Relationship between dynamin 1 mutation status and characteristics of recurrent episodes of exercise-induced collapse in Labrador Retrievers

Eva Furrow, VMD, DACVIM; Katie M. Minor, RN; Susan M. Taylor, DVM, DACVIM; James R. Mickelson, PhD; Edward E. Patterson, DVM, PhD, DACVIM

Objective—To identify characteristics of exercise-induced collapse in Labrador Retrievers and compare characteristics for dogs with various dynamin 1 gene (*DNM1*) mutation statuses.

Design—Retrospective cross-sectional study.

Animals—109 Labrador Retrievers with a history of recurrent exercise-induced collapse, clinically normal behavior and gait between episodes, and no reason for collapse identified via medical evaluation.

Procedures—Data were collected via surveys from owners of dogs that were tested for an autosomal recessive *DNM1* mutation causing *DNM1*-associated exercise-induced collapse (d-EIC). Dogs were identified as having d-EIC (homozygous for the mutation) or not having d-EIC (heterozygous for or without the mutation). Survey data were reviewed by an investigator unaware of the genotypes of dogs, and collapse characteristics were compared between groups.

Results—74 dogs had d-EIC; 35 dogs did not have d-EIC. Dogs with d-EIC were young (median age, 12 months) at the time of the first collapse episode; collapse in such dogs typically originated in the hind limbs and was characterized by low muscle tone, clinically normal mentation, and rapid recovery. Dogs without d-EIC were older (median age, 23 months) than dogs with d-EIC; such dogs had various characteristics of collapse that were not consistent with a single disease.

Conclusions and Clinical Relevance—Characteristics of exercised-induced collapse in Labrador Retrievers with various *DNM1* genotypes were identified in this study; findings may help distinguish dogs with d-EIC from those with other types of collapse conditions. Characteristics of collapse in Labrador Retrievers that were not homozygous for the *DNM1* mutation differed substantially among dogs and may have been attributable to multiple causes. (*J Am Vet Med Assoc* 2013;242:786–791)

The disorder EIC in Labrador Retrievers is characterized by episodic limb weakness, ataxia, and collapse induced by intense exercise and excitement in young adult, athletic dogs. Recovery is typically rapid, but severe episodes can result in death. Behavior, physical examination findings, and diagnostic test results are unremarkable between EIC episodes.[1,2] Until recently, a diagnosis of EIC in Labrador Retrievers was presumptive and made on the basis of a description of clinical signs consistent with EIC and an absence of signs of other identifiable diseases that cause exercise intolerance.[3]

Abbreviations

d-EIC	*DNM1*-associated exercise-induced collapse
DNM1	Dynamin 1 gene
EIC	Exercise-induced collapse

In 2008, a mutation in the gene encoding the dynamin 1 protein (ie, *DNM1*) was identified that has a strong, significant association with EIC in Labrador Retrievers.[4] This finding indicated a major molecular basis for EIC. Dynamin 1 belongs to a family of enzymes that catalyze hydrolysis of guanosine triphosphate and subsequently undergo conformational changes to form proteins that perform and affect various cellular processes. Dynamin 1 is expressed at synaptic terminal membranes in the CNS and is required for synaptic vesicle endocytosis and neurotransmission during sustained neuronal stimulation (eg, during strenuous exercise).[5] The *DNM1* mutation (Arg256Leu) identi-

From the Departments of Veterinary Clinical Sciences (Furrow, Minor, Patterson) and Veterinary Biosciences (Mickelson), College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108; and the Department of Small Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK S7N 5B4, Canada (Taylor). All work was performed at the College of Veterinary Medicine, University of Minnesota, Saint Paul, MN 55108.

Support for development of the dynamin 1 gene mutation test was provided by the AKC Canine Health Foundation. A portion of the proceeds of the test are returned to the AKC Canine Health Foundation. Drs. Mickelson, Patterson, and Taylor and Ms. Minor have the rights to US patent 8,178,l297 for the test, and a portion of the proceeds are royalties.

There were no external sources of funding for this study.

Presented as an oral presentation at the American College of Veterinary Internal Medicine Forum, Anaheim, Calif, June 2010 and as a poster presentation at the Conference for Advances in Canine and Feline Genomics and Inherited Diseases, Baltimore, September 2010.

Address correspondence to Dr. Furrow (furro004@umn.edu).

fied in Labrador Retrievers has an autosomal recessive mode of inheritance, resulting in clinical disease only in dogs homozygous for this gene mutation.[4] A DNA test for identification of the Arg256Leu *DNM1* mutation is commercially available and has been used by veterinarians to diagnose the associated disorder known as d-EIC in Labrador Retrievers.[6,a]

Although collapse during exercise in Labrador Retrievers is frequently attributable to homozygosity for the Arg256Leu *DNM1* mutation (d-EIC), some Labrador Retrievers that collapse during exercise do not have that mutation or are heterozygous for the mutation. As for dogs with d-EIC, dogs with recurrent collapse that are not homozygous for the *DNM1* mutation may be behaviorally normal and may have unremarkable results of clinical and gait examinations between episodes. In the study[4] in which the *DNM1* mutation was identified, 33 of the 211 (15.6%) Labrador Retrievers with a history of EIC did not have or were heterozygous for the mutation. The investigators in that study indicated the dogs with a history of EIC that were not homozygous for the *DNM1* mutation had collapse episodes that were not typical of those observed for dogs with d-EIC. Further discussion was not provided because complete descriptions of collapse episodes were not available for analysis. Results of a recent study[6] indicate as many as one-third of Labrador Retrievers tested for d-EIC that had at least 1 episode of collapse before they were 4 years old did not have or were heterozygous for the *DNM1* mutation. However, as for the other report,[4] a description of the collapse characteristics was not provided.

The primary objective of the study reported here was to identify characteristics of EIC in Labrador Retrievers and compare characteristics for dogs that are homozygous for the *DNM1* mutation with those for dogs that are not homozygous for the mutation. Our hypothesis was that dogs without or heterozygous for the *DNM1* mutation would have different characteristics of collapse versus those of dogs that were homozygous for the mutation (ie, dogs with d-EIC). Another objective of the study was to determine whether dogs with episodes of collapse that were not homozygous for the *DNM1* mutation had evidence of a distinct neuropathic or myopathic disease.

Materials and Methods

Animals—Labrador Retrievers tested for the Arg256Leu *DNM1* mutation at the University of Minnesota Veterinary Diagnostic Laboratory between July 2008 and September 2009 were identified via a medical records database search. The *DNM1* mutation testing was performed in accordance with a published[4] procedure. Owners of dogs were contacted if they had reported ≥ 1 episode of collapse for their dog on the test submission form and provided an e-mail or postal address. Owners were asked to complete and return a survey that was modified from a survey used in another study.[1] Surveys collected during a prior study[4] of EIC in dogs were also included. Inclusion criteria for dogs were a known *DNM1* genotype, ≥ 2 episodes of collapse, clinically normal behavior and gait between collapse episodes, clinical evaluation by a veterinarian who did not indicate a definitive reason for collapse, and a > 6-month history since the first collapse episode without signs of systemic disease. Dogs were excluded from the study if any collapse episodes had occurred while dogs were at rest (ie, collapse was not associated with exercise) or if collapse had been attributed to a diagnosis other than EIC, as determined by a veterinarian. Medical records were requested but not required for inclusion of dogs in the study.

Approval by the University of Minnesota Institutional Animal Care and Use Committee was not required because of the retrospective cross-sectional study design. Confidentiality of patient and owner information was maintained, and all University of Minnesota regulations for research in animals were followed.

Collection of data—Owner-completed surveys were reviewed by a veterinarian (EF) who was unaware of the *DNM1* genotypes of the dogs. Information regarding signalment (sex and age of dogs at the time of the first collapse episode) was collected from surveys. Previous medical conditions and medications administered were reviewed for determination of study inclusion or exclusion of dogs. Information for dogs with a history of seizures was recorded, but such dogs were not excluded unless the descriptions of collapse episodes were consistent with generalized seizures. Owner knowledge regarding EIC in other dogs that were related to their dog was recorded. Age and total number of collapse episodes of dogs were recorded, and the frequency of collapse episodes (number of collapse episodes/mo) was calculated for each dog. The activity of dogs during each episode of collapse was categorized as low (sleeping, sitting, or standing), moderate (walking), or high (running or swimming). Dogs were excluded from the study if any of the collapse episodes occurred during low activity because the objective of the study was to evaluate dogs that collapsed only during exercise.

Both open-ended and directed questions were included in owner surveys to obtain detailed descriptions of collapse episodes of dogs. Information was obtained regarding limb involvement during collapse episodes and included the limbs (forelimbs, hind limbs, or all limbs) that were affected first and whether dogs were able to ambulate on all limbs (incomplete collapse), able to ambulate only with forelimbs (hind limb collapse), or not able to ambulate (full collapse) during collapse. Muscle tone during collapse episodes was scored as high (ie, higher than clinically normal resting muscle tone), low (ie, lower than clinically normal resting muscle tone), both high and low (in any order during episodes), or clinically normal (ie, no recognized alteration in muscle tone). Owners were asked to describe the mentation of dogs during collapse episodes; owners typically responded with terms that had been suggested in the questionnaire (such as alert, disoriented, or unconscious). For analysis of mentation data, dogs were scored as having normal mentation (clinically normal or alert mentation) or abnormal mentation (all other responses). Time to recovery from collapse episodes (ie, time to a return to clinically normal status) was analyzed as an ordinal variable (< 30, 30 to 60, or > 60 minutes). Diagnostic test results were recorded, although availability of such information was not required for inclusion of dogs in the study.

Statistical analysis—Data were compared between dogs with d-EIC (ie, homozygous for the Arg256Leu *DNM1* mutation) and dogs without d-EIC (ie, dogs that did not have or were carriers [heterozygous] for the mutation). Data for all dogs were not available for some variables because not all owners responded to every survey question. A χ^2 test was used to analyze categorical variables. A 2-tailed Fisher exact test was used when the theoretical expectation for counts were low (< 5 for a given response). Median and range values were determined for continuous variables. Analyses were performed with a Wilcoxon signed rank test for data that was not normally distributed, and analyses were performed with a Welch's *t* test when variances in data between the 2 groups of dogs were unequal. Values of $P < 0.05$ were considered significant. Statistical software[b] was used for the analyses. Sensitivity and specificity for detection of d-EIC were calculated for survey responses that were significantly more common for dogs that were homozygous for the Arg256Leu *DNM1* mutation versus dogs that did not have or were heterozygous for that mutation. Positive and negative predictive values were determined for an assumed disease prevalence equal to that in the study population of dogs (68%).

Results

Survey response—Of the 377 surveys distributed to owners of Labrador Retrievers tested for the Arg256Leu *DNM1* mutation, 159 (42%) were returned. Surveys were also reviewed for an additional 143 Labrador Retrievers with EIC that had been included in another study.[4] In total, surveys for 302 Labrador Retrievers were reviewed. Of these 302 dogs, 193 were excluded from the study; 114 of these dogs had not been evaluated by a veterinarian for collapse episodes, 44 had only 1 episode of collapse, 19 had a < 6-month history since the first collapse episode, 3 collapsed during rest, and 13 had an alternate diagnosis (eg, cardiac disease, hypoglycemia, laryngeal paralysis, or vestibular disorders caused by otitis interna) to which collapse was attributed. Therefore, 109 dogs were included in the study; 74 of these dogs were homozygous for the *DNM1* mutation, and 35 were not homozygous for the mutation (26 dogs that did not have an allele with the mutation and 9 dogs that were heterozygous for the mutation).

Signalment and descriptive data—Signalment and descriptive data were summarized (**Table 1**). Sixty-three female and 46 male dogs were included in the study. Sex distribution was similar between dogs with d-EIC and those without d-EIC. However, there was a significantly ($P = 0.012$) higher percentage of sexually intact dogs in the group of dogs with d-EIC versus the group of dogs without d-EIC. Age at the time of the first collapse episode was significantly lower for dogs with d-EIC (median, 12 months; range, 5 to 58 months) than it was for dogs without d-EIC (median, 23 months; range, 5 to 86 months). The proportion of dogs that participated in hunt tests or field trials was similar between groups. Only 4 (4%) dogs had a history of recurrent, generalized seizures that were not temporally associated with collapse episodes; the percentage of dogs with seizures in each group was not significantly different. The proportion of dogs reported by owners to have relatives with a known history of collapse did not differ between groups.

Collapse episode characteristics—Characteristics of collapse episodes of dogs were summarized (**Table 2**). Activity level at the time of collapse was not significantly different between groups of dogs; > 90% of collapse episodes occurred during a high level of activity. Dogs with d-EIC were significantly ($P = 0.034$) more likely to have collapse of hind limbs first (68/74 [92%] dogs) versus dogs without d-EIC (19/35 [54%] dogs). Therefore, dogs without d-EIC had collapse of forelimbs first or collapsed in all (fore- and hind-) limbs simultaneously more often than dogs with d-EIC. The proportions of dogs in each group that had full collapse and those that had incomplete collapse were not significantly different. However, a significantly ($P < 0.001$) greater proportion of dogs with d-EIC only had collapse in hind limbs (31/73 [42%] dogs) versus dogs without d-EIC (2/34 [6%] dogs). A significantly ($P = 0.013$) greater proportion of dogs with d-EIC had low muscle tone during collapse (65/74 [88%]) versus dogs without d-EIC (16/35 [46%]). Dogs without d-EIC were significantly more likely to have high or clinically normal muscle tone during collapse episodes versus dogs with d-EIC. Less than 10% of owners detected both high and low muscle tone in dogs during a collapse episode, and no significant difference was detected between groups regarding this finding. No cerebellovestibular signs (intention tremors, nystagmus, or head tilt) were detected by owners; owners were not specifically asked if their dog had loss of balance. Fewer dogs with d-EIC had

Table 1—Signalment and descriptive data for 109 Labrador Retrievers with EIC that were homozygous for or not homozygous for the Arg256Leu *DNM1* mutation.

Variable	Homozygous	Not homozygous	*P* value
Sex			0.18
Male	28/74 (38)	18/35 (51)	
Female	46/74 (62)	17/35 (49)	
Sexually intact	20/59 (34)	3/31 (10)	0.012
Age at time of first collapse (mo)*	12 (5–58)	23 (5–86)	< 0.001
Hunt test or field trial participant	21/41 (51)	14/25 (56)	0.80
Recurrent generalized seizures (presumed idiopathic epilepsy)	3/74 (4)	1/34 (3)	1.00
Related dogs had collapse	18/70 (26)	4/32 (13)	0.19

Data are reported as number/total responses for group (%) unless otherwise specified. Values of $P < 0.05$ were considered significant. For some variables, data for all dogs were not available.
*Age of time of first collapse is reported as median (range) in months.

clinically abnormal mentation during collapse episodes (20%) versus dogs without d-EIC (58%). Clinically abnormal mentation was described as disorientation by owners of all except 3 dogs (2 dogs with d-EIC and 1 dog without d-EIC; owners reported that these dogs were unconscious during collapse episodes). Time to recovery from collapse episodes was similar between groups; most (> 70% in both groups) dogs recovered in < 30 minutes. Frequency of observed collapse episodes (0.14 episodes/mo for dogs with d-EIC; 0.13 episodes/mo for dogs without d-EIC) and total number of observed collapse episodes (median [range], 4 [2 to 50] for dogs with d-EIC and 5 [2 to 35] for dogs without d-EIC) were not significantly different between groups.

Sensitivity, specificity, and predictive values were calculated for the following variables that had been determined to be associated with d-EIC: hind limbs affected first, collapse limited to hind limbs, low muscle tone, and clinically normal mentation during collapse (**Table 3**). Three of these variables had high sensitivities for detection of d-EIC (hind limbs affected first, 92%; low muscle tone, 88%; and clinically normal mentation, 80%). However, these variables had low specificities for detection of d-EIC (hind limbs affected first, 46%; low muscle tone, 54%; and clinically normal mentation, 58%). A finding of collapse only in hind limbs had the highest specificity (94%) and positive predictive value (94%) for detection of d-EIC, although sensitivity was poor (42%) for this variable.

Data for dogs without d-EIC were evaluated to identify subgroups of dogs with similar characteristics of collapse episodes. Small numbers (3 to 5 dogs for various combinations of responses) of such dogs had identical responses for survey questions regarding characteristics of collapse episodes (Table 2), but characteristics for such dogs typically were not indicative of a distinct disease.

Medical evaluations—A complete physical examination was performed by a veterinarian for all dogs included in this study, and no reason for collapse was identified for any of the dogs. The number of diagnostic

Table 2—Characteristics of collapse episodes for the Labrador Retrievers in Table 1.

Variable	Homozygous	Not homozygous	*P* value for subgroup of variable	*P* value for all groups of variable
Activity level				0.083
High	72/74 (97)	31/35 (89)		
Moderate	2/74 (3)	4/35 (11)		
Limbs affected first				< 0.001
Forelimbs	2/74 (3)	7/35 (20)	0.005	
Hind limbs	68/74 (92)	19/35 (54)	0.034	
All limbs	4/74 (5)	9/35 (26)	0.006	
Extent of collapse				< 0.001
Full (all limbs)	26/73 (36)	19/34 (56)	0.15	
Hind limbs only	31/73 (42)	2/34 (6)	< 0.001	
Incomplete (ambulatory in all limbs)	16/73 (22)	13/34 (38)	0.16	
Muscle tone during collapse				< 0.001
Low	65/74 (88)	16/35 (46)	0.013	
High	1/74 (1)	7/35 (20)	0.001	
Low and high (in any order)	3/74 (4)	4/35 (11)	0.17	
Clinically normal	5/74 (7)	8/35 (23)	0.030	
Mentation during collapse				< 0.001
Clinically normal	57/71 (80)	14/33 (42)		
Clinically abnormal	14/71 (20)	19/33 (58)		
Time to recovery from collapse				0.87
< 30 min	53/74 (72)	26/34 (76)	0.88	
30–60 min	13/74 (18)	5/34 (15)	0.69	
> 60 min	8/74 (11)	3/34 (9)	0.73	

See Table 1 for key.

Table 3—Sensitivity, specificity, and positive and negative predictive values of collapse episode characteristics for detection of d-EIC for the Labrador Retrievers in Table 1.

Variable	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Hind limbs affected first	92	46	28	73
Collapse limited to hind limbs	42	94	94	43
Low muscle tone during collapse	88	54	80	68
Clinically normal mentation during collapse	80	58	80	58

Data are percentage values.
Only collapse episode characteristics that were significantly more common in dogs homozygous for the Arg256Leu *DNM1* mutation versus dogs that were not homozygous for that mutation are reported.

tests performed varied substantially among dogs. Only 84 owners provided medical records or reported information regarding diagnostic tests performed for dogs. The most commonly performed diagnostic test was serum or plasma biochemical analysis (54/84 [64%] dogs). The only clinically relevant findings for diagnostic tests were myoglobinuria (3 dogs without d-EIC) and dramatically elevated circulating creatine kinase activity (≥ 5,000 U/L; 2 dogs without d-EIC [one of these dogs also had myoglobinuria]).

Discussion

In the present study, owner-completed survey data for Labrador Retrievers with a history of recurrent collapse during exercise were analyzed on the basis of Arg256Leu *DNM1* mutation status. All dogs in this study had been evaluated by a veterinarian, and no other diseases were identified to which collapse episodes could be attributed. Only dogs with a > 6-month history since the first collapse episode that did not have evidence of systemic or progressive disease were included. One hundred nine Labrador Retrievers met the study inclusion criteria. Seventy-four (68%) dogs were homozygous for the *DNM1* mutation and therefore had d-EIC; 35 (32%) dogs did not have or were carriers (heterozygous) for the mutation. Results of this study indicated multiple characteristics of collapse that differed between these 2 groups of dogs. Dogs that were homozygous for the *DNM1* mutation had similar characteristics of collapse episodes; such characteristics may be used for determination of a clinical diagnosis of the neurologic collapse disorder, d-EIC.[6] In contrast, collapse episode characteristics varied among dogs that were not homozygous for the mutation, and no consistent clinical features could be identified among these dogs. The findings of the present study suggest that, although homozygosity for the *DNM1* mutation is the most common risk factor for EIC in otherwise clinically normal Labrador Retrievers, there are other causes of exercise intolerance and collapse in dogs of that breed.

The following characteristics were identified in > 80% of Labrador Retrievers with d-EIC in this study: first episode of collapse when dogs were < 2 years old, collapse originating in hind limbs with or without progression to forelimbs, low muscle tone in the affected limbs during collapse, clinically normal mentation during collapse, and rapid recovery (< 60 minutes) from collapse episodes. One characteristic that had a poor sensitivity (42%) but high specificity (94%) for identification of dogs with d-EIC was collapse of hind limbs only (such dogs could continue to move forward by use of forelimbs); 31 of 73 dogs with d-EIC for which results were available had this characteristic. Of the dogs without d-EIC, only 2 (1 dog without the *DNM1* mutation and 1 dog that was heterozygous for that mutation) had similar hind limb collapse during episodes.

The influence of heterozygosity for the Arg256Leu *DNM1* mutation on the characteristics of collapse could not be statistically evaluated in this study because only 9 dogs that were heterozygous for the mutation were included. However, the small number of heterozygous dogs that had collapse characteristics similar to those of dogs with d-EIC supported conclusions of other authors[6] that dogs that are carriers for the *DNM1* mutation are not susceptible to d-EIC related collapse.

In addition to determination of the clinical characteristics of d-EIC episodes in dogs, we evaluated data to identify disorders to which recurrent collapse in Labrador Retrievers without d-EIC could be attributed. Small numbers (3 to 5 dogs for various combinations of responses) of such dogs had identical responses for survey questions regarding characteristics of collapse episodes. However, most dogs in this group had at least 1 characteristic of collapse that was different from those of other dogs in the group. Thus, the group of dogs with collapse that were not homozygous for the *DNM1* mutation likely comprised dogs with various disorders.

More than half (58%) of dogs with recurrent collapse that were not homozygous for the *DNM1* mutation had abnormal mentation during collapse episodes, whereas dogs with d-EIC were typically alert and aware of their surroundings during such episodes. Altered mentation can be detected in animals during metabolic diseases, syncopal episodes, or brain diseases (eg, idiopathic epilepsy), whereas altered mentation is not associated with myopathies or peripheral neuropathies. Labrador Retrievers are predisposed to idiopathic epilepsy[7]; exercise, excitement, and hyperventilation can trigger seizures in epileptic humans,[8–10] and such variables may trigger seizures in epileptic dogs. No significant difference was detected in the rate of occurrence of seizures between dogs with d-EIC and those without d-EIC in this study; however, partial seizures in dogs may not be identified as seizures by owners or veterinarians.[11] Narcolepsy with cataplexy is also rarely reported for Labrador Retrievers; this disorder can be characterized by repeated episodes of collapse with rapid recovery, with clinically normal behavior and unremarkable clinical examination results between episodes.[12,13]

Differences were detected in signalment between groups of dogs in the present study. More sexually intact dogs were included in the d-EIC group versus the group of dogs that were not homozygous for the *DNM1* mutation. Dogs with d-EIC also had a younger age of onset of collapse versus dogs without d-EIC. The higher proportion of sexually intact dogs in the d-EIC group versus the group of dogs without d-EIC may have been due to the younger age of onset of collapse of dogs in this group because testing may have been conducted before neutering of these dogs.

Clinical aspects of EIC in Labrador Retrievers have been previously reported. Prior to the discovery of the *DNM1* mutation, results of a study[1] of 225 Labrador Retrievers that were clinically normal at rest but had collapse during exercise were reported. Those authors presumed that all of the dogs in the study had the same EIC condition. The most commonly detected clinical characteristics of collapse in dogs in that study[1] were similar to those identified in dogs in the present study; dogs typically remained alert and responsive and had paresis of hind limbs that progressed to collapse. Although most of the dogs in that other study[1] had these characteristics of collapse, nearly one-quarter (18% to 23%) had other characteristics of collapse, such as involvement of all 4 limbs simultaneously or abnormal

mentation during collapse. Although it was not possible to confirm which of the dogs in that other study[1] were homozygous for the *DNM1* mutation, we suspect, on the basis of results of the present study, that most of the dogs with atypical characteristics did not have d-EIC (ie, they were not homozygous for the *DNM1* mutation). Investigators of another study[2] determined clinical and metabolic variables in 14 Labrador Retrievers with collapse induced via a strenuous exercise protocol. Similar to the results of the present study and those of the other study,[1] those authors[2] reported that abnormalities were most pronounced in hind limbs of dogs and included a wide-based stance, ataxia, low muscle tone, and a crouched posture; 13 of the 14 dogs in that study were later confirmed to have d-EIC. Most of the dogs with d-EIC in that study[2] also had a loss of balance or fell to 1 side during collapse or recovery from collapse. Ataxia, a crouched posture, and loss of balance were not evaluated for dogs in the present study because owners without medical training were not expected to reliably identify these signs and differentiate them from other gait abnormalities.

The present study had several limitations. Descriptions of the clinical characteristics of dogs with d-EIC are widely available on a laboratory website for the *DNM1* test,[14] on other publicly accessible websites, and in journal and newsletter publications. This may have caused recall bias; owners may have responded to survey questions on the basis of information that they had read or heard, rather than on the basis of observations of their dogs. This type of bias could have falsely homogenized survey question responses. A strength of this study was that the primary investigator was unaware of the *DNM1* mutation status of the dogs and had not been involved in prior studies of EIC in dogs. Thus, bias in interpretation of responses was minimized and would have been similar for both groups of dogs in this study.

Ideally, descriptions of collapse episodes would have been obtained directly from veterinarians rather than via owner surveys in this study. Unfortunately, veterinarians rarely witnessed EIC episodes. Intentional induction of a collapse episode to facilitate medical evaluation can be dangerous or fatal for dogs. Veterinarians must often rely on owner recall and interpretation of characteristics of collapse episodes, unless an owner has videotaped an episode. We believe that the descriptions of collapse episodes provided by owners of dogs in this study, although potentially affected by bias, will be valuable for distinguishing dogs with d-EIC from those with other types of collapse.

Variability in medical evaluations among dogs is another limitation of this study. All dogs underwent a complete physical examination that was performed by a veterinarian who was trying to identify a cause of collapse; however, diagnostic tests varied among dogs. More stringent inclusion criteria, including availability of results of serum or plasma biochemical analyses, CBCs, thoracic radiography, and ECG, may have improved the study. Because of variability in diagnostic tests performed, we cannot eliminate the possibility that dogs with collapse secondary to an undetected metabolic or cardiac condition were inappropriately included in this study. We may have also excluded a small number of dogs with d-EIC because only dogs with episodes of collapse occurring during moderate to high levels of activity were included. Two dogs were excluded from the study because they only collapsed during low levels of activity; these dogs were homozygous for the *DNM1* mutation, but their observed collapse episodes were likely caused by a disorder other than d-EIC.

Results of the present study suggested that the clinical characteristics of collapse in Labrador Retrievers that are not homozygous for the Arg256Leu *DNM1* mutation differ from the characteristics of collapse in Labrador Retrievers that are homozygous for that mutation (ie, dogs with d-EIC). Findings of this study may help distinguish dogs with d-EIC from those with other types of recurrent EIC. The heterogenous characteristics of collapse among Labrador Retrievers that were not homozygous for the *DNM1* mutation suggested that multiple disorders may cause exercise intolerance in dogs of that breed.

a. Veterinary Diagnostic Laboratory, College of Veterinary Medicine, University of Minnesota, Saint Paul, Minn.
b. JMP Statistical Discovery Software, version 8, SAS Institute Inc, Cary, NC.

References

1. Taylor SM, Shmon CL, Shelton GD, et al. Exercise-induced collapse of Labrador Retrievers: survey results and preliminary investigation of heritability. *J Am Anim Hosp Assoc* 2008;44:295–301.
2. Taylor SM, Shmon CL, Adams VJ, et al. Evaluations of Labrador Retrievers with exercise-induced collapse, including response to a standardized strenuous exercise protocol. *J Am Anim Hosp Assoc* 2009;45:3–13.
3. New C, Cosford KM, Taylor SM. Exercise intolerance in retrievers. *Vet Med* 2010;105:64–74.
4. Patterson EE, Minor KM, Tchernatynskaia AV, et al. A canine *DNM1* mutation is highly associated with the syndrome of exercise-induced collapse. *Nat Genet* 2008;40:1235–1239.
5. Ferguson SM, Brasnjo G, Hayashi M, et al. A selective activity-dependent requirement for dynamin 1 in synaptic vesicle endocytosis. *Science* 2007;316:570–574.
6. Minor KM, Patterson EE, Keating MK, et al. Presence and impact of the exercise-induced collapse associated *DNM1* mutation in Labrador Retrievers and other breeds. *Vet J* 2011;189:214–219.
7. Jaggy A, Faissler D, Gaillard C, et al. Genetic aspects of idiopathic epilepsy in Labrador Retrievers. *J Small Anim Pract* 1998;39:275–280.
8. Ogunyemi AO, Gomez MR, Klass DW. Seizures induced by exercise. *Neurology* 1988;38:633–634.
9. Sturm JW, Fedi M, Berkovic SF, et al. Exercise-induced temporal lobe epilepsy. *Neurology* 2002;59:1246–1248.
10. Guaranha MSB, Garzon E, Buchpiguel CA, et al. Hyperventilation revisited: physiologic effects and efficacy on focal seizure activation in the era of video-EEG monitoring. *Epilepsia* 2005;46:69–75.
11. Berendt M, Gram L. Epilepsy and seizure classification in 63 dogs: a reappraisal of veterinary epilepsy terminology. *J Vet Intern Med* 1999;13:14–20.
12. Lin L, Faraco J, Li R. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 1999;98:365–376.
13. Tonokura M, Fujita K, Nishino S. Review of pathophysiology and clinical management of narcolepsy in dogs. *Vet Rec* 2007;161:375–380.
14. University of Minnesota Veterinary Diagnostic Laboratory. Exercise induced collapse. Available at: www.vdl.umn.edu/ourservices/canineneuromuscular/eic/home.htm. Accessed Oct 29, 2012.