Inherited myopathy in a litter of Labrador retrievers

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Muscular dystrophies are rarely encountered in dogs, but golden retrievers, Labrador retrievers, and Irish terriers are occasionally afflicted with these hereditary conditions (1). In Labrador retrievers, a form of myopathy exists that is distinct from other breed-specific dystrophies in both its mode of inheritance and its histological appearance. The following report summarizes the findings in 4 littermates afflicted with this unusual disorder.

A litter of 3 female and 4 male black Labrador retriever puppies was born uneventfully. The puppies were the product of a first-time breeding of normal, noninbred parents. This was the 1st litter for the dam, but the stud had previously sired many normal litters.

At weaning, the breeders noticed that the puppies did not exhibit the voracious appetite that they had observed in other litters. Four of the 7 puppies (2 male, 2 female) appeared to have abnormal skeletal conformation, characterized by "flat" feet and arched backs. Between 3 and 6 mo of age, these 4 puppies developed progressively increasing exercise intolerance, manifested by a wobbly, unsteady gait and an inability to stand after moderate exertion. The 3 remaining puppies, 2 male and 1 female, did not exhibit these abnormalities and are still normal at the age of 15 mo.

Three of the 4 affected puppies were presented to the Veterinary Teaching Hospital (VTH), Western College of Veterinary Medicine, between 7 (1st dog) and 8 (2nd and 3rd dogs) mo of age for examination. The 4th was hit by a car and died at approximately 10 mo of age.

On presentation to the VTH, all 3 affected dogs showed similar clinical signs. Physical examination of the 7-month-old bitch (1st dog) revealed a small, thin dog weighing 17 kg, with very poor muscle development. She assumed a posture with an arched back and overextended carpi and hocks. On neurological examination, patellar, triceps brachii, and extensor carpi radialis reflexes were absent. Normal strides were occasionally interrupted by simultaneous protraction of the hindlimbs ("bunny-hopping").

The abnormal gait was markedly exacerbated by exertion. Within 1 min of sustained exercise, signs of weakness in the hindlimb muscles were clearly visible. Within 4 to 5 min the dog became completely unable to use its hindlimbs, which were by this time plantigrade. Nonetheless, it continued to pull itself forward using its forelimbs in pursuit of a toy. There was no evidence of pain. After a short rest, the dog was again able to walk, although the hindlimbs remained very weak.

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The 2nd female exhibited muscle fasciculations in the face and hindlimbs, in addition to the same clinical signs seen in the 1st dog. The 3rd dog, a male, was unable to walk without showing weakness in the hindlimbs.

A complete blood cell count, serum biochemical profile, and urinalysis were unremarkable on the 1st dog, although analysis at 6 mo had shown a mild increase of creatinine phosphokinase (CK) activity. Creatinine phosphokinase activity was mildly elevated in both littermates at the time of presentation (851 and 590 U/L in the male and female, respectively; normal, 0 to 300 U/L). No other laboratory abnormalities were detected.

Edrophonium chloride (Tensilon, ICN Canada, Montreal, Quebec) at a dose of 0.18 mg/kg body weight (BW) administered IV to the 1st dog immediately after the onset of exercise-induced fatigue did not alleviate the extreme weakness and, in fact, seemed to considerably delay recovery. This response made a diagnosis of myasthenia gravis unlikely. A light plane of anesthesia was obtained in the 1st dog with acepromazine (Atravet, Ayerst Laboratories, Montreal, Quebec) at a dose of 0.05 mg/kg BW, IV, and thiamylal (Thiopental, Abbott Laboratory, Montreal, Quebec) at a dose of 8 mg/kg BW, IV. Electromyography of the vastus lateralis, gluteal, biceps femoris, semimembranosus, semitendinosus, cranial tibial, and superficial digital flexor muscles was performed. In addition, the left sciatic nerve was subjected to a repetitive stimulation test and measurements of response by the left gastrocnemius muscle were obtained. The electromyographic profiles of the muscles studied showed normal activity, but fibrillation potentials were observed in one part of the left cranial tibial muscle. Repetitive nerve stimulation did not yield a repeatable abnormal result.

The 7-month-old bitch was anesthetized and biopsies from the middle gluteal, vastus lateralis, cranial tibial, triceps brachii, and biceps femoris muscles, as well as the sciatic nerve, were collected. These biopsies were sent to Dr. G. Diane Shelton of the Comparative Neuromuscular Laboratory at the University of California at San Diego. Muscle sections were stained according to several techniques, including hematoxylin and eosin (H&E), myosin adenosine triphosphatase (ATPase) at pH 9.8 and 4.3, and modified Gomori trichrome. The dog was then euthanized at the owner's request. A full necropsy was carried out, and tissues for histological examination were collected, including samples of the temporalis, supraspinatus, trapezius, sartorius, diaphragm, tongue, and esophageal muscles, and of the brain, spinal cord, and radial and sciatic nerves. These were fixed in 10% neutral-buffered formalin, embedded in paraffin, cut at 5 μm, and stained with H&E. Some muscle sections were also stained with hematoxylin-basic fuchsin-picric acid (HBFP).

The histological appearance of all biopsy and postmortem muscle samples was abnormal. There was a mild to marked variation in myofiber size in all muscles. The ATPase stains showed that atrophic fibers belonged to both type I and type II fibers. Hypertrophic myofibers

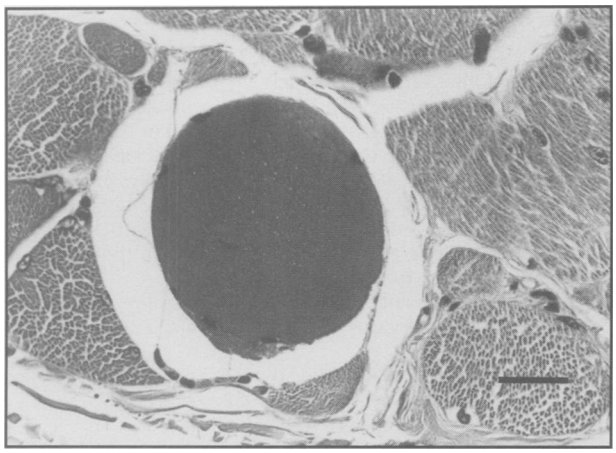

Figure 1. Transverse section of striated muscle in a Labrador retriever with myopathy. In the center is a degenerative myofiber, which is swollen and rounded, has glassy, highly eosinophilic sarcoplasm, and pyknotic nuclei. Formalin fixed section. H&E stain. Bar = 25 μm.

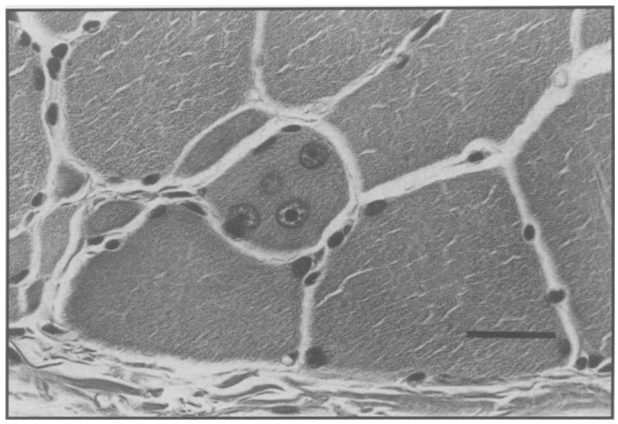

Figure 2. Transverse section of striated muscle in a Labrador retriever with myopathy. In the center is a small regenerative myofiber with multiple internal nuclei that are large, vesicular, and have a prominent nucleolus. Formalin fixed section. H&E stain. Bar = 25 μm.

with a whorled appearance of the myofibrils were also present. Throughout the sections of muscle, there were individual degenerative myofibers with intensely stained eosinophilic sarcoplasm, loss of cross-striation, and pyknotic nuclei (Figure 1). These degenerative myofibers were most prominent in the HBFP-stained sections. Other myofibers had basophilic, nonstriated sarcoplasm and large centrally located nuclei that were occasionally arranged in rows. These myofibers are typical of regenerating fibers (Figure 2). No abnormalities were seen in the sections of brain, spinal cord, nerves, or intramuscular nerve branches.

Tensilon testing (IV administration of edrophonium chloride), electromyography, and antemortem muscle biopsies were not performed on this dog's 2 affected littermates. The dogs were euthanized, a full necropsy was done, and a similar range of tissues for histological examination was collected as for the 1st dog. The striated muscles had more or less the same histological lesions as seen in the 1st dog. Samples from the female showed the most subtle lesions, with the masseter and supraspinatus muscles most markedly affected. The male showed the most marked histological changes of all 3 littermates, with the biceps femoris muscle demonstrating the most severe atrophy. No lesions were detected in the central nervous system or in peripheral nerves.

A diagnosis of Labrador retriever myopathy was made in the 3 dogs on the basis of their signalment, clinical presentation, and histological appearance of striated muscles. In the absence of electrolyte and biochemical abnormalities, myasthenia gravis and muscular dystrophy were the only diseases likely to cause the characteristic and severe signs of weakness shown by these dogs. Myasthenia gravis was ruled out by the 1st dog's failure to improve with edrophonium chloride administration and its normal electromyographic response to repetitive stimulation. Muscle lesions, characterized by myofiber atrophy, degeneration and regeneration, and the absence of nerve lesions, were consistent with the muscular dystrophy that afflicts Labrador retrievers (2).

Labrador retriever myopathy is an autosomal recessive disorder, first described by Kramer *et al* (3) in 1976; since then, it has been reported in both black and yellow Labrador retrievers in Great Britain (4), the United States (5), and Australia (6). To the authors' knowledge, this is the first publication reporting the disorder in Labrador retrievers from Canada. Labrador retriever myopathy differs from the muscular dystrophies occurring in Irish terriers and golden retrievers, which are X-linked (1). Variation in the presentation and severity of clinical signs is great, but the loss of patellar and triceps brachii reflexes is a consistent finding (1,5). A low head carriage, a stiff, stilted gait, bunny hopping, carpal overextension, and generalized skeletal muscle atrophy are reported, and the signs are often exacerbated by stress or cold (1). An affected dog typically begins to exhibit signs at 8 to 12 wk of age, and these signs progressively increase in severity up to approximately 12 mo of age (2). After this time, progression of the disease ceases or slows. In these respects, the dogs we describe are fairly typical.

Routine hematological and biochemical analyses are of little help in diagnosing Labrador retriever myopathy, although serum CK activity is often moderately elevated (1,5). In Labrador retriever myopathy, the administration of edrophonium chloride may worsen clinical signs of disease (3).

Electromyography performed in affected dogs often shows spontaneous electrical activity and bizarre high frequency discharges (1). While these abnormalities generally reflect denervation and axonal damage, they may also occur when areas of muscle are sequestered from an end-plate by a necrotic region, or when regenerating fibers have not been innervated (7). It is possible, therefore, for these electromyographic changes to occur with a myopathy without a denervative component.

It is surprising that fibrillation potentials were found in only one area of the cranial tibial muscle, and that all other muscles studied had normal electromyographic tracings, despite the severity of the dog's clinical signs. Possibly the needle electrode had been placed in an area of muscle separated from its nerve by the myopathic process.

Muscle histopathology in Labrador retriever myopathy has been well described (2). The key morphologic features, though variable, include atrophic muscle fibers, either individual or in groups; scattered hypertrophic fibers, often with a whorled myofibrillar pattern and

clefts; and increased numbers of fibers with internal nuclei, necrosis, and fibrosis. Most of these lesions were found in the 3 dogs described here. Atrophic and hypertrophic fibers are of both types I and II, as was seen in the 1st dog, but a deficiency of type II fibers is sometimes found, mainly in animals over the age of 12 mo (2).

The distinction between a primary myopathy and a neuropathy is often difficult to make, but the absence of certain reflexes and the presence of fibrillation potentials are suggestive of a denervative disorder (1). These features, which suggest a neuropathic basis, make this disease distinct from other known myopathies in dogs. Other characteristics of Labrador retriever myopathy, such as, increased internal nuclei counts, necrosis, regeneration, and fibrosis, are more characteristic of a muscular dystrophy or destructive myopathy (2). While it is possible for such lesions to occur secondarily to denervation, no abnormalities have been found in either peripheral nerves or spinal cord from affected dogs (1).

The pathogenesis of Labrador retriever myopathy is unknown. Muscle microvascular function in affected dogs appears normal (8). However, skeletal muscles of Labrador retrievers with hereditary myopathy contain significantly increased total concentrations of sodium and significantly lower total concentrations of potassium compared with normal dogs (9). The calculated intracellular concentrations show the same imbalance, and the intracellular potassium:sodium ratio is low. The derangement in the normally low sodium and high potassium concentrations inside muscle cells, which is maintained by the membrane-bound sodium pump, probably results in a resting membrane potential that is significantly lower (less negative) than normal (9).

To produce puppies affected with this autosomal recessive disease, each of the normal parents must be a carrier of the defective gene (10). On average, only 1 of every 4 offspring is likely to be an affected homozygote from a breeding of carriers. In this litter, however, 4 of the 7 puppies were affected. The unusually high proportion is most likely attributable to chance, although only 4.4% of litters of 7 puppies can be expected to have 4 affected puppies (11). Alternatively, it is possible that 1 of the parents is a subclinically affected homozygote. While severe cases are most often reported, homozygotes with very mild disease may occur.

The finding of Labrador retriever myopathy in a Canadian litter warrants the consideration of this diagnosis in any exercise-intolerant young dog of this breed in Canada. Correct diagnosis is crucial to enable breeders to eradicate the disorder from their genetic lines. The bitch of the affected dogs in this litter was spayed. Our inability to screen for carrier parents means that limiting spread of the disease may be difficult. Furthermore, the lack of a screening test for puppies before adoptive age means difficult choices for the new owners of affected dogs.

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