

# Myasthenia Gravis and Hypothyroidism in a Dog With Meningomyelitis

A 12-year-old, spayed female miniature poodle was evaluated because of a 4-day history of paraparesis, dysuria, and tenesmus. Neurological assessment suggested peripheral nervous system dysfunction, predominantly pelvic limb weakness with a possible concurrent sixth lumbar (L<sub>6</sub>) to second sacral (S<sub>2</sub>) myelopathy. Further studies supported the diagnoses of myasthenia gravis, hypothyroidism, and meningomyelitis. To the authors' knowledge, this is the first reported case of concurrent myasthenia gravis and meningomyelitis in the dog. It was unclear whether the identified conditions evolved from a shared etiopathogenesis or were merely coincidental. *J Am Anim Hosp Assoc* 2005;41:247-251.

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## Introduction

Acquired myasthenia gravis is a disease of the neuromuscular junction that results from autoimmune-induced loss of nicotinic acetylcholine receptors.<sup>1,2</sup> Acetylcholine receptor destruction is a T-cell-dependent process that is mediated predominantly by polyclonal IgG antibodies directed against the main immunogenic region on the alpha subunit.<sup>1,2</sup> Immunoglobulins may interfere with acetylcholine receptor activity, potentiate increased receptor turnover, or lead to complement-mediated postsynaptic membrane damage.<sup>1,2</sup> The clinical signs associated with myasthenia gravis are variable and include either generalized (e.g., appendicular muscle weakness) or focal (e.g., megaesophagus, facial weakness, and/or laryngeal paresis) abnormalities.<sup>3</sup> Appendicular neuromuscular signs may involve all four limbs or exclusively the pelvic limbs, and weakness is not necessarily provoked by exercise.<sup>3</sup>

A presumptive diagnosis of myasthenia gravis may be made by electrodiagnostic testing such as supramaximal repetitive nerve stimulation or single-fiber electromyography, and by a positive edrophonium response test.<sup>4-7</sup> Improvement is not always observed after the administration of edrophonium chloride, however.<sup>4</sup> The diagnosis of myasthenia gravis is confirmed by the demonstration of circulating acetylcholine receptor antibodies, which document an autoimmune response against nicotinic acetylcholine receptors.<sup>6,8</sup>

The purpose of this paper is to illustrate that myasthenia gravis may be associated with multiple inflammatory and autoimmune diseases. Myasthenia gravis has not previously been reported with concurrent meningomyelitis in a dog.

## Case Report

A 12-year-old, 12.3-kg, spayed female miniature poodle was referred to Texas A&M University Veterinary Medical Teaching Hospital with a 4-day history of dysuria, tenesmus, and paraparesis. Two days prior to presentation, cephalexin<sup>a</sup> (20 mg/kg per os [PO] *q* 12 hours), prednisone<sup>b</sup> (0.5 mg/kg PO *q* 12 hours), and a supplement containing 600 mg glucosamine HCl and 400 mg of assorted herbs were started for the clinical signs.

Pertinent physical examination findings included obesity, profound dorsal truncal hypotrichosis, mild dental disease, and an intermittent, left apical, grade II-III/VI systolic murmur. The bladder was not palpable during initial evaluation, and dysuria and tenesmus were not observed during hospitalization. Abnormalities found on neurological assessment included bilateral pelvic limb hypotonia with reduced withdrawal reflexes. Postural reactions, cranial nerve assessment, pain perception, anal tone, and other segmental spinal reflexes (i.e., patellar, thoracic limb withdrawal, extensor carpi radialis, perineal) were normal. The dog's paraparesis did not worsen with exertion, and patellar reflexes were not fatigable. These findings suggested peripheral nervous system dysfunction manifesting as pelvic limb weakness with possible concurrent sixth lumbar (L<sub>6</sub>) to second sacral (S<sub>2</sub>) myelopathy. Differential diagnoses included acquired myasthenia gravis, polyradiculoneuritis, polyneuropathy, and polymyositis. Spinal cord syndromes such as infectious and noninfectious inflammatory myelitis, central nervous system (CNS) neoplasia, and intervertebral disk disease were also considered, given the multifocal neuroanatomical localization.

Complete blood count abnormalities included neutrophilia ( $12.6 \times 10^3/\mu\text{L}$ ; reference range 3 to  $11.5 \times 10^3/\mu\text{L}$ ) and lymphopenia ( $0.5 \times 10^3/\mu\text{L}$ ; reference range 1 to  $4.8 \times 10^3/\mu\text{L}$ ), which were compatible with a stress leukogram. Hyperglobulinemia (3.9 g/dL; reference range 1.7 to 3.8 g/dL), increased alkaline phosphatase (273 U/L; reference range 24 to 147 U/L), decreased total carbon dioxide (17 mmol/L; reference range 21 to 28 mmol/L), and increased anion gap (20 mmol/L; reference range 10 to 18 mmol/L) were detected on serum biochemical analyses. A urinalysis was within normal limits. Hypothyroidism was suspected based on a subnormal free thyroxine (T<sub>4</sub>) via equilibrium dialysis (0.51 ng/dL; reference range 0.7 to 3.1 ng/dL), and decreased total T<sub>4</sub> (0.5  $\mu\text{g}/\text{dL}$ ; reference range 1.61 to 3.6  $\mu\text{g}/\text{dL}$ ). The thyroid-stimulating hormone (TSH) level was normal (0.14 ng/dL; reference range 0 to 0.32 ng/dL).

A mild, diffuse bronchial pattern was present on thoracic radiographs. On abdominal ultrasonography, moderate, generalized hepatomegaly with slight mottling of the hepatic parenchyma was present, suggesting a steroid hepatopathy or an infiltrative process. Aspirates of the liver were obtained via ultrasonographic guidance, and cytology was unremarkable. While infiltrative or diffuse inflammatory hepatic disease could not be definitively excluded, the animal's age, the relatively normal biochemical profile, and a history of exogenous steroid administration suggested these conditions were unlikely. Liver biopsies were not performed because of client concerns related to morbidity and monetary cost. Echocardiography demonstrated subclinical mitral regurgitation. A laryngeal examination, performed because of peripheral nervous system dysfunction, revealed moderate, bilateral paresis of the vocal folds.

Myelography performed by subarachnoid puncture at the fifth lumbar (L<sub>5</sub>) to L<sub>6</sub> space revealed mild dorsal contrast column attenuation over the body of the second lumbar (L<sub>2</sub>)

vertebra and slight dorsal deviation of the ventral contrast column over the L<sub>6</sub> to seventh lumbar (L<sub>7</sub>) disk space. Axial and sagittal, digitally reformatted, computed tomographic images of the L<sub>6-7</sub> and L<sub>7</sub> to the first sacral (S<sub>1</sub>) articulations showed clinically insignificant protrusion of the annulus fibrosus at L<sub>6-7</sub>. No compression of the cauda equina was seen.

No electromyographic abnormalities were identified in the pelvic or thoracic limbs. Sciatic motor nerve conduction velocity was within normal limits for a 12-year-old dog (56 m per second; reference range >50 m per second).<sup>9,10</sup> Repetitive, supramaximal, sciatic nerve stimulation at a rate of 3 to 7 Hz showed a decremental response, suggestive of a junctional neuropathy. The response did not abate with the administration of edrophonium chloride<sup>c</sup> (0.8 mg/kg intravenously [IV]). A 0.25 mg/kg IV bolus of edrophonium was also administered while the dog was awake, and no improvement in clinical signs was observed.

Cerebrospinal fluid (CSF) obtained prior to myelography via lumbar puncture had an elevated white blood cell count (125 cells/ $\mu\text{L}$ ; reference range <5 cells/ $\mu\text{L}$ ), mildly increased red blood cell count (23 cells/ $\mu\text{L}$ ; reference range <5 cells/ $\mu\text{L}$ ), and an increased protein (71 mg/dL; reference range <35 mg/dL) level. Eleven small lymphocytes and three large monocytes were found on a cytospin preparation of the CSF. Cerebrospinal fluid culture was not performed because of inadequate sample volume.

Serum antibody titers for common CNS pathogens were obtained to rule out an infectious myelopathy. *Toxoplasma gondii* titers were positive for immunoglobulin M (IgM) (1:512; reference value <1:64) and were negative for immunoglobulin G (IgG), suggesting recent infection or exposure. Titers for *Neospora caninum* IgG were also positive (1:512; reference value <1:64), indicating past exposure to the antigen (IgM <1:64). Serum was negative for *Cryptococcus neoformans* antigen via latex agglutination and for *Blastomyces* spp., *Coccidioides* spp., and *Histoplasma* spp. antibodies via agarose gel immunodiffusion. Serum was also negative for antibodies to *Ehrlichia canis* and *Rickettsia rickettsii*. An acetylcholine receptor antibody titer confirmed the diagnosis of acquired myasthenia gravis (2.62 nmol/L; reference range <0.6 nmol/L). Bone marrow aspiration and cytology were performed to help exclude occult neoplasia that could be a cause of the neurological syndrome. The bone marrow had normal cellularity, with a myeloid:erythroid ratio of 3:1 and an orderly maturation of both the myeloid and erythroid cell lines.

Treatment consisted of IV fluid administration and medical therapy with various agents. Levothyroxine<sup>d</sup> (0.01 mg/kg PO *q* 12 hours) was given to control hypothyroidism. Doxycycline<sup>e</sup> (4 mg/kg PO *q* 12 hours) and clindamycin<sup>f</sup> (12.5 mg/kg PO *q* 12 hours) were started while awaiting the results of infectious disease titers. Prednisone (0.8 mg/kg PO *q* 24 hours) was given to reduce CNS inflammation. Additionally, it was felt that prednisone might offer some therapeutic benefit for the concurrent myasthenia gravis, although the dose was higher than what has been recommended for myasthenia gravis in dogs.<sup>4</sup> No

specific treatment was instituted for the historical tenesmus and dysuria, because these signs were absent during hospitalization. Three days after initiating medical therapy, the dog was able to ambulate with minimal pelvic limb weakness. The treatment, including antimicrobial drugs, was continued for 1 month, at which time the dog was reevaluated. Pyridostigmine was not used, because there was no response to edrophonium.

Neurological assessment was normal 1 month after initial presentation. A thoracic radiograph was taken to reevaluate the chest for any evidence of pulmonary pathology. Generalized megaesophagus was observed in addition to the previously noted mild, diffuse bronchial pattern. Retrospective evaluation of the thoracic radiographs obtained at presentation suggested mild esophageal dilatation.

Antibiotic therapy was discontinued. Prednisone was increased to 0.8 mg/kg PO *q* 12 hours. Azathioprine<sup>g</sup> (1.5 mg/kg PO *q* 24 hours) was started as an adjunctive therapy for the myasthenia gravis.<sup>11</sup> A low dose was chosen because of concerns of immunosuppression in a dog with possible infectious meningomyelitis. At additional follow-up evaluations 2 and 3 months after presentation, the dog was neurologically normal and had significant regrowth of hair along the dorsal trunk.

Five months after the onset of clinical signs, the referring veterinarian indicated that the dog remained neurologically normal and had no radiographic evidence of megaesophagus. An acetylcholine receptor antibody titer was submitted at the 5-month recheck and was normal (<0.6 nmol/L), indicating improvement from either drug therapy or a true remission. Reevaluation of the CSF was not performed because of the positive clinical response to therapy and client concerns regarding morbidity associated with the procedure. Currently, the dog remains on prednisone and azathioprine at the same dosage.

## Discussion

The diagnoses in the dog reported here included acquired myasthenia gravis, hypothyroidism, and infectious or noninfectious meningomyelitis. Decremental responses after repetitive nerve stimulation were seen in this dog and were compatible with myasthenia gravis. The responses did not abate with edrophonium, and the dog did not clinically improve after an injection of edrophonium. Facilitation is not always observed after the administration of edrophonium chloride, however, and this failure of response may be related to a subpopulation of labile neuromuscular junctions, posttetanic exhaustion, or operator error.<sup>5,12</sup> Likewise, awake animals with myasthenia gravis do not always have an improvement in muscle strength after edrophonium administration.<sup>4</sup> The diagnosis of myasthenia gravis was confirmed in this case by the demonstration of circulating acetylcholine receptor antibodies.

Canine myasthenia gravis has been associated with other autoimmune and endocrine disorders such as hypothyroidism, hypoadrenocorticism, thrombocytopenia, hemolytic anemia, polymyositis, and inflammatory bowel disease.<sup>13-18</sup>

Myasthenia gravis may also occur as a paraneoplastic phenomenon.<sup>14</sup> Hypothyroidism was documented in this dog by laboratory testing and a positive clinical response to thyroid supplementation (i.e., regrowth of hair along the dorsal trunk). Although TSH is typically elevated in hypothyroid animals, it was within the reference range in this dog. Some hypothyroid dogs may have normal TSH values from lack of sensitivity of the assay.<sup>19</sup> While the use of prednisone has been shown to reduce T4 and free-T4 without elevating TSH levels, only doses substantially greater than what were given to the dog in this report produce this effect.<sup>20,21</sup> Sick euthyroid syndrome was not definitively excluded, but free-T4 is typically normal in this condition.<sup>19</sup>

While the pathophysiology of canine hypothyroidism is not completely understood, the presence of lymphoplasmacytic infiltrates in some animals may indicate an autoimmune component to this disorder.<sup>22</sup> It is possible that at least two autoimmune diseases, hypothyroidism and myasthenia gravis, were present in the dog of this report and may have shared a common cause. A recent human case of multiorgan autoimmune syndrome consisting of hypothyroidism, myasthenia gravis, and polymyositis suggested that a common immunopathological process led to the production of discrete autoreactive lymphocytes.<sup>24</sup>

While the diagnoses of myasthenia gravis and hypothyroidism were fairly straightforward in this dog, the etiopathogenesis of the meningomyelitis was not. Although not evaluated in this dog, it is possible that other autoantibodies may have played a role. Multiple, concurrent autoantibodies have been documented in dogs with myasthenia gravis, such as acetylcholine receptor, ryanodine receptor, and thyroid autoantibodies.<sup>4,25</sup> Autoantibodies against nicotinic ganglionic acetylcholine receptors have recently been described in human autonomic neuropathies and in a subpopulation of dogs with dysautonomia.<sup>26,27</sup> It is theoretically possible that autoantibodies against ganglionic acetylcholine receptors in the autonomic nervous system may have resulted in the dysuria and tenesmus observed prior to clinical presentation, although sacral spinal cord disease could also have explained these historical problems. In addition, in humans, both Rasmussen's encephalitis and cerebellar degenerations have been associated with autoimmune responses to glutamate receptors, demonstrating that epilepsies and central degenerative diseases can be caused by antibody-mediated autoimmune responses.<sup>28-30</sup> An autoimmune syndrome may have explained the meningomyelitis found in this dog, especially given the presence of other antibody-mediated diseases. Disordered immune regulation may have contributed to the genesis of several autoimmune syndromes in the same individual.

Other inflammatory CNS syndromes, such as granulomatous meningoencephalomyelitis, could also have caused the meningomyelitis identified in this dog. Granulomatous meningoencephalomyelitis may cause mononuclear pleocytosis similar to that observed in this case and may also have an autoimmune basis.<sup>32-34</sup> Histopathology is necessary for the definitive diagnosis of granulomatous meningoencephalomyelitis, but response to corticosteroids along with

exclusion of other etiologies allows a presumptive diagnosis.<sup>35-37</sup> The clinical history of this dog, the neurological signs, and a response to medical therapy that included immunosuppressive agents, made granulomatous meningoencephalomyelitis a reasonable consideration.

The clinical relevance of the positive antibody titers against *Toxoplasma gondii* and *Neospora caninum* was unknown. Titers for *Toxoplasma gondii* were repeated 2 weeks after initial presentation and were still positive for IgM (1:128) and negative for IgG. While the inciting factors of autoimmune diseases are not fully understood, infectious agents may sometimes trigger an aberrant immune response.<sup>38-41</sup> The rapid onset and prompt resolution of clinical signs with antimicrobial, antiinflammatory, and hormonal therapies in this dog were compatible with either an autoimmune or inflammatory syndrome. Toxoplasmosis was also perhaps directly responsible for the meningomyelitis. Infectious diseases affecting the CNS may respond quickly to antiinflammatory and antimicrobial therapies.<sup>42</sup>

It is uncertain what roles the meningomyelitis, myasthenia gravis, and hypothyroidism played in the dog's clinical presentation. All three diseases may have contributed to the observed clinical signs. Esophageal dilatation and laryngeal paresis/paralysis are typical of myasthenia gravis, particularly the focal form.<sup>43</sup> Hypothyroidism has also been associated with megaesophagus.<sup>44</sup> The pelvic limb hypotonia with normal proprioception and isolated segmental hyporeflexia may have been caused by junctional disease, such as myasthenia gravis. A myopathic syndrome secondary to hypothyroidism might also explain these abnormalities; however, the absence of proprioceptive deficits makes hypothyroid neuropathy less likely.<sup>44,45</sup> Finally, meningomyelitis may have contributed to the neurological presentation, but the apparent sparing of proprioception would require a very focal lesion involving predominantly the ventral gray matter. Focal, inflammatory, ventral gray matter lesions that spare proprioception have not been reported in animals, although similar anterior horn syndromes have been noted in humans.<sup>46-48</sup>

The dog's response to medical therapy did not necessarily support the relative clinical importance of myasthenia gravis, meningomyelitis, or hypothyroidism. Animals with hypothyroid myopathies can show significant response to thyroid supplementation.<sup>49</sup> Animals with meningomyelitis may respond quickly to corticosteroids or antibiotics, and individuals with myasthenia gravis may also have spontaneous remissions.<sup>50</sup> Although corticosteroid therapy for myasthenia gravis may result in clinical deterioration via some unknown myopathic effects, it is not a universal phenomenon, and improvement in the clinical signs did not detract from the potential clinical importance of myasthenia gravis in this dog.<sup>4</sup> The poor response to corticosteroids administered by the referring veterinarian did not necessarily suggest a particular etiopathogenesis in this case. Absence of an initial response may have been explained by an insufficient prednisone dosage, short duration of treatment, inadequate time for spontaneous remission of myasthenia gravis, or the lack of appropriate concurrent antibiotic administration.

## Conclusion

Myasthenia gravis, meningomyelitis, and hypothyroidism occurred in a dog with lower motor neuron paresis. A positive clinical response was seen with antiinflammatory, antimicrobial, and hormonal therapies. Based on the results of this report, concurrent conditions stemming from immune system dysregulation or inflammation should also be considered in dogs with autoimmune diseases affecting the nervous system.

<sup>a</sup> Cephalexin; Teva Pharmaceuticals, North Wales, PA 19454

<sup>b</sup> Prednisone; Mutual Pharmaceutical Corporation, Philadelphia, PA 19124

<sup>c</sup> Edrophonium; Baxter Healthcare Corporation, Deerfield, IL 60015

<sup>d</sup> Levothyroxine; Daniels Pharmaceuticals, St. Petersburg, FL 33713

<sup>e</sup> Doxycycline; Mutual Pharmaceutical Corporation, Philadelphia, PA 19124

<sup>f</sup> Clindamycin; Pharmacia and Upjohn, Kalamazoo, MI 49001

<sup>g</sup> Azathioprine; Geneva Generics, Broomfield, CO 80020

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