WSAVA Hereditary Disease Committee:

Canine Exercise Induced Collapse (EIC)
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Synonyms:
Exercise-induced hyperthermia, Exercise related weakness, dynamin-associated exercise-induced collapse (d-EIC)

Disease description:
Exercise intolerance and weakness is a clinical syndrome with a number of potential underlying causes. Dynamin associated exercise-induced collapse (d-EIC) is an autosomal recessive disease caused by a mutation in the dynamin 1 gene. (Patterson 2008) Dogs, best described in young adult Labrador Retrievers, homozygous for the mutation are at risk of exercise-induced hind limb weakness to collapse and death. Heterozygotes (carriers) do not show signs but can pass the mutant allele on to the next generation and thereby produce affected or carrier offspring. Though most apparent in Field Trial dogs, d-EIC has been documented in conformation, service and pet Labrador Retrievers with a 30-40% carrier rate within all sub-populations (Minor 2011). The d-EIC mutation has been found in Labradors from 46 states, and more than 15 countries to date. Labrador Retrievers are the predominant breed that is affected, but d-EIC has also been confirmed in some other breeds.

Genetic Basis/Mode of Inheritance: Gene name/abbreviation: Dynamin 1/ DNM1, c.767G>T mutation resulting in R256L, Autosomal Recessive. All dog breeds thus far recognized have the same mutation suggesting an ancestral origin (Minor 2011).

Etiology: Genetic, hereditary

Breed predilection: Labrador Retrievers mainly, but it is also found in and confirmed in other breeds, including Curly-Coated and Chesapeake Bay Retrievers, Boykin Spaniels, German Wirehaired Pointers and Pembroke Welsh Corgis (Minor 2011).

Age predilection:
Juvenile
Young adult

CLINICAL SIGNS

Signs usually begin between 6 months and 4 years of age in Labradors that have had 5 to 15 minutes of strenuous exercise such as quartering for upland game, retrieving birds, balls or Frisbee's and excited play with other dogs. Mild exercise and play do not induce crises. At first affected dogs develop weakness in the rear limbs and if exercise is continued, forelimb weakness and collapse may occur. **A few affected dogs have died during exercise or while resting immediately after an episode of severe exercise-induced collapse. Thus, an affected dog's exercise should ALWAYS be stopped at the first hint of incoordination or wobbliness.** During the collapse, the rear limbs are flaccid and patellar reflexes are often absent and there may be increased extensor tone to the front limbs. It is common for the signs to worsen for 3 to 5 minutes even after stoping exercise. Physical (including high body temperature), cardiovascular, neuromuscular, and pulmonary examinations are no different from those of unaffected dogs exercised in the same manner. Body temperature is often elevated in most dogs that exercise (108F [42C] or even higher). (Taylor 2009)

Not every exercise period will result in signs indicating that there are unidentified factors important in inducing an episode. Affected dogs do not appear to be in pain and remain conscious. They usually return to normal after resting for 5 to 25 minutes (Taylor 2008).

If weakness is noted during exercise, the exercise should be stopped and the dog should be allowed to rest because some dogs have died while exercising. Seizure activity was noted prior to death in some dogs.

DIAGNOSIS

The clinical diagnosis of D-EIC is based on the clinical description and ruling out other cardiovascular, metabolic, neurologic, and muscular causes of exercise related weakness and the diagnosis is confirmed by identifying the mutation in dynamin 1 gene. (Univerisity of Minnesota http://www.cvm.umn.edu/vdl/ourservices/canineneuromuscular/home.html). European testing is done by Laboklin http://www.laboklin.com/. Dynamins are protein molecules important for normal synaptic activity; defects can impair motor function and other functions. In recent studies, 97% of affected dogs were homozygous for the c.767G>T mutation. Nine per cent of dogs with no history of collapse were also homozygous, indicating these dogs may either have not been exposed to severe exercise conditions necessary to precipitate signs or there may be some other compensatory factors involved (Patterson 2008). Dogs can be tested by DNA test at any age by submitting a cheek swab or 1-2 mls of blood.

Clinical findings: Dogs with d-EIC are normal at rest. They are usually extremely fit and well muscled. Cardiovascular and respiratory examinations are unremarkable with normal auscultation, electrocardiograms, thoracic radiographs and cardiac ultrasound before exercise. Dogs susceptible to EIC develop signs within 20-60 min of exercising. After exercise and during a collapse, dogs are tachycardic and hyperthermic (often >42C), but notably not different from unaffected dogs exercised in the same manner. The

time it takes for dogs with EIC to return to their resting temperature after exercise is not different from normal healthy dogs without the mutant allele. These dogs are not lame and they do not have sore joints, muscles or bones before or after exercise. Nervous system examination including mentation are normal at rest, but patellar reflexes are diminished or absent in collapsing dogs with EIC. Routine blood analysis (CBC, serum biochemistry) is normal at rest and there are only minor changes following exercise when compared with normal exercising Labradors. Arterial blood gas analysis in the EIC and the normal Labrador Retrievers revealed severe respiratory alkalosis and metabolic acidemia post-exercise, reflecting hyperventilation and strenuous anaerobic activity. Similar results have been reported in Labrador Retrievers participating in field training and competition. Blood lactate and pyruvate concentrations after exercise are similar in EIC dogs and normal dogs, and muscle histopathology is normal, making an abnormality of oxidative metabolism unlikely (Taylor 2009).

Thyroid evaluation (T4, TSH) and adrenal function testing (ACTH stimulation) have been normal in the affected dogs.

Brain stem auditory evoked response (BAER) testing has also been determined to be normal in a few affected dogs.

PROGNOSIS

Clinical signs generally stabilize and some affected dogs seem to "get better" with maturity and aging, perhaps because their activity and excitement levels naturally decrease. Symptomatic dogs are, however, rarely able to continue training or competition. As long as intense exercise, excitement and training stress are avoided, they can live normal lives as pets. (Taylor 2009)

Clinical findings:

Ataxia ascending
ATAXIA, INCOORDINATION
Collapse of patient
Coma, unconsciousness
Exercise intolerant or reluctant to move
GAIT ABNORMAL
Gait choppy
Hindlimb paresis
Hindlimb weakness
Hyporeflexia
Malaise
Muscle weakness
Paraparesis
Patellar reflex absent
Spinal reflexes depressed
Walking difficulty
WEAKNESS

Treatment/Management/Prevention:
SPECIFIC
1) None known at current time.

SUPPORTIVE: There are anecdotal reports of dogs being able to resume trigger activities if they are managed with Phenobarbital (2mg/kg PO q 12h). Treatment with phenobarbital and other sedative drugs may simply decrease the level of excitement or anxiety associated with inducing an episode of collapse. Many affected dogs will seem to "get better", having less episodes of collapse as they age or when they are neutered. Some affected dogs have died during an episode of collapse--these dogs have not always been considered to be the most severely affected dogs (Taylor 2009).

GENETIC CONTROL:
1) Strongly discourage breeding of homozygous affected and carrier dogs with each other. Produce less carrier dogs in each successive generation (i.e. the breed and replace strategy) by breeding carriers with normal/clear animals.

2) Screen breeding individuals for the mutation.

Special considerations:
This disease can be distinguished clinically from myasthenia gravis by the fact that the clinical signs only occur during vigorous exercise and by having negative myasthenia gravis antibody titers.

EIC can be distinguished from malignant hyperthermia because dogs with collapse due to MH typically develop muscle contractions and rigid muscles (as opposed to flaccid ones with EIC) and extremely increased serum CK concentrations. Histologically muscles in dogs with MH show rhabdomyolysis (EIC dogs' muscles are normal). Dogs with MH often hypoventilate due to persistent muscular contraction so they are hypercarbic (whereas dogs with EIC hyperventilate).

Differential Diagnosis:
Polymyositis
Myasthenia gravis

Mitochrondrial myopathy

Epilepsy
Toxoplasma myositis

Heat Stroke
Orthopedic disease
Cardiac disease
Malignant hyperthermia

Human Disease Homolog: Online Mendelian Inheritance in Man - OMIM 602377/OMIA 001466-9615

Available Test/Testing Facility: Genetic Disease Testing Laboratory. University of Minnesota Veterinary Diagnostic Lab, 1333 Gortner Avenue, St. Paul MN 55108-1098, www.vdl.umn.edu, vdl@umn.edu.

Disclosure: Dr. Ned Patterson is a patent owner of the genetic test for d-EIC and co-director of the Canine Genomics Laboratory at the University of Minnesota.

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