

Labrador Retriever Hereditary Myopathy
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A degenerative myopathy that is inherited as an autosomal recessive trait has been reported in Labrador Retriever dogs in the United States and United Kingdom, and has been seen in Continental Europe and Australia. The condition has been called Labrador Retriever hereditary myopathy (LRHM), Labrador Retriever myopathy, type 2 muscle fiber deficiency and muscular dystrophy. The disorder affects male and female dogs and has been seen in animals with both black and yellow coat color. The age at onset and the severity of clinical signs may be variable. Some puppies have clinical signs at 6 to 8 weeks of age. In others, a later onset at 6 to 7 months has been observed. Cases of both early (8 weeks) and late (6 months) onset have been observed within the same litter. In typical cases, clinical signs become obvious at 3 to 4 months of age and include muscle weakness, abnormalities of gait and posture, and decreased exercise tolerance. Severely affected puppies may have a low head posture, with ventroflexion of the neck. The back is arched, and the gait is characterized by short, stilted strides in which the hind legs are often advanced simultaneously in a synchronous, bunny hopping fashion. Clinical signs become more accentuated as the animal tires, and, if encouraged to continue, the puppy may collapse forward with the head and neck to one side. There is no loss of consciousness or cyanosis. Exercise tolerance may be reduced to 20 yards in severely affected animals. Severe tetraparesis, inability to walk, hyporeflexia, and elevated serum CK levels have been seen in two 4 month old littermates. However, mildly affected dogs may be presented because they seem to be "slow" puppies that are less playful than their littermates and less willing to exercise. These dogs may not collapse unless forcibly exercised, at speed, for several minutes. Rest results in some improvement, but the clinical signs rapidly recur on resumption of exercise. Joint posture is often abnormal, with affected dogs having carpal overextension, carpal valgus, splaying of the digits, and a "cow-hocked" stance. As the condition progresses, generalized atrophy of skeletal muscles develops. The proximal muscles of the limbs and the muscles of the head are particularly affected, but in milder cases, the atrophy may not be dramatic. Signs may be exacerbated by excitement or stress and particularly by exposure to cold weather. After exposure to cold, an affected dog may be unable to stand or to lift its head. Moving the animal to a warm kennel usually results in improvement within a few hours. A less common complication observed in adult dogs (some of whom have been pregnant) is the development of a transient megaesophagus. Other sporadic complications that have been observed include the presence of a luxating patella and clinical and radiographic evidence of degenerative joint disease in the hip of one affected dog that was obese. Affected dogs are bright and alert, although often poorly muscled when compared with their normal littermates. Temporal muscle atrophy is often a feature, but cranial nerve functions are otherwise normal. Muscle tone may be normal or reduced. There is no muscle pain on palpation nor dimpling on percussion. Severely affected puppies are obviously weak and may have difficulty wheelbarrowing or hopping, although in less affected puppies, postural testing may indicate no abnormalities. Proprioceptive function is normal, and no sensory deficits have been observed. Tendon reflexes are generally reduced or absent, even in mildly affected dogs with little muscle atrophy. There is no impairment of bladder function and no signs of autonomic nervous system dysfunction.

Serum CK levels may be within normal limits or moderately elevated. Levels may increase following exacerbation of signs after exposure to cold weather but do not reach the levels reported in other degenerative muscle diseases, such as the inherited muscular dystrophy described in Golden Retrievers. Other routine hematological and blood biochemical parameters are within normal limits. Motor nerve conduction velocities are within the normal range in affected dogs, and there is no decremental response to repetitive nerve stimulation. On EMG examination, there frequently is spontaneous activity, particularly in the proximal limb muscles, musculature of the head, and the thoracolumbar paraspinal muscles. The most commonly recorded abnormalities are fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges. Myotonic-like discharges and fasciculation potentials are recorded infrequently. EMG changes may be less pronounced in mildly affected dogs and may be difficult to detect in very young dogs. Results of electrocardiographic examination of affected adults and puppies have indicated no cardiac involvement. Despite the abnormal joint posture seen in many affected dogs, there have been no abnormalities on radiography of hocks, carpi, and the vertebral column. In some cases, however, changes consistent with hip dysplasia have been present.

A wide range of morphological features may be observed in muscle biopsies from affected dogs. The changes reported include small and large group atrophy, small fibers of both fiber types that tend to have a round rather than angular appearance, occasional fiber type grouping, large numbers of internal nuclei,

disturbances in myofiber architecture, necrosis, regeneration, and replacement of muscle fibers with fat and fibrous tissue. Alterations in fiber type percentages are a common finding. In most muscles there is a reduction in the proportion of type 2 fibers (except for the cranial tibial muscle in which an increase in the percentage of type 2 fibers has been noted). These changes in fiber type proportions appear to become more accentuated as the disease progresses. No abnormalities have been found in brain, spinal cord, or peripheral nerves. Note that similar histological findings have been observed in clinically normal Labrador Retrievers closely related to those with LRHM. It has been suggested that an additional gene or an environmental factor is responsible for expression of the subclinical form of the disease.

The underlying pathophysiological mechanisms involved in this disease are still unclear, although the myopathy has genetic, clinical, pathological, and histochemical similarities to the limb-girdle form of muscular dystrophy in people. Myofiber dystrophin staining is normal. However, immunocytochemical and Western blot studies reveal that sarcoglycans, alpha-actinin, dysferlin, and calpain 3 are present in affected dogs. These sarcolemmal and Z-disc (alpha-actinin) proteins have been incriminated in various limb-girdle muscular dystrophies in people. Muscle biochemical studies indicate significantly elevated concentrations of sodium, calcium, zinc, copper, and chloride and reduced levels of potassium and magnesium in muscles from affected adult Labrador Retrievers. There is a significant increase in the intracellular water and sodium levels and a concomitant reduction of intracellular potassium content. In addition, a significant decrease in muscle-specific proteins has been identified in the biceps femoris muscle of affected dogs. Also, lipid fluidity of erythrocyte membranes is significantly different in affected Labrador Retrievers. Results of other studies have not supported the hypothesis of a possible vascular defect.

Diagnosis is based on signalment, clinical signs, and muscle biopsy data. Prognosis is generally favorable for longevity. In most cases, the clinical signs stabilize between 6 months and 1 year of age. There may be some improvement in ability to exercise, particularly in those dogs with the mildest signs. The atrophy of skeletal muscles persists, however, and although affected dogs may be acceptable house pets, they are not suitable for work. Owners of affected dogs should be warned that stress, including exposure to low temperatures, can result in a dramatic worsening of clinical signs, even in clinically stable adults. The life span of affected dogs does not appear to be directly affected by the condition, although the prognosis for dogs with megaesophagus should be more guarded because of the risk of developing inhalation pneumonia.

There is no definitive treatment for this condition, although various forms of medication have been used. **Diazepam**, given orally at a dose of 10 mg twice daily, may have some ameliorating effect. Diphenylhydantoin has little effect, and edrophonium chloride may worsen clinical signs. Anabolic steroids have apparently been beneficial in some cases; however, the evidence for this is anecdotal. Low muscle carnitine levels have been found in a few dogs tested suggesting that administration of **L-carnitine** (at 50 mg/kg PO bid) might be beneficial. Because there is no way of detecting heterozygous carriers at this time, breeders should be advised against breeding from parents or siblings of affected puppies. Molecular studies are currently being undertaken at the Scott-Ritchey research Center, Auburn University College of Veterinary Medicine. There has been a recent preliminary report of a condition termed "canine centronuclear-like myopathy" in Labrador Retrievers in which onset, clinical signs, pathology (including centrally-placed myofiber nuclei) and histochemistry are virtually identical to those seen in LRHM. The authors report that the gene for this condition (CNM gene) is localized on canine chromosome CFA2 and suggest that the disorder is a homologue of the human autosomal centronuclear myopathy. The relationship of this disorder to LRHM, if any, remains to be seen.