

Inherited predisposition to myasthenia gravis in Newfoundlands

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- ▶ Acquired myasthenia gravis in dogs is an immune-mediated disorder affecting neuromuscular transmission.
- ▶ Identification of acquired myasthenia gravis in 6 Newfoundlands from 2 distinct lineages supports a genetic predisposition for development of this autoimmune disease.
- ▶ Breeders should consider removing Newfoundlands with acquired myasthenia gravis from breeding programs.

A 14-month-old 51-kg (111-lb) male Newfoundland (dog 1; Table 1) with a 5-day history of paraparesis was evaluated at the University of Wisconsin Veterinary Medical Teaching Hospital. Results of CBC and serum biochemical analyses performed by the referring veterinarian were within reference limits. Physical examination revealed a pulse rate of 90 beats/min, respiratory rate of 36 breaths/min, and rectal temperature of 38.3 C (101 F). Mentation and results of a cranial nerve examination were considered typical. The dog was paraparetic; it would walk for several steps, but eventually it sat down after appearing to become stiff and tired. Conscious proprioception was not detected in the pelvic limbs but was detected in the thoracic limbs. All spinal reflexes were within acceptable limits, and signs of pain were not elicited during palpation of the vertebral column. The neuroanatomic diagnosis was motor unit disease. Differential diagnoses included myasthenia gravis, acute polyradiculoneuritis, polymyopathy, and polyneuropathy.

An increase in muscle strength and an improvement in gait was detected 30 seconds following administration of edrophonium chloride (0.2 mg/kg [0.09 mg/lb] of body weight, IV). Evidence of megaesophagus or aspiration pneumonia was not detected on thoracic radiographs. Serum acetylcholine receptor-specific antibody concentration was high (2.86 nmol/L; reference range, < 0.6 nmol/L) and a diagnosis of myasthenia gravis was made. Treatment with pyridostigmine bromide (1 mg/kg [0.45 mg/lb], PO, q 8 h) was initiated. The dog improved during the first 2 weeks of treatment, but then it became exercise intolerant again. Prednisone (0.5 mg/kg [0.23 mg/lb], PO, every other

day) was added to the treatment regimen. After 10 days, the dog was reexamined, and neuromuscular abnormalities were no longer apparent.

Serum acetylcholine receptor-specific antibody concentration measured 4 months later was 1.23 nmol/L. The dog also was clinically normal at this time. Treatment with pyridostigmine bromide and prednisone at the initial dosages continued. Six months later, serum acetylcholine receptor-specific antibody concentration was 1.0 nmol/L, and the dog remained clinically normal.

About the same time that dog 1 was initially examined, 1 of its female littermates (dog 2; Table 1 and Fig 1) was evaluated in Missouri because of anorexia, dysphagia, and weight loss. Thoracic radiography revealed megaesophagus and aspiration pneumonia. Serum acetylcholine receptor-specific antibody concentration was 1.06 nmol/L and confirmed a diagnosis of myasthenia gravis. Treatment with pyridostigmine bromide (1 mg/kg, PO, q 8 h) and ciprofloxacin (5 mg/kg [2.27 mg/lb], PO, q 12 h) was initiated, but 10 weeks later, dog 2 developed acute respiratory failure and died. A relative of dogs 1 and 2 (dog 3; 1-year-old female), with a 2-day history of paraparesis and exercise intolerance, was examined in Virginia. Serum acetylcholine receptor-specific antibody concentration was 7.41 nmol/L, confirming a diagnosis of myasthenia gravis. Treatment with pyridostigmine bromide (1 mg/kg, PO, q 8 h) was initiated. One month later, the dog was reexamined and found to be clinically normal.

Three other Newfoundlands (dogs 4, 5, and 6; Table 1) that were not related to dogs 1, 2, or 3 were examined in Wisconsin (dog 4) and Minnesota (dogs 5 and 6). On the basis of clinical signs and high serum acetylcholine receptor-specific antibody concentrations, myasthenia gravis was diagnosed in these 3 dogs. Dogs 4 and 5 were littermates, whereas dog 6 shared a common ancestry with dogs 4 and 5 (Fig 2). Dog 4 had paraparesis and megaesophagus and responded well to treatment with pyridostigmine bromide (1 mg/kg, PO, q 8 h) and prednisone (0.5 mg/kg, PO, every other day). Dog 5 had megaesophagus and aspiration pneumonia and died of respiratory failure 2 weeks after treatment with pyridostigmine bromide (1 mg/kg, PO, q 8 h) and cefazolin (22 mg/kg [10 mg/lb], IV, q 8 h) was initiated. Dog 6 had an acute onset of paraparesis. Treatment with pyridostigmine bromide (1 mg/kg, PO, q 8 h) and prednisone (0.5 mg/kg, PO, every other day) resulted in partial improvement in clinical signs, but the owners elected to have the dog euthanatized 1 month later.

In acquired myasthenia gravis in dogs, autoantibodies against nicotinic acetylcholine receptors at the neuromuscular junction result in excessive muscle

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Table 1—Summary of clinical findings in 6 Newfoundlands with acquired myasthenia gravis

Dog No.	Age (sex)	Clinical signs			Test results		
		Weak	Megasophagus	Asp pneum	Edrophonium challenge*	AchR antibody†	Treatment (outcome)
1	14 mo (M)	Yes	No	No	Positive	2.86 nmol/L	Pyr and pred (CN)
2	14 mo (F)	No	Yes	Yes	Not done	1.06 nmol/L	Pyr and cip (N)
3	1 y (F)	Yes	No	No	Positive	7.41 nmol/L	Pyr (CN)
4	18 mo (CM)	Yes	Yes	No	Negative	1.13 nmol/L	Pyr and pred (CN)
5	2 y (SF)	No	Yes	Yes	Negative	1.07 nmol/L	Pyr and cef (D)
6	11 mo (F)	Yes	No	No	Negative	6.48 nmol/L	Pyr and pred (E)

*Improvement in clinical signs 30 to 60 seconds after administration of edrophonium chloride (0.2 mg/kg [0.09 mg/lb] of body weight, IV) was considered a positive result. †Serum concentration; reference range, < 0.6 nmol/L.

Asp pneum = Aspiration pneumonia. AchR = Acetylcholine receptor. M = Sexually intact male. Pyr = Pyridostigmine bromide (1 to 2 mg/kg [0.45 to 0.9 mg/lb], PO, q 8 h). Pred = Prednisone (0.5 mg/kg [0.23 mg/lb], PO, every other day). F = Sexually intact female. Cip = Ciprofloxacin (5 mg/kg [2.27 mg/lb], PO, q 12 h). CN = Clinically normal. CM = Castrated male. SF = Spayed female. Cef = Cefazolin (22 mg/kg [10 mg/lb], IV, q 8 h). D = Died. E = Euthanized.

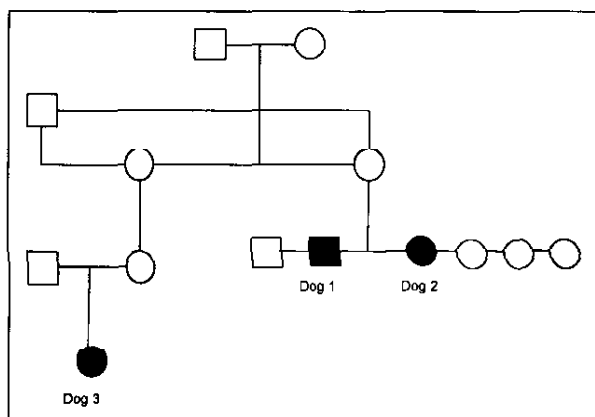


Figure 1—Pedigree analysis of 3 Newfoundlands with acquired myasthenia gravis. Dogs 1 and 2 are from a litter of 6; the other 4 littermates remain unaffected. ■ = Affected males. □ = Unaffected males. ● = Affected females. ○ = Unaffected females.

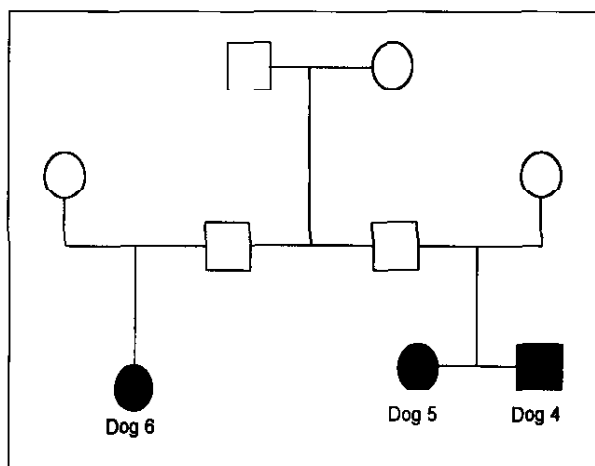


Figure 2—Pedigree analysis of 3 Newfoundlands with acquired myasthenia gravis. These dogs are not related to dogs described in Figure 1. Dogs 4 and 5 are littermates; size of litter is unknown. See Figure 1 for key.

weakness and fatigability.¹⁻⁶ A net loss of acetylcholine receptors develops, because as receptors are cross-linked by antibodies, rate of receptor internalization and complement-mediated destruction increases.⁷ A spectrum of clinical signs has been described in dogs with myasthenia gravis, including exercise-related

weakness, weakness limited to pharyngeal, esophageal, and facial muscles, and generalized collapse.^{1-6,8-10} The history of and clinical signs in the dogs described in our report did not differ from those reported for other dogs with acquired myasthenia gravis. Acquired myasthenia gravis has been associated with other immune mediated disorders, such as hypothyroidism,¹¹ thymoma, and other neoplasias.¹² A diagnosis can be confirmed by detection of circulating acetylcholine receptor-specific antibodies, using ¹²⁵I-labeled bungarotoxin in an immunoprecipitation radioimmunoassay. A presumptive diagnosis of myasthenia gravis can be made by an obvious improvement in muscle strength following IV administration of edrophonium (0.1 to 0.2 mg/kg [0.045 to 0.09 mg/lb]). A negative response does not exclude the diagnosis of myasthenia gravis, because animals with pharyngeal and esophageal forms may not respond, and animals with other neuromuscular disorders may also have a positive response.⁴ Although a high acetylcholine receptor-specific antibody titer (> 0.6 nmol/L for dogs) is diagnostic of acquired myasthenia gravis, there is poor correlation between the magnitude of the acetylcholine receptor-specific antibody titer and the severity of weakness in animals with myasthenia gravis. This is attributable in part to the fact that the acetylcholine receptor is large and comprises many antigenic epitopes. Autoantibodies formed against the different epitopes vary in pathogenicity; those directed against the acetylcholine binding site result in the most severe muscle weakness.

To our knowledge, this is the first report describing familial acquired myasthenia gravis in dogs. Dogs 1 and 2 were from a litter of 6 puppies and to date, other littermates have not been affected. Dogs 4 and 5 were littermates; however, their litter size was unknown. Risk factors for acquired myasthenia gravis in dogs have been determined and support predisposition based on breed, with age and sex as contributing factors.¹³ Dogs with the highest risk include the terrier group, Akita, Scottish Terrier, German Shorthaired Pointer, and Chihuahua.¹³ Although the odds ratio (OR) for development of myasthenia gravis in Newfoundlands (OR, 2.0; 95% confidence interval, 1.2 to 3.6) is greater than that for mixed-breed dogs, several other breeds have an even higher relative risk for developing this disease.¹³ The 6 Newfoundlands we described in our report are from 2 distinct lineages, pro-

viding support for a genetic predisposition in this breed.

Unequivocal evidence indicates that susceptibility to autoimmune disease primarily is genetically determined.¹⁴ In humans and mice, the most clearly established genetic association with predisposition for development of autoimmune disease is related to the major histocompatibility complex (MHC) class-II gene.¹⁴ Non-MHC genes encoding lymphoid cell antigen receptors, immunoglobulins, and T-cell antigen receptors have also been implicated.¹⁵ Significant associations with particular DR and DQ MHC class-II antigens and early-onset, nonthymoma-associated myasthenia gravis have been identified in humans.¹⁶ Major histocompatibility complex class-II genes are also implicated in development of experimental autoimmune myasthenia gravis in mice.¹⁷

Four histocompatibility class-I genes (dog lymphocyte antigen [DLA] system) are recognized in dogs: DLA-12, DLA-88, DLA-79 and DLA-64.^{18,19} Development of several autoimmune diseases, including atopy²⁰ and early onset inherited diabetes mellitus in Keeshonds,²¹ may be associated with expression of specific DLA alleles. Additionally, an association between complement C4 allotype expression and development of pyrexia, seronegative polyarthritis, and antinuclear antibodies has been identified in dogs.²² Expression of > 1 specific DLA genes may predispose Newfoundlands to development of myasthenia gravis. However, the DLA haplotypes of the 6 dogs described in our report were not determined.

Although there is a clear genetic predisposition for development of certain autoimmune diseases, the immunopathogenesis of myasthenia gravis is multifactorial and includes hormonal, environmental, and infectious disease factors. The high incidence of myasthenia gravis in these 2 distinct lineages of Newfoundlands, a breed with a low relative risk factor for development of this disease, suggests an underlying genetic mechanism. However, mode of inheritance could not be determined from this small number of dogs. Regardless, breeders should be alerted to this disorder, and they should consider removing Newfoundlands with acquired myasthenia gravis from breeding programs.

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