What’s new in muscle and peripheral nerve diseases?

G. D. Shelton
Department of Pathology, University of California-San Diego, La Jolla, California, USA

Summary
It is likely that most neuromuscular diseases that are described in humans will have a counterpart in our companion animals. With the advent of molecular genetics and the completion of the canine and feline genomes, an ever expanding number of DNA-based tests should become available for the diagnosis of muscle and peripheral nerve diseases. Molecular testing procedures should enable us to continue to unravel the molecular basis of neuromuscular diseases for which the cause is still unknown. It is important that accurate clinical evaluations and diagnostic testing, including muscle and peripheral nerve biopsies, are performed in order to reach these goals. This review focuses on recently identified inherited neuromuscular diseases in companion animals.

Keywords
Muscle, myopathies, nerve, neuropathies, inherited diseases

Introduction
Most of the recently identified muscle and peripheral nerve diseases (neuromuscular diseases) are breed associated and fall into the inherited category (1–3). Although inherited neuromuscular diseases in general are relatively uncommon; within a breed, a genetic disorder may be quite common. For example, in a recent study that documented pyruvate dehydrogenase phosphatase 1 (PDP1) deficiency in Clumber Spaniels (see p. 252), the carrier rate was 20% (4). Genetic diseases involving muscle and peripheral nerves may be difficult to diagnose. For this group of diseases it is particularly important to obtain a correct neuroanatomic localization, and perform specialized screening and diagnostic tests, including muscle and peripheral nerve biopsies.

Muscular dystrophies
Muscular dystrophies are a heterogeneous group of inherited, degenerative, mostly non-inflammatory disorders characterized by progressive muscle weakness and wasting (for reviews see 1, 3). In humans, the genetic basis of over 30 different forms of muscular dystrophy (MD) has been defined over the past decade. Although not all forms of MD have been identified yet in companion animals, dystrophies associated with an absence of or abnormalities in dystrophin, sarcoglycans, and laminin alpha 2 (Fig. 1) have been recognized in several breeds. Similar to MD in humans, dystrophin deficient MD will likely be the most common form of MD in animals, given the large size of dystrophin and propensity for mutation. Muscular dystrophy should be considered in any young dog or cat (male or female, mixed breed or purebred) with persistent muscle weakness, muscle atrophy or hypertrophy, gait abnormality or contractures beginning in the first few months of life. Serum creatine kinase (CK) concentrations are usually dramatically elevated. For clinical purposes, a diagnosis of MD is made by demonstration of a dystrophic phenotype in muscle biopsy sections, and immunohistochemical (Fig. 2) demonstration of decreased or absent dystrophy related proteins in muscle. Currently there are no specific treatments available for this group of diseases.

Myopathies affecting Labrador Retrievers
Inherited myopathies that affect the Labrador Retriever breed are relatively common and clinicians working with this breed should be aware of these disorders as they
can mimic orthopaedic or cardiovascular diseases.

**Dystrophin deficient muscular dystrophy**

A persistent, markedly elevated CK concentration in a young Labrador Retriever puppy with a myopathic clinical presentation should provide a presumptive diagnosis of this form of muscular dystrophy (1, 3, 6), differentiating it from the other inherited myopathies that affect this breed. The diagnosis is confirmed by demonstration of a dystrophic phenotype in a muscle biopsy specimen, and by demonstration of dystrophin deficiency by immunocytochemical or immunoblotting techniques. If multiple puppies in a litter are affected, or there are known affected related dogs, an inherited

---

**Fig. 1** Dystrophin glycoprotein complex spans the muscle plasma membrane, linking the intracellular myocyte to the extracellular matrix. A mutation in any of the proteins of this complex may result in a muscular dystrophy. (Reprinted from Schatzberg SJ, Shelton GD. Vet Clin North Am 2004; 34: 1497–1524, with permission from Elsevier).

**Fig. 2** Immunofluorescence staining of skeletal muscle from a dog with muscular dystrophy (D). Compared to similar staining of muscle in a normal dog (N), staining was absent with the antibody against the rod domain of dystrophin, and staining for utrophin was increased. Staining patterns with other antibodies were similar to control tissue. This staining pattern confirmed the diagnosis of a muscular dystrophy. (Reprinted from Jones BR, Brennan S, Mooney CT et al. J Neurol Sci 2004; 217.143–149, with permission from Elsevier).
familial disorder would be most likely. Spontaneous mutations are also possible given the propensity of the dystrophin protein for mutations.

**Centronuclear myopathy**

Centronuclear Myopathy used to be known as inherited myopathy of Labrador Retrievers, Type 2 fibre deficiency and autosomal recessive muscular dystrophy. A widespread inherited myopathy affecting male and female, yellow and black Labrador Retrievers less than six months of age was first described in 1976 (7). Poor conformation and reduced muscle mass, a stiff ‘bunny hopping’ gait, and abnormal head and neck posture beginning at a young age are typical clinical findings (Fig. 3). Multiple littermates are usually affected. The serum CK concentration is usually normal or only mildly elevated. A presumptive diagnosis can be made based on appropriate clinical signs and evaluation of muscle biopsy specimens. The underlying cause of this myopathy eluded clinicians for many years, since pathological changes in muscle biopsy specimens are variable (8) and central nuclei are not evident at a young age when biopsies are usually collected. Serial investigations of muscle biopsies in a colony of Labrador Retrievers in France allowed for the identification of central nuclei in muscle of affected dogs at older ages. The specific mutation for this disorder has recently been identified in this French pedigree (9). The same mutation is also present in USA and UK pedigrees (Shelton, unpublished data). A website is currently available with information on genetic testing for this myopathy (http://www.labradorcnm.com). Specific therapies are currently not available. Housing in a warm area has been advised as exposure to cold may exacerbate the condition. Supplementation with L-carnitine (50 mg/kg BID) may improve muscle strength.

**Exercise induced collapse in Labrador Retrievers (EIC)**

A syndrome of exercise intolerance and collapse has been observed with increasing frequency in young adult Labrador Retrievers. Most, but not all, affected dogs have been from field-trial breeding. Black, yellow and chocolate Labrador Retrievers of both sexes can be affected. Clinical signs become apparent in young dogs as they encounter heavy training or perform strenuous activity, but usually between seven months and two years of age. Affected dogs are described as being extremely fit, muscular, and prime athletic specimens of their breed (Fig. 4A) with an excitable temperament and lots of drive (unpublished data).

Affected dogs can tolerate mild to moderate exercise, but following 5–20 minutes of strenuous exercise they develop profound ataxia followed by collapse (Fig. 4B). Several dogs have died during exercise, or while resting immediately after an episode of EIC, hence exercise should always be stopped at the first sign of ataxia. This is not a malignant hyperthermia. Affected dogs are rarely able to continue training or competition; however, if they are removed from training and not exercised excessively, the condition will not progress and they will be fine as pets. Until now, a presumptive diagnosis of EIC could only be made by ruling out other muscle disorders and by observation of characteristic clinical features with a typical history. While a specific therapy currently does not exist, the avoidance of strenuous activity should result in a relatively normal lifespan.

A DNA based test for this interesting syndrome is on the horizon (http://medicine.ucsd.edu/vet_neuromuscular, October 2006 Case of the Month). The chromosomal locus for an EIC gene has been identified with microsatellite DNA markers and an associated DNA mutation has been found. A genetic test for confirmation of affected dogs and identification of carriers should soon be available. This valuable test will hopefully help to eradicate this disabling disease from breeding populations.
Pyruvate dehydrogenase phosphatase 1 (PDP1) deficiency in Clumber and Sussex Spaniels

Exercise intolerance and lactic acidosis associated with mitochondrial pyruvate dehydrogenase complex deficiency was described several years ago in Clumber and Sussex Spaniels in the United Kingdom (10, 11), then many years later in a Clumber Spaniel in Finland (12) and the USA and Belgium (13). Routine laboratory, electrophysiological and histological examinations are normal. A consistent abnormality is markedly elevated blood lactate and pyruvate concentrations with a lactate to pyruvate ratio (L/P) <10, and severe metabolic acidosis. The measurement of blood lactate and pyruvate concentrations at rest and post-exercise is an easy screening procedure and should be part of a minimum data base for any young Clumber or Sussex Spaniel that is admitted with exercise intolerance within the first year of life.

A null mutation has been identified in PDP1, the phosphatase enzyme that activates the pyruvate dehydrogenase complex (4). This same mutation affects both the Clumber and Sussex Spaniel breeds. In that report, 20% of the current Clumber and Sussex Spaniel population are carriers for a null mutation in PDP1, and that homozygoticy produces severe exercise intolerance. Knowledge of the molecular defect has allowed for the institution of a rapid restriction enzyme test for the canine mutation that will allow for selective breeding. Genetic testing is now available for confirmation of the PDP1 mutation in Clumber and Sussex Spaniels at the University of Missouri-Columbia, USA. Instructions for sample submissions are available at www.caninegeneticdiseases.net.

Although specific therapies are not available, dietary alterations and vitamin supplements may result in clinical improvement. Dogs with PDP1 deficiency are sensitive to carbohydrate in the diet and may develop life-threatening acidosis from such diets. A diet that is high in fat (50% or more of the calories in fat and 20% in carbohydrate) leads to a reduction in the concentration of lactate and improvement in general condition. Thiamine pyrophosphate is an integral component of the PDH enzyme complex and should be supplemented since a decreased affinity for the cofactor may be overcome by increasing the concentration. Excessive accumulation of acyl-CoA esters in the mitochondria may result in deficiency of muscle carnitine. Supplementation with L-carnitine (50 mg/kg BID PO) is suggested. Although not yet used clinically, treatment with dichloroacetate may also be of benefit based on the biochemical abnormalities (4).

Glycogen storage disease type IIIa in Curly-Coated Retrievers

An autosomal recessive inherited disorder has recently been described in curly-coated Retrievers (CCR) (14). Glycogen storage disease type IIIa (GSD IIIa) is a metabolic disorder that results from deficient activity of the glycogen debranching enzyme (GDE). Intracellular storage and the retrieval of glucose is affected which causes disease primarily of the liver and skeletal muscle.

The dogs that were diagnosed with GSD IIIa were clinically normal at the time they were neutered at six to nine months of age. There was no history of weakness or exercise intolerance. However, presurgical blood tests revealed high levels of the liver (ALT, AST, and ALP) and muscle (CK) enzymes in otherwise normal dogs. Recovery from surgery was uneventful, but over the ensuing months and years, the dogs became lethargic, had delayed recovery from moderate exercise, and suffered episodes of hypoglycemic collapse that responded rapidly to oral administration of glucose-containing supplements. ALT, AST, and ALP activities steadily increased, but CK activity had been intermittently normal or extremely elevated.

Early in the course of the disease the clinical signs of GSD IIIa are sufficiently vague and non-specific that it is likely that some affected dogs have not been diagnosed. Other than the genetic test, the most probable finding that can alert a veterinarian to the problem is the elevation of liver and muscle leakage enzymes in serum. However, many dogs have routine surgical procedures without presurgical blood tests, so the disorder may not be apparent until the dog has an episode of collapse or is not as active as expected. Liver and muscle biopsies show hepatocytes and scattered myocytes swollen and full of glycogen, which suggests some form of glycogenosis. Carriers are entirely normal, both in their physical behaviour and in blood tests, such as serum transaminase and CK activities. The mutation has been identified at the Laboratory of Comparative Medical Genetics at the Michigan State University, USA, as a single base deletion in the GDE gene leading to undetectable enzyme production. A polymerase chain reaction (PCR) based test is now available through this laboratory for the diagnosis of affected animals and the detection of obligate carriers, utilizing simple cheek brushing, or in a small sample of blood or semen. Sample submission instructions and forms can be downloaded via a link from http://www.mmg.msu.edu/faculty/fyfe.htm.

Hypertonicity (episodic falling) in Cavalier King Charles Spaniels

An electrically silent hypertonicity syndrome beginning at about three months of age has been described in male and female Cavalier King Charles Spaniel dogs. The original reports described dogs in the UK (15–17), but since then, additional affected dogs have been identified in Australia and the USA (18–19). All of the dogs had a history of exercise and excitement-induced ‘collapse’ that was preceded by a ‘deer-stalking’ action or development of a ‘praying’ position (Fig. 5). An increase in extensor tone of muscles of all four limbs was evident during the time of collapse with recovery occurring in about 10 minutes. Progression of the disorder has not been reported, and stabilization or improvement may occur. While mitochondrial and morphological abnormalities were described morphologically within muscle biopsy speci-
Inherited myopathy of Great Dane dogs

A hereditary, non-inflammatory myopathy with distinct histological myopathic features has been described in young Great Dane dogs (Fig. 6) (21, 22). The onset of clinical signs is usually before one year of age and both sexes are affected. Clinical signs are characterized by exercise intolerance, muscle wasting, and an exercise-induced tremor. While originally reported as a ‘central core myopathy’ in this breed (21), the histochemical characteristics of the distinct cytoarchitectural structures differ from those of the well-characterized central core myopathy in human beings. For comparative purposes and consistency in nomenclature, the name of this myopathy has been changed to ‘inherited myopathy of Great Dane’ dogs until the underlying cause of this disease has been identified and a specific mutation has been found. Further studies of this very interesting myopathy are in progress. An autosomal recessive mode of inheritance is most likely. No specific treatments are available.

Inherited polyneuropathy in Leonberger dogs

A distal, symmetrical, progressive polyneuropathy has been identified in several related Leonberger dogs with age of onset one to eight years (23). Although it was not reported until 2004, a polyneuropathy affecting this breed was suspected as early as the 1960s in Germany and the Netherlands. Clinical cases have recently been confirmed in the USA, Canada, United Kingdom, France, Germany, The Netherlands, Belgium, Finland, Sweden and Denmark (Shelton, unpublished data). The clinical presentation is similar to an axonal form of hereditary motor and sensory neuropathy (Charcot-Marie-Tooth disease) described in humans (24, 25). Clinical presentation includes: exercise intolerance and weakness, a high steppage pelvic limb gait, and dyspnoea associated with laryngeal paralysis. Marked atrophy of the distal limb muscles is typical with depressed spinal reflexes and weak or absent movement of the laryngeal and pharyngeal muscles. Electrophysiological evaluation and muscle biopsy findings are consistent with denervation. Peripheral nerve biopsies show nerve fibre loss, axonal degeneration, and secondary demyelination. Although an X-linked mode of inheritance was initially considered based on pedigree analysis, an autosomal recessive inheritance cannot be ruled out.

For many reasons, clinicians under appreciate the frequency and variability of inherited neuropathies (24). The age of onset...
is variable, and clinical signs in the same disorder can begin at a few months of age, or not until an older age. For example, in Leonberger dogs with inherited polyneuropathy, the age of onset can range from one to three years up to eight to nine years of age, although the disease tends to be more severe in the younger age group (Shelton, unpublished data). The onset of disease may be insidious and not be recognized for many years, which suggests false information regarding the course of disease. The dog may be considered to be ‘clumsy’, have unexplained orthopaedic injuries, or treatment of an ‘acquired’ disease may be unresponsive. Finally, inherited neuropathies are often painless and thus neurologic impairments may go unnoticed. The involvement of related animals may be incorrectly attributed to another cause. The critical assessment and correct identification of peripheral nerve disease may prevent unnecessary or harmful treatments. A good neurological evaluation can help to avoid misdiagnosis. There are reports of inherited polyneuropathies that affect other breeds of dogs and cats (26). Recently, laryngeal paralysis-polyneuropathy complex with concurrent megaesophagus was reported in young related Pyrenean Mountain Dogs (27). A distal sensorimotor polyneuropathy has been reported in mature Rottweiler dogs (28). Adult-onset breed-associated polyneuropathies also likely occur in the Italian Spimoni (3) and Bouvier des Flandres (Fig. 7) (29) dogs. A sensory neuropathy has been identified in young Border Collie dogs (30, 31). The underlying cause is not yet known for any of these neuropathies and specific mutations have not yet been identified.

**Discussion**

Our knowledge of the spectrum of inherited neuromuscular diseases in companion animals, and neuromuscular diseases in general, has widely expanded over the past 10 years (32) and will continue to do so. The importance of including neuromuscular diseases in the differential diagnosis in dogs with exercise intolerance and weakness, of astute clinicians reaching an accurate clinical assessment, and of pathologists trained in muscle and nerve diseases reaching a correct diagnosis, cannot be stressed enough. In the past, cases with chronic muscle atrophy, gait abnormalities, contractures, and weakness carried a poor prognosis as a diagnosis could rarely be made, and unless inflammatory, there were not any available treatments. It is still true that some muscle and peripheral nerve diseases are treatable, and that others are not. As the molecular basis of more muscle and peripheral nerve diseases becomes known, new treatment options may become available, and genetic testing procedures can be developed in order to eliminate inherited muscle and nerve diseases from breeding programs.

**References**


Correspondence to:
G. Diane Shelton DVM, PhD
Department of Pathology
University of California, San Diego
La Jolla, CA 92093–0709, USA
Phone: +1 858 534 1537, Fax: +1 858 534 0391
E-mail: gshelton@ucsd.edu