most reliable diagnostic technique for the diagnosis of acquired MG in humans<sup>7,8</sup> and other animals.<sup>9</sup> The test is objective and quantitative, and proves an autoimmune response against AChR, which differs from other causes of muscle weakness.<sup>7</sup> Other methods of diagnosis are problematic: clinical signs of MG may be similar to several neuromuscular disorders, the edrophonium chloride challenge typically used to make a presumptive diagnosis of MG is neither sensitive nor specific,<sup>9</sup> and evaluation of a decremental response of the compound muscle action potential following repetitive stimulation lacks specificity.<sup>10</sup>

All cats tested had various forms of muscle weakness, exercise intolerance, dysphagia, acquired megaesophagus, or a cranial mediastinal mass; 105 of these cats had AChR antibody titers > 0.3 nmol/L. It has been established in our laboratory that serum AChR antibody titers > 0.3 nmol/L are diagnostic for acquired MG. The database generated from this population of cats was used to determine the most common clinical signs of, and risks associated with, acquired MG relative to breed, sex, age, and state or country of origin. The month of clinical referral was also evaluated for evidence of seasonality that may exacerbate a subclinical case into a clinical one.

## Criteria for Selection of Cases

Cats that resided in the United States, Canada, or the United Kingdom between 1986 and 1998 and had variable clinical signs associated with generalized or focal neuromuscular weakness, including esophageal dilatation or hypomotility, and pharyngeal, laryngeal, or facial muscle paresis, were included in the study. After quantification of AChR antibody titers, cats were categorized as having confirmed MG or having other causes of neuromuscular weakness (controls).

## Procedures

Physical and neurologic examinations were performed and described by numerous veterinarians who submitted serum samples to the laboratory. Diagnosis of MG was confirmed by use of immunoprecipitation radioimmunoassay as described<sup>11</sup> and recorded in a similar report describing risk factors associated with acquired MG in dogs.<sup>12</sup> For this study, a feline fetal muscle extract was used as antigen. Briefly, AChR was solubilized from muscle tissue of near-term fetuses in 2% nonionic detergent buffer. Concentration of AChR was determined and expressed as moles of <sup>125</sup>I-labeled

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$\alpha$ -bungarotoxin binding sites per liter. Aliquots of serum from cats suspected of having MG were incubated overnight at 4 C with labeled muscle extract. Labeled AChR-anti-AChR complexes were precipitated, and titers were expressed as moles of <sup>125</sup>I-labeled-bungarotoxin binding sites per liter of serum. The upper limit of the reference range had been established for this laboratory at 0.3 nmol/L.

### Statistical Analyses

Proportionate changes in the risk for acquired MG by breed, state, month of onset of clinical signs, and age were evaluated by use of unconditional logistic regression.<sup>13</sup> Mixed-breed cats were used as a reference breed for comparison; California was used as a reference state for comparison. Results are given as **odds ratios (OR)** and **95% confidence intervals (95% CI)**. Because the incidence of MG was < 5% within all levels of covariates, OR were used to estimate relative risk.

### Results

Between 1986 and 1998, acquired MG was diagnosed in 105 cats with AChR antibody titers > 0.3 nmol/L. Clinical signs consisted of generalized weakness without megaesophagus (28.6%; n = 30), generalized weakness and megaesophagus or dysphagia (20%; 21), generalized weakness associated with a cranial mediastinal mass (thymoma; 25.7%; 27), megaesophagus or dysphagia without generalized weakness (14.3%; 15), and generalized weakness associated with hyperthyroidism and treatment with methimazole (4.8%; 5). Cats with a cranial mediastinal mass ranged in age from 3 to 16 years. Data regarding initial clinical signs were not available for 7 cats.

**Relative risk determined by breed**—Relative risk for acquired MG was calculated for 6 breeds, including Abyssinian (including related Somali), Himalayan, Maine Coon, Persian, Siamese, and for other purebred cats, including Balinese, Bengal, Korat, Manx, Oriental Shorthair, Rex, Scottish Fold, and Tonkinese. Using mixed-breed cats as a reference group for comparison, only Abyssinians (OR = 4.47; 95% CI, 2.29 to 8.71) were determined to be at high relative risk (Table 1).

**Relative risk determined by age**—Using cats < 3 years old as the reference group, relative risk increased for cats > 3 years old; this risk remained fairly constant (OR = 2.48; 95% CI = 1.24 to 4.94) until the age of 17 years, when risk again became indistinguishable from that of the reference group.

Table 1—Relative risk for acquired myasthenia gravis in various breeds of cats

Breed	No. of cases	No. of controls	OR	95% CI	P value*
Mixed	68	388	1.00	—	—
Abyssinian†	18	23	4.47	2.3–8.70	< 0.001
Himalayan	3	19	0.90	0.3–3.10	0.87
Maine Coon	0	15	0.00	0.0–∞	0.99
Persian	4	17	1.30	0.4–4.10	0.61
Siamese	7	33	1.21	0.5–2.85	0.66
Others	5	15	1.90	0.7–5.41	0.23

\*H<sub>0</sub>: odds ratio is equal to 1.00. †Includes Somali.  
OR = Odds ratio. CI = Confidence interval.

**Relative risk determined by sex, state or country of origin, and month of onset of clinical signs**—Information was available for all cats with acquired MG and control cats. Meaningful differences in risk for any of these categories were not detected.

### Discussion

Determination of AChR antibodies by use of immunoprecipitation radioimmunoassay has proven reliable; it is the gold standard for diagnosis of MG in humans and dogs.<sup>7-9</sup> Reference range for cats was determined in our laboratory by calculating the mean antibody titer ± 4 SD from the mean in 50 cats without clinically detectable neuromuscular disease. Although these stringent parameters make it difficult to have false-positive results in cats without MG, false negatives may be detected. A similar problem in the diagnosis of MG in humans and dogs has been observed.<sup>9,14</sup>

There are also certain limitations to this study that may restrict generalization to the entire cat population. Cats that had serum submitted to the Comparative Neuromuscular Laboratory presumably belonged to owners who were more likely to seek advanced diagnostic methods than owners who declined to have their cat's neuromuscular disease identified. If potential risk factors, such as age or breed, are associated with the decision to seek advanced medical care, then the measured associations may only apply to the source population of cats belonging to these owners and not all cats in general with or without neuromuscular disease. A similar argument can be made for cats with varying severity of disease: if severe disease is more likely to be diagnosed than mild or subclinical disease, then inferences cannot be extended to all cats. Although internal validity is always a concern in observational studies, we have no reason to believe there was any selection bias in this study, because all cats in this study had some form of neuromuscular dysfunction, and preliminary testing for MG was not performed that would alert owners to the likelihood of the diagnosis. Although only newly diagnosed cases were included in this study, there was a variable period, at the owner's discretion, of how long symptoms persisted before the initial diagnosis of MG was obtained.

The number of cases of MG diagnosed in cats at our laboratory is considerably smaller than the number of cases of MG diagnosed in dogs. During a 12-year period (1986 to 1998), acquired MG was diagnosed in 105 cats, compared with 1,154 dogs during a 4-year period (1991 to 1995).<sup>12</sup> Similar to Akitas with MG, Abyssinians (and Somalis) were at the highest relative risk for MG, supporting the theory that there is a genetic basis for this autoimmune disorder. Two domestic shorthair littermates living in separate households were affected with acquired MG at 2 years of age, which also supports this theory. There was no statistical evidence of an effect of sex, month of initial clinical signs, or state or country of origin on the incidence of MG.

Similar to those of MG in dogs, clinical signs in cats were variable. The 2 most common clinical manifestations of MG observed in cats were generalized weakness without megaesophagus (30/105 cats;

28.6%) and generalized weakness associated with a cranial mediastinal mass (27/105 cats; 25.7%). Although megaesophagus and dysphagia developed as focal forms of MG (15/105 cats; 14.3%), the incidence of these 2 disorders was lower in cats than is typically observed in dogs. This is compatible with the different distributions of skeletal muscle between the feline and canine esophagus. In our study of MG in dogs,<sup>12</sup> the 2 most common clinical manifestations were generalized weakness with megaesophagus (440/1,154 dogs; 38.1%) and megaesophagus without generalized weakness (367/1,154 dogs; 31.8%). A cranial mediastinal mass was detected in only 3.4% (35/1,025) of dogs.<sup>12</sup>

Thyroid disorders, some of which are clearly autoimmune in origin, develop in humans with MG.<sup>15,16</sup> In dogs with MG, similar associations with hypothyroidism have been suggested.<sup>17</sup> In cats, naturally developing hypothyroidism is an extremely rare clinical disorder<sup>18</sup> and was not associated with MG in any of the cats in the study reported here. However, hyperthyroidism was associated with MG in 5 cats receiving treatment with methimazole.<sup>3</sup>

Clinical signs of neuromuscular dysfunction have been described in cats with hyperthyroidism and most, if not all, of the manifestations of weakness resolve with correction of the hyperthyroid state.<sup>19</sup> In 5 cats in our study, weakness developed 2 to 4 months after beginning treatment with the antithyroid drug methimazole. Paresis developed in all 5 cats, and decreased palpebral reflexes were detected in 4 of the 5 cats. Strong positive edrophonium response test results were observed in 2 cats tested for MG. Serum AChR antibody titers were positive (0.55 to 12.1 nmol/L; reference range, < 0.3 nmol/L) in all 5 cats, which was consistent with a diagnosis of autoimmune MG. Treatment with methimazole was discontinued in 1 cat; resolution of clinical signs and return of AChR antibody titer to reference range was observed. Two cats were treated with a combination of methimazole and prednisone, with improvement in muscle strength observed. Follow-up evaluation was not available for 2 cats.

In humans, treatment with D-penicillamine has been associated with a reversible MG-like illness that is indistinguishable from naturally developing MG in clinical features, electrophysiologic characteristics, and presence of AChR antibodies.<sup>20</sup> These findings indicate that tolerance to self-AChR can be reversibly broken by a pharmacologic agent in susceptible individuals, adding support for a drug-induced etiology in cats. The development of antinuclear antibodies and positive results of Coombs' tests have also been associated with treatment with methimazole in hyperthyroid cats.<sup>21</sup>

Although there are several similarities in the clinical manifestations of acquired MG in dogs and cats, important differences have also been observed. The greater number of thymomas diagnosed in the myasthenic cats of this study highlights the importance of evaluating thoracic radiographs in all cats with MG, even in the absence of clinical signs of respiratory dis-

stress or esophageal dysfunction. Acquired, drug-induced MG should also be considered in hyperthyroid cats that become weak after initiation of treatment with methimazole. With increasing recognition by clinicians of the spectrum of clinical signs in cats with MG, larger numbers of affected cats will certainly be identified.

<sup>a</sup>Shelton GD, Joseph R, Richter K, et al. Acquired myasthenia gravis in hyperthyroid cats on tapazole therapy (abstr). *J Vet Intern Med* 1997;11:120.

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