Focal myasthenia gravis in a dog

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Abstract — A 10-month-old American cocker spaniel was evaluated for megaesophagus, aspiration pneumonia, but no appendicular muscle weakness. During hospitalization, weakness of the facial muscles developed, this resolved with anticholinesterase administration. Serum antibodies against acetylcholine receptors were documented, confirming the diagnosis of focal myasthenia gravis. Diagnosis, mangement, and medical treatment are discussed.

Résumé — Myasthénie grave focale chez un chien. Un mégacœsophage et une pneumonie par aspiration ont été diagnostiqués chez un cocker américain de 10 mois qui par ailleurs ne manifestait pas de faiblesse des muscles des membres. Une faiblesse des muscles faciaux s'est manifestée au cours de l'hospitalisation et la condition s'est améliorée suite à l'administration d'un anticholinestérase. Des anticorps sériques contre les récepteurs à l'acétylcholine ont été retrouvés, ce qui confirmait le diagnostic de myasthénie grave focale. Le diagnostic, les soins et le traitement font l'objet d'une discussion.

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Acquired myasthenia gravis (MG) is an immune-mediated disorder in which autoantibodies are produced against postsynaptic nicotinic acetylcholine receptors (AChRs), resulting in impaired neuromuscular transmission (1). Characteristic clinical features include progressive appendicular weakness that worsens with exercise and improves with rest, weakness of the facial and extraocular muscles, difficulty in swallowing, and aspiration pneumonia secondary to megaesophagus and regurgitation (2,3). More recently, a focal form of MG has been described in which megaesophagus with regurgitation is the principal feature. There may also be variable involvement of pharyngeal, laryngeal, or ocular muscles (4–7). We describe herein the clinical features, diagnostic evaluation, and treatment of a young dog with focal acquired MG.

A 10-month-old, 9.9 kg, castrated male, American cocker spaniel was referred to the Small Animal Clinic at the Western College of Veterinary Medicine (WCVM) for evaluation. Three weeks previously, the dog had exhibited vomiting or regurgitation lasting 1 wk. After the vomiting or regurgitation had subsided, a fever developed (40.1°C) and amoxicillin trihydrate (Nu-Amoxi, Nu-Pharm, Richmond Hill, Ontario) was administered (22 mg/kg body weight [BW], PO, q12h for 7 d). On the day prior to evaluation at the WCVM, thoracic radiographs were taken and a distal esophageal foreign body suspected.

Physical examination at the WCVM revealed a thin dog in poor bodily condition. Body temperature was elevated (40.7°C). There was a persistent left-sided mucopurulent nasal discharge, and on auscultation, crackles were heard in both ventral lung fields. The physical and neurologic examinations were otherwise unremarkable.

Thoracic radiographs were taken. The entire esophagus was widely dilated. There were ill-defined patchy areas of lung consolidation, particularly in the left middle lung lobe, suggesting aspiration pneumonia. A complete blood cell count and serum biochemistry profile were carried out and the results were within normal limits. A transtracheal wash was performed and the sample submitted for cytological evaluation, bacterial culture and sensitivity testing. The sample obtained was cellular, consisting primarily of degenerate neutrophils and mucus. No bacteria were seen. Culture yielded *Klebsiella* spp. and *Pasteurella* spp.

Intravenous fluids (Lactated Ringer's solution at 60 mL/kg BW, q24h for 5 d) were administered. Nebulization with sterile water for 45 min followed by coupage was performed every 8 h. Intravenous cefoxitin sodium (Mefoxin, NovoPharm, Scarborough, Ontario) was administered (22 mg/kg BW, q8h) for 2 d, until culture results were obtained. Antimicrobial therapy was then changed to oral enrofloxacin (Baytril, Bayer, Etobicoke, Ontario) at 3.5 mg/kg BW, q12h.

Differential diagnoses for megaesophagus in this dog included hypothyroidism, hypoadrenocorticism, acquired MG, polymyositis, esophagitis, systemic lupus erythematosus, and neoplasia. There was no evidence of

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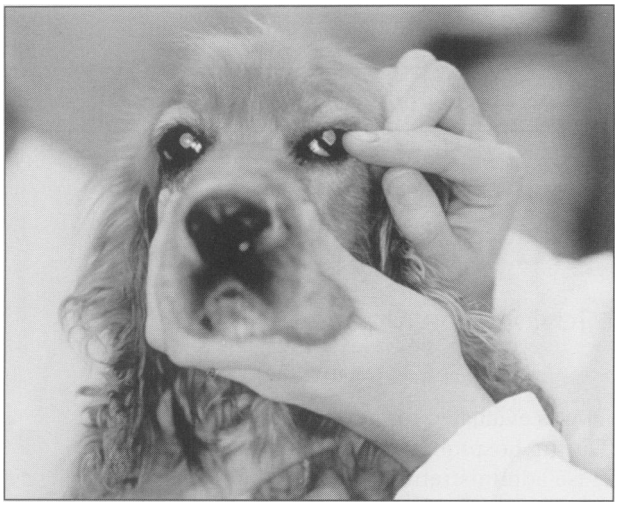

Figure 1. The blink response to palpebral stimulation is weak bilaterally in this dog with acquired myasthenia gravis.

Figure 2. One minute following the administration of edrophonium chloride, the palpebral blink response is improved.

muscle or joint pain, or other systemic disease. A thyroid-stimulating hormone (TSH) response test was normal (resting T_4: 10 nmol/L; 6 h post 0.1 IU TSH/kg BW T_4: 53 nmol/L). Response to an adrenocorticotrophic hormone (ACTH) stimulation test was slightly exaggerated (cortisol pre ACTH: 354 nmol/L; cortisol 1 h post ACTH: 847 nmol/L), ruling out hypoadrenocorticism. The lack of physical or biochemical evidence for hyperadrenocorticism made chronic stress the most likely cause for this exaggerated response.

During day 3 of hospitalization, it was noted that the lower eyelids appeared to droop and that palpebral stimulation resulted in incomplete lid closure, bilaterally (Figure 1). Edrophonium chloride (Tensilon, ICN Canada, Montreal, Quebec), an ultrashort acting anticholinesterase, was administered (0.11 mg/kg BW, IV). There was immediate improvement in ocular muscle strength and the palpebral response returned for 3 min (Figure 2). This response to anticholinesterase administration was most suggestive of a diagnosis of MG. Serum was submitted for identification of serum antibodies to canine muscle AChR (Comparative Neuromuscular Laboratory, University of California); results (1.41 nmol/L; normal <0.6 nmol/L) were diagnostic of acquired MG .

Treatment was initiated with a short-acting, SC-administered anticholinesterase, neostigmine methylsulfate (Neostigmine, Sabex, Boucherville, Quebec, 0.04 mg/kg BW, q6h). The dog developed diarrhea, muscle fasciculations, and hypersalivation following the 2nd dose, so the dosage was decreased (0.01 mg/kg BW, q6h). The dog was fed upright and maintained in that position for 30 min after feeding to facilitate the passage of food from the dilated esophagus into the stomach. The dog was clinically improved and regurgitation was no longer observed. After 3 d of parenteral therapy, the oral anticholinesterase pyridostigmine bromide (Mestinon, ICN Canada) was administered (0.76 mg/kg BW, q6h). Thoracic radiographs taken 5 d later revealed marked improvement in the radiographic appearance of the lung parenchyma but persistent generalized esophageal dilation. The dog was discharged from the hospital with instructions to the owner for the oral anticholinesterase therapy and upright feedings to be continued at home.

The dog was clinically normal at home for 2 mo while treatment continued. Several months later, however, the owner discontinued the medication. The dog has continued to do well, rarely regurgitating, except when fed dry dog food. Periodically, the dog develops a fever or a cough and is treated empirically with antibiotics by the local veterinarian. The owner declines further evaluation or treatment.

While generalized canine acquired MG has been well documented, a focal form in which megaesophagus with regurgitation is the principal clinical sign has only recently been characterized (4–7). Some dogs with the focal form of MG also have weakness involving the pharyngeal, laryngeal, and facial muscles. In humans, MG can cause a generalised weakness or a focal disorder involving only the extraocular muscles (8). The presence of striated muscle in the canine but not in the human esophagus explains the predominance of esophageal dysfunction in dogs but not humans with MG (4). Acquired MG should be considered as a differential diagnosis in all dogs evaluated for regurgitation due to megaesophagus; 25% to 38% of all dogs with adult onset, idiopathic megaesophagus may have detectable antibody against AChR, confirming the diagnosis of MG (4,9).

The reasons for selective involvement of particular muscle groups in dogs with focal MG are not known. There may be differences among muscle groups in the safety margin for neuromuscular transmission (4). In humans, antigenic differences between AChRs of different muscle groups have been implicated as an explanation for the occurrence of the focal ocular form of MG (4,8). Antigenic differences between AChRs in other muscle fiber endplates may occur; these have not been evaluated in canine esophageal, pharyngeal, and ocular muscles. Diagnosis of the focal form of acquired MG is best made by demonstrating circulating antibodies against AChRs by immunoprecipitation radioimmunoassay. A positive titer is diagnostic for this disorder. Serum antibody titers documented in dogs with focal MG are lower than those reported in dogs with the generalized form of MG (4). Rarely, affected dogs are

seronegative for circulating AChR antibody but have detectable immune complexes at the neuromuscular junction (4).

The "Tensilon response" test is a useful test for the diagnosis of generalized MG causing appendicular muscle weakness; it has been less valuable in the diagnosis of focal MG involving the esophagus. When there is concurrent facial muscle weakness, as in this case, an improved palpebral reflex after edrophonium chloride (Tensilon) administration can make a presumptive diagnosis of MG likely (2,4). Electrodiagnostic testing, when performed, can demonstrate a decremental response of muscle action potentials to repetitive nerve stimulation, even in dogs with no apparent muscular weakness. This test is rarely recommended as an initial diagnostic test for MG, however, because of limited availability and the risk of aspiration associated with general anesthesia in dogs with megaesophagus.

Treatment of focal MG resulting in esophageal dysfunction should include supportive care and the administration of anticholinesterase drugs or immunosuppressive agents (2,4,10). Elevation of food and water for upright feeding will facilitate movement of esophageal contents into the stomach and decrease the chance of aspiration. Multiple small feedings each day are preferable to 1 or 2 large meals. Dogs should be maintained in an upright position for at least 10 min after each meal. Aspiration pneumonia should be treated, if present, with appropriate antibiotics, humidification, and coupage.

Anticholinesterase drugs can be administered to increase the number of successful acetylcholine-ACHR interactions and improve neuromuscular transmission (1). In animals with generalized appendicular muscle weakness, the dosage of these drugs can be titrated to achieve a satisfactory clinical response. The optimum dose is more difficult to determine in dogs with focal MG. The esophageal musculature may not respond to anticholinesterase drugs as consistently as limb muscles typically do. Anticholinesterase drugs should be administered cautiously, since the risk of overdosing is increased due to an inability to monitor the clinical response. When anticholinesterase drugs are used as part of the treatment regime, feeding should be scheduled to coincide with peak drug effect.

Corticosteroids may be used alone or in conjunction with anticholinesterase agents in an attempt to decrease the production of antibody against AChRs in dogs with MG, when there is no apparent aspiration pneumonia (10). More aggressive immunosuppression can also be considered (2,3). The administration of drugs to improve esophageal motility has not been shown to be beneficial (2).

The prognosis for recovery in dogs with focal acquired MG involving the esophagus is variable. Aspiration pneumonia can be a fatal complication or can become a chronic recurrent problem resulting in debilitation or euthanasia. Appropriate management of dogs with megaesophagus to prevent aspiration pneumonia may be the most important aspect of therapy. Some dogs respond well to anticholinesterase drugs or immunosuppressive therapy. Spontaneous clinical improve ment in association with a decrease in AChR antibody titer has been documented in many dogs with focal acquired MG treated with only supportive care (4). The time course from onset of clinical signs until remission can vary from days to months, so it is recommended that the serum AChR antibody titer be monitored every 4 to 8 wk (2). CVJ

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