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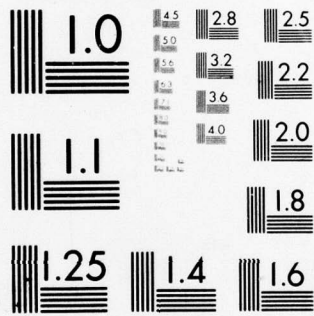
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## Anticholinesterase-Responsive Weakness in the Canine Similar to Myasthenia Gravis of Man

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*A disease resembling human myasthenia gravis was diagnosed in a canine. Diagnosis was based on clinical signs, clinicopathological findings, and clinical response to anticholinesterase agents. A review of previously reported canine cases is presented. Diagnosis, treatment, and possible etiologies are discussed.*

### Introduction

Myasthenia gravis (MG) is a disease of man characterized by excessive muscular weakness and intolerance to exercise.<sup>12</sup> A syndrome similar to MG in man has been described in domestic animals, with 20 cases reported in the canine<sup>10,14,15,17,21,24,26,33</sup> and one case reported in the feline.<sup>6</sup> The diagnosis of MG in man is established by a combination of clinical signs, clinicopathological findings, and positive pharmacological testing. The purpose of this article is to present a case of anticholinesterase-responsive weakness in the dog similar to MG of man and to discuss the common clinical signs and methods of diagnosis.

### Case Report

A three-year-old collie-cross bitch weighing 50 lb was referred to the Texas A&M University Small Animal Clinic 27 days after the onset of clinical signs. History supplied by the referring veterinarian included vomiting, anorexia, change in the tone of voice, and intermittent muscular weakness characterized by muscle fasciculations of the extremities, and extreme abduction of the hind limbs. The bitch had whelped 22 days after onset of clinical signs. Four days after whelping the animal developed purulent metritis and mastitis. Rectal temperature increased to 104.0 F. Treatment for metritis had included tetracycline orally, one benzathine penicillin injection, and intrauterine infusion of diethylstilbestrol and saline.

Physical examination at Texas A&M revealed dyspnea, rales, mastitis, and muscular weakness exhibited by complete abduction of the hind limbs. With cage rest, the muscular weakness was no longer observed. During 10 days of observation, the dog remained anorectic but had a normal temperature, minimal vaginal discharge, and demonstrated a progressive increase in strength. Treatment during this time was supportive and included intravenous fluids and electrolytes for correction of dehydration. At the end of this observation period, the dog's exercise tolerance was tested and found to be

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below normal. After running approximately 25 yards, the dog began taking shorter and shorter strides and subsequently collapsed onto its nose if forced to go on. No muscular wasting was observed and muscle tone of the limbs felt normal. At rest, neurological examination revealed no sign of deficit attributable to a lesion of the spinal cord. The dog had some difficulty in swallowing and it continually drooled saliva; otherwise no abnormality of the cranial nerves was detected. Following brief periods of rest, the dog was able to regain its ability to stand but subsequent periods of exercise became progressively shorter before recurrence of signs. Laboratory data was within normal limits and included: complete blood counts, urinalysis, and plasma calcium, phosphorus, sodium, potassium, and chloride. Megaesophagus extending from the thoracic inlet to the diaphragm was demonstrated on an esophagram. Due to the clinical signs of excessive muscular fatigue generated by exercise and the presence of megaesophagus, MG was suspected. In an attempt to confirm the diagnosis, a 2-mg dose of neostigmine,<sup>3</sup> an anticholinesterase drug, was administered intramuscularly following a subcutaneous injection of 2 mg of atropine. A marked increase in tolerance to exercise was evident within 15 minutes. Six hours later, the dog was again exercised. Muscle fasciculations and reluctance to run were shown, but the animal did not collapse. Twenty hours after injection, muscle fasciculations and collapse while running occurred. This response to neostigmine was consistent with a diagnosis of MG.

The treatment instituted on dismissal was 15 mg pyridostigmine,<sup>5</sup> given orally as needed. While at home, two additional episodes occurred, each of which responded to pyridostigmine therapy. Twenty-two days later, the dog was again admitted to Texas A&M in a myasthenic state. Clinical signs on readmission were those of muscular weakness and reduced exercise tolerance. Megaesophagus was still present. The pyridostigmine therapy was adjusted during the next five days to a dose of 60 mg given orally twice daily. The dog responded well and was dismissed. Eighteen days later, the dog was readmitted with a purulent nasal discharge, increased pulse and respiration, pyrexia, a deep cough, and moist rales. A diagnosis of pneumonia was made. Probable cause appeared to have been aspiration of regurgitated material. The dog failed to respond to therapy and died on the fifth day of hospitalization. Request for necropsy was denied by the owner.

## Discussion

### Diagnosis

Since MG is often precipitated by other conditions and the clinical signs are often misleading, the diagnosis may be overlooked. Most of the canine cases reported went undiagnosed by the referring practitioners;<sup>17,18,21,26</sup> it is possible, therefore, that this disease may be more common in the canine than has been reported.

Young adult dogs are more commonly affected, but the age range is from two months to 11 years.<sup>18,26</sup> Most of the reported cases are dogs of large breeds.<sup>5,19,24</sup> There has been no significant sex predominance.<sup>17,26</sup> The clinical signs are most pronounced following a period of exercise and are related to skeletal muscle dysfunction exhibited in the extremities by ataxia, complete abduction of the hind limbs, a reluctance to exercise, and collapse if forced to exercise.<sup>6,21,26</sup> Dysfunction may also be exhibited as a change in voice tone especially noticeable after prolonged vocalization<sup>6,21,26</sup> and drooping of the eyelids, ears, and facial features.<sup>18,21,26</sup> Difficult prehension, dysphagia, choking, regurgitation of saliva, and sialosis have been reported.<sup>5,18,21</sup> Megaesophagus has been demonstrated in at least seven cases.<sup>5,21,26</sup> In three other cases, megaesophagus was suspected because regurgitation occurred shortly after eating; however, results of radiographic examinations were not reported.<sup>18</sup>

Results of neurological examinations vary with relation to exercise. Following periods of exercise, abnormal findings include poor patellar reflex, decreased resistance to passive movement of limbs, and overall depressed spinal reflexes.<sup>18,21,26</sup> Following periods of rest all reflexes appear normal.<sup>5,18,21</sup> Spinal radiography performed in one case detected no abnormalities.<sup>5</sup>

Laboratory data is characteristically normal in human and canine MG patients.<sup>12,17,18,21</sup> This data includes: complete blood count, BUN, glucose and serum electrolytes, SGOT, creatine phosphokinase, total serum protein, lactate dehydrogenase, serum alkaline phosphatase, plasma calcium, and plasma phosphorus. The histological abnormalities common to MG in man are lymphocytic infiltrations (lymphorrhages) associated with degeneration and atrophy of affected muscle fibers.<sup>27</sup> Although histological abnormalities of muscle fibers have been reported in only one canine case, the lesions were similar to those reported in man.<sup>5</sup>



A useful diagnostic aid available to teaching institutions is the electromyogram. Electromyographical changes are characteristic for MG in man. There is a marked fall in induced action potentials of the muscle after repeated nerve stimulation and a reduced decline following administration of anticholinesterase drugs.<sup>10,12,18,33</sup> In one reported canine case, *in vitro* electrophysiological studies on intercostal muscle revealed no abnormality of the muscle itself, but the miniature endplate potentials could not be detected.<sup>26</sup> In man, miniature endplate potentials are known to be reduced in MG.<sup>26</sup>

Probably the most important diagnostic aid to practitioners is pharmacological testing. The characteristic response of MG to administration of anticholinesterase agents is an obvious increase in muscular strength. Testing with facilitatory agents (eg— edrophonium<sup>c</sup> and neostigmine) alone will confirm the diagnosis in the majority of MG cases.<sup>11</sup> It is recommended that atropine be administered prior to testing in order to block the muscarinic side effects of the anticholinesterase agent.

Edrophonium is the most widely employed facilitatory agent.<sup>11</sup> The main advantage of edrophonium is the rapid onset and short duration of its action. The effects evaluated 30 to 90 seconds after administration are negligible within three to five minutes.<sup>11</sup> In normal subjects, edrophonium generally causes no change, while in MG patients it usually improves muscle strength significantly.

The use of intramuscular neostigmine for confirmation of the diagnosis of MG in man was first recommended in 1935,<sup>11</sup> and is the method used in most of the reported canine cases.<sup>5,21,26</sup> The dose used in the canine cases varied from 0.075 mg to 2.5 mg.<sup>5,18,21,26</sup> Improvement of the performance of the involved muscles should begin in 5 to 10 minutes, become maximal in 20 to 30 minutes and subside in one to three hours.<sup>11</sup> The effects in the case of this report lasted approximately six hours. The neostigmine test is strongly positive for MG in man.<sup>11</sup> The disadvantage of this test is that if the dose used is too large or too small, it cannot be repeated on the same day.

Pharmacological testing is very diagnostic but not without hazard. Anticholinesterase given to a nonmyasthenic dog, although it is suspected of suffering from the disease, can lead to excessive depolarization and paralysis of muscle, including the respiratory muscles.<sup>26</sup> Cardiac arrest has occurred in man following administration of ed-

rophonium.<sup>22</sup> For these reasons, when conducting such a test, it is always advisable to have resuscitation equipment on hand.<sup>26</sup>

#### Differential Diagnosis

A myasthenic crisis may be associated with many concurrent conditions. Cold weather, infections, and stress have been known to precipitate a crisis.<sup>12,17,18,26</sup> Corticosteroids administered daily with concurrent anticholinesterase administration have caused exacerbations in the canine.<sup>31</sup> However, corticosteroids administered without concurrent anticholinesterase agents have been effective in producing clinical remission in man.<sup>8</sup> Streptomycin, neomycin, kanamycin, colistin, polymixin, bacitracin, diphenylhydantoin, and trimethadione have each been incriminated as the precipitating cause of myasthenic crisis in man.<sup>1,8</sup> In many cases, the concurrent condition is diagnosed while the underlying MG goes undetected. Diseases to be considered in the differential diagnosis of MG in the canine should include rabies, puerperal tetany, achalasia, organophosphate toxicity, and polyneuritis.

Rabies should be considered in any case exhibiting signs of hypersalivation and apparent pharyngeal paralysis. However, once clinical signs develop, a rapid progression to a point of death is usually seen. In the case at hand, the protracted 27-day course and the dog's vaccination history made rabies an unlikely diagnosis.

Puerperal tetany usually occurs after whelping but is rare in large breeds. Blood calcium levels are usually 4 to 7 mg/dl. Clinical signs include nervousness, anxiety, muscle spasms, and possible convulsions.<sup>3</sup> The case presented in this report began to show signs of weakness at 38 days of pregnancy and had a blood calcium level of 10.2 mg/dl. Thus, puerperal tetany was ruled out as a cause of the muscular weakness.

Achalasia in older dogs occurs due to degeneration or postinflammatory involvement of the vagus. Megaesophagus usually involves the cervical and thoracic esophagus and signs usually develop slowly.<sup>3</sup> In the case of this report, megaesophagus did not involve the cervical esophagus, and muscular weakness was noticed at the same time esophageal dysfunction occurred, thus eliminating achalasia as a diagnosis.

Organophosphate toxicity might be considered as a possible diagnosis due to the similarity of clinical signs.<sup>3,6</sup> An accurate history revealing a

source of toxicity would be useful in differentiating this condition from MG. The intravenous edrophonium test mentioned previously would also differentiate the two conditions.

In the incipient stage, polyneuritis, such as in coonhound paralysis, may closely resemble MG. Affected animals initially demonstrate weakness in the pelvic limbs with loss of spinal reflexes.<sup>21</sup> Paralysis usually progresses rapidly and is of the ascending type. Recumbent animals remain alert and afebrile. Atrophy of muscle becomes severe.<sup>21</sup> Frequently, the voice is feeble and facial weakness may be evident. The paralysis usually reaches a peak within 10 days of onset after which the condition remains stable for a variable period before paralysis abates.<sup>4</sup> In the case of this report, absence of a continually progressive, ascending paralysis, absence of neurological deficit at rest, and absence of muscle atrophy eliminated polyneuritis as a possible diagnosis.

#### Treatment

The objective of treatment in MG is to allow the patient to function in a near normal capacity. To accomplish this objective, anticholinesterase drugs (which permit maximal muscle function) are employed. The anticholinesterase drugs of choice are neostigmine (Prostigmin) and pyridostigmine bromide (Mestinon). Effective treatment of MG may be difficult. The response to initial treatment is dramatic and rewarding; however, in long-term therapy the dose of anticholinesterase must be continually adjusted to maintain proper management of the symptoms. Difficulty in swallowing due to pharyngeal weakness and megaesophagus may necessitate parenteral administration of anticholinesterase, and may be associated with severe and fatal aspiration pneumonia.<sup>18,26</sup>

Although neostigmine is effective in the treatment of the majority of patients, it does have disadvantages such as short duration of action and muscarinic side effects (*ie*— epigastric distress, sweating, salivation, lacrimation, nausea, abdominal cramps, and diarrhea). At times these muscarinic side effects are difficult to control despite the use of atropine.<sup>25</sup> Adjustment of the dose of neostigmine is based on the degree of relief of myasthenic symptomatology and upon the side reactions which may indicate that overdosage — a cholinergic crisis — is being approached. Doses reported in the canine ranged from 2.5 to 5.0 mg orally twice daily for a 16-kg animal to 15 mg orally once daily for a six-year-old English coon-

hound.<sup>18,21</sup> Menstrual periods, infection, or emotional stress can alter the daily requirement of neostigmine in humans.<sup>25</sup>

Pyridostigmine is an analogue of neostigmine, and, therefore, has a similar pharmacological action. Pyridostigmine is less potent but it has a slightly longer duration of action than does neostigmine.<sup>26</sup> In man, pyridostigmine has several advantages over neostigmine. There is a low incidence of muscarinic side effects and a reduction in the nicotinic side effects such as skeletal muscle cramps. Atropine was discontinued in 75% of the patients who had required it with neostigmine.<sup>25</sup> It is also more effective than neostigmine in the relief of myasthenic symptoms affecting small muscles innervated by cranial nerves.<sup>25</sup> In this report, pyridostigmine was used effectively, but previous reports have indicated that it is only moderately effective in the canine.<sup>10,33</sup>

The optimal dose of anticholinesterase can be determined by one of three methods: clinical evaluation, edrophonium testing, or intravenous titration with the selected medication, which is an accurate but dangerous procedure.<sup>25</sup> Of these, the edrophonium test is probably the most widely used in man. For this purpose, edrophonium is injected intravenously 60 to 90 minutes after the patient's customary oral dose of anticholinesterase. If there is improvement, the dose may be less than optimal, and if there is deterioration, it may be greater than optimal.<sup>11</sup> Means of resuscitation should be available when this test is performed.

It has been noted that human patients may become resistant to neostigmine, requiring ever increasing amounts of the drug, especially when intervening infection or psychic trauma occurs.<sup>25</sup> When a patient becomes resistant to neostigmine he is usually equally resistant to the other anticholinesterase agents.<sup>25</sup> This observation may also occur in the canine, and clients should be made aware of the possibility.

Some human patients have been treated effectively with prednisone after they did not respond to anticholinesterase.<sup>8</sup> In man, treatment with adrenocorticotrophic hormone (ACTH) in high doses usually leads to a clinical remission after an initial increase in myasthenic symptoms.<sup>30</sup>

#### Etiology

The etiology of MG is still unknown, but electrophysiological changes indicate the defect is at the myoneural junction.<sup>17,18,21</sup> Much data sup-



ports the notion that autoimmune reactions may contribute by interfering with the activity of the motor endplate.<sup>9</sup> Human patients with MG have an increased incidence of autoantibodies and autoimmune disorders.<sup>29</sup> Some authors also have reported autoimmune cell-mediated immunity against muscle, thymus, and brain tissue in humans.<sup>20</sup> Another theory suggests that MG is due to morphological abnormalities of the motor endplates.<sup>28</sup> The deformation of endplates may be due to a disturbance of a normal remodeling process dependent on the thymus and possibly on the adrenal glands. Several other theories have been postulated, but most indicate association with the

thymus. The possibility exists that there are several types of MG, each having different etiologies while sharing in a final expression of a defect in neuromuscular transmission.<sup>28</sup> New scientific discoveries, such as the possibility that purification of receptor proteins from the electric organ of the electric eel may induce a state in experimental animals similar to MG in man, may enlighten us as to the cause of MG and provide a more suitable means of management of the disease.<sup>9</sup>

<sup>a</sup> Prostigmin, Roche Laboratories, Nutley, NJ.

<sup>b</sup> Mestinon bromide, Roche Laboratories, Nutley, NJ.

<sup>c</sup> Tensilon, Roche Laboratories, Nutley, NJ.

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