Clinical features of dilated cardiomyopathy in Great Danes and results of a pedigree analysis: 17 cases (1990–2000)

Kathryn M. Meurs, DVM, PhD, DACVIM; Matthew W. Miller, DVM, MS, DACVIM; Nicola A. Wright, BS

Objective—To determine clinical features of dilated cardiomyopathy (DCM) in Great Danes and to determine whether DCM is familial in this breed.

Design—Retrospective study.

Animals—17 Great Danes with DCM.

Procedure—Medical records of Great Danes in which DCM was diagnosed on the basis of results of echocardiography (fractional shortening < 25%, end-systolic volume index > 30 ml/m^2 of body surface area) were reviewed. Pedigrees were obtained for affected animals, as well as for other Great Danes in which DCM had been diagnosed.

Results—Dilated cardiomyopathy appeared to be familial and was characterized by ventricular dilatation, congestive heart failure (left-sided or biventricular), and atrial fibrillation. Pedigree analysis suggested that DCM was inherited as an X-linked recessive trait, but the mode of inheritance could not be definitively identified.

Conclusions and Clinical Relevance—Results suggest that DCM may be an X-linked recessive trait in Great Danes. Thus, dogs with DCM probably should not be used for breeding, and female offspring of affected dogs should be used cautiously. Male offspring of affected females are at an increased risk of developing DCM and should be evaluated periodically for early signs of disease. Results of pedigree analysis were preliminary and should be used only as a guide for counseling breeders, rather than as a basis for making breeding decisions. (*J Am Vet Med Assoc* 2001;218:729–732)

Dilated cardiomyopathy (DCM) is a primary heart muscle disease characterized by ventricular dilatation and systolic dysfunction and is one of the most common acquired heart diseases in dogs.[1,2] Breeds predisposed to developing DCM include Cocker Spaniels, Dalmatians, Boxers, Doberman Pinschers, Newfoundlands, Portuguese Water Dogs, and Great Danes, among others.[3-10] Although the term DCM is used to describe similar myocardial diseases in each of these breeds, the etiopathogenesis, clinical and pathophysiologic abnormalities, response to treatment, and prognosis differ.[4,6,7,9,10]

The Great Dane reportedly is the second most common breed of dog with DCM.[11] However, little information on the clinical features of DCM in this breed and on potential causes has been published.[8,11] The purposes of the study reported here were to determine the clinical features of DCM in Great Danes and to determine whether DCM is familial in this breed.

From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210 (Meurs, Wright); and the Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843 (Miller).

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Criteria for Selection of Cases

Medical records of Great Danes examined at The Ohio State University College of Veterinary Medicine or at the Texas A&M University College of Veterinary Medicine between 1990 and 2000 in which DCM had been diagnosed were reviewed. Dogs were eligible for inclusion in the study only if results of a complete physical examination, electrocardiography, and echocardiography were available. A diagnosis of DCM was made if **fractional shortening (FS)** was < 25% and **end-systolic volume index (ESVI)** was > 30 ml/m^2 of body surface area.[12-14]

Procedures

Pedigree evaluation—Attempts were made to obtain pedigrees from owners of affected dogs included in the study, as well as from owners of other Great Danes in which DCM had been diagnosed. Owners were questioned about whether parents, siblings, and offspring of affected dogs had a history of cardiomyopathy and results of echocardiography, if echocardiography had been performed. Dogs in which DCM had been diagnosed at a veterinary hospital other than the 2 participating veterinary teaching hospitals were included in the pedigree analysis portion of the study but were not included in the analyses of clinical findings.

Pedigrees were assembled and examined for evidence of a specific mode of inheritance. Autosomal dominant, autosomal recessive, X-linked, and mitochondrial modes of inheritance were considered.[15] Autosomal dominant inheritance was defined as evidence of the disease in multiple generations, equal proportions of affected males and females, and male-to-male transmission, with the offspring of affected individuals having a 50% chance of expressing the disease. Autosomal recessive inheritance was defined as equal proportions of affected males and females with most affected individuals having clinically normal parents and with all offspring having the disease if both parents had the disease. X-linked recessive inheritance was defined as an absence of sire-to-male offspring transmission and a higher proportion of affected males than affected females, with all affected females having an affected sire and affected or carrier dam. X-linked dominant inheritance was defined as an absence of sire-to-male offspring transmission, with all female offspring

having the disease. Mitochondrial inheritance is maternal; thus, all affected individuals must have had an affected mother.

Results

Clinical evaluation—Seventeen Great Danes met the criteria for inclusion in the study. Age at the time DCM was diagnosed ranged from 1.5 to 8 years (mean ± SD, 4.8 ± 2.3 years; median, 5.0 years). One was a spayed female, 12 were castrated males, and 4 were sexually intact males.

The most common clinical abnormalities at the time DCM was diagnosed were coughing (8 dogs), exercise intolerance (6), and weight loss (5). The most common physical abnormalities at that time were a systolic left apical murmur (11 dogs), ascites (4), and a gallop rhythm (3).

Electrocardiographic abnormalities included atrial fibrillation (12 dogs) and ventricular premature complexes (3). Radiographic abnormalities included pulmonary edema (10 dogs), generalized cardiac enlargement (9), left atrial enlargement (4), and pleural effusion (2). Left ventricular systolic and diastolic diameters, determined by means of echocardiography, ranged from 4.0 to 9.4 cm (mean ± SD, 6.1 ± 1.3 cm; median, 6.1 cm) and from 5.0 to 11.1 cm (7.28 ± 1.49 cm; 7.38 cm), respectively. Left ventricular systolic and diastolic diameters indexed to body surface area (cm/m^2) ranged from 2.69 to 7.52 cm/m^2 (3.96 ± 1.2 cm/m^2; 3.53 cm/m^2) and from 3.3 to 8.9 cm/m^2 (4.6 ± 1.5 cm/m^2; 4.2 cm/m^2), respectively. Fractional shortening ranged from 8 to 23% (15 ± 4%; 15%). End-systolic volume index ranged from 108 to 564 ml/m^2 (219 ± 112 ml/m^2; 199 ml/m^2).

Pedigree evaluation—Pedigrees for 11 affected dogs (1 female, 10 males) were linked to a single family (**Fig 1**). Evaluation of the family pedigree excluded a mitochondrial mode of inheritance, because not all affected dogs had an affected mother. An autosomal dominant mode of inheritance was determined to be unlikely, because in 3 instances, 2 apparently unaffected parents produced affected offspring (dogs 17, 26, and 27). An autosomal recessive mode of inheritance was determined to be unlikely, because a high percentage of family members were affected, the trait did not skip generations, and affected individuals produced affected as well as unaffected offspring. Autosomal dominant and autosomal recessive modes of inheritance were also considered unlikely because of the very unequal sex distribution.

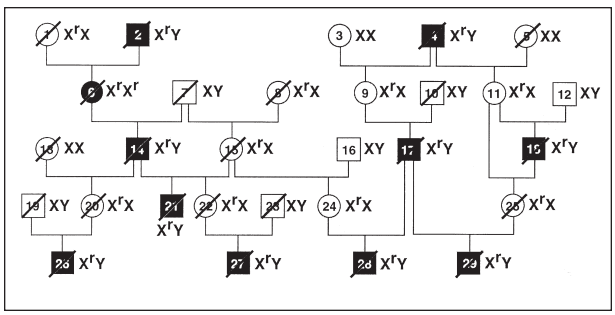

Figure 1—Pedigree of a family of Great Danes with familial dilated cardiomyopathy (DCM). Circles are female dogs; squares are male dogs. A solid black symbol denotes that the dog was known to have DCM. A solid white symbol denotes that the dog did not have a history of cardiac disease. A line through the symbol denotes that the dog had died. Results of echocardiography were not available for all dogs that died. The true genotype could not be determined, but presumed genotypes given an X-linked recessive mode of inheritance are indicated. XX = Unaffected female. XY = Unaffected male. X^rX = Carrier female. X^rY = Affected male. X^rX^r = Affected female.

An X-linked mode of inheritance was determined to be most likely because of the predominance of affected males. Several affected males (dogs 14, 17, 26, and 29) had dams that were descendants of affected male dogs and, therefore, could be carrier females. Initial evaluation of the pedigree provided some evidence of sire-to-male offspring transmission of the trait, which would have ruled out an X-linked mode of inheritance; however, in all instances, affected males were the offspring of females that could have been carriers, making it possible that affected males inherited the causative gene from the maternal side of the family. An X-linked dominant mode of inheritance could be excluded, because not all female offspring of affected males had the trait. Therefore, an X-linked recessive mode of inheritance appeared to be the most likely.

Discussion

Results of the present study suggested that DCM in Great Danes is characterized by adult-onset ventricular dilatation, congestive heart failure (left-sided or biventricular), and atrial fibrillation. Male dogs were overrepresented in the present study (16/17; 94%), and in a previous study of dogs with DCM,[8] 4 of 5 affected Great Danes were male. The prevalence of atrial fibrillation (12/17; 71%) in the present study was higher than that suggested for most other breeds of dogs with DCM.[5,6,11] This may be related to the large size of the atria in Great Danes; however, this percentage is higher than that reported for Newfoundlands (38%), another giant breed with DCM.

Dilated cardiomyopathy has previously been shown to be inherited in at least some breeds, including Doberman Pinschers, Boxers, and Portuguese Water Dogs.[9,16,17] Evaluation of pedigrees from affected Great Danes in the present study suggested a strong familial tendency and was suggestive of an X-linked mode of inheritance, although an autosomal recessive mode of inheritance could not be completely ruled out. The unequal sex distribution would be uncommon for an autosomal recessive trait, and an autosomal recessive mode of inheritance would imply that the predominance of affected male dogs was simply a matter of chance. There is always some degree of uncertainty in the evaluation of pedigrees in a retrospective manner, because it is impossible to know whether mature dogs that died of noncardiac disease would have eventually developed DCM. However, 9 of the dogs for which clinical data were lacking died at ≥ 8 years of age, and 1 additional dog was alive at 9 years of age. These ages are much greater than the mean and median ages of dogs in which DCM was diagnosed. A more accurate method of determining the mode of inheritance of familial diseases is to perform breeding studies with animals that have been clearly identified as affect-

ed or unaffected and following up the offspring for life to confirm development of disease or lack of it. Unfortunately, this type of study is expensive and time consuming when examining adult-onset diseases, because it may take 4 to 8 years before the appearance of disease, and it may take at least 3 generations to fully understand the inheritance. Useful information can, however, be gained from careful retrospective evaluation of available clinical data. This is, in fact, the way that familial diseases in humans are studied, because breeding studies are impossible.

The suggestion that DCM in Great Danes is familial and inherited as an X-linked recessive trait has 2 implications. First, this would imply that female offspring of affected dogs could be carriers of the trait and should be used cautiously, if at all, in breeding programs, because they could produce affected sons and carrier daughters. Second, male offspring of affected females would be at an increased risk of developing DCM and, therefore, should be periodically evaluated for early signs of disease. However, results of the present study are still preliminary and, therefore, should be used only as a guide for counseling breeders, rather than as a basis for making breeding decisions.

Results of the present study may help direct future studies into the cause of DCM in Great Danes. In humans, 5 subtypes of familial DCM have been identified.[18] Two of these subtypes have an autosomal mode of inheritance, including the classic form of DCM (ventricular dilatation and systolic dysfunction) and a form of DCM characterized by conduction defects (second- and third-degree atrioventricular block and bundle branch blocks). Two other subtypes have an autosomal recessive mode of inheritance, including one characterized by skeletal muscle involvement and one characterized by rapid progression and a poor prognosis. The fifth subtype has an X-linked recessive mode of inheritance. Genetic mutations in the actin, desmin, lamin, tafazzin, and dystrophin genes have been associated with development of these various subtypes of familial DCM in human beings.[19-24] In particular, mutations in the dystrophin gene have been implicated in the development of X-linked DCM in humans.[20] Thus, the possibility that DCM in Great Danes is a familial defect inherited as an X-linked recessive trait would suggest that evaluation of the dystrophin gene in affected dogs may be warranted.

Dilated cardiomyopathy in dogs is characterized by several general clinical abnormalities (eg, ventricular dilatation, decreased systolic function); however, there are many unique attributes that define DCM in each affected dog breed, including age of onset, sex predisposition, rate of progression, presence and type of arrhythmias, response to nutritional supplements, and tendency to die suddenly or develop congestive heart failure.[3-5,7-10,25] It is possible that these breed variations are a result of variations in the underlying causes that ultimately lead to development of DCM. In human beings, it has been suggested that at least 75 distinct diseases can lead to development of chamber dilatation and systolic dysfunction consistent with DCM. Dilated cardiomyopathy is likely the end result of a common pathway for a variety of cytotoxic, metabolic, immunologic, infectious (especially viral), and familial mechanisms.[26,27] Evaluation of affected animals of each breed with reference to environment, clinical abnormalities, and family history will help elucidate possible causes for the disease. Eventually, this information may be used to help guide therapeutic decisions and breeding recommendations.

One of the important limitations of this study is its retrospective nature. Because records were examined retrospectively, we were compelled to accept the medical diagnosis as it was given in the medical record. It is possible that for some of the dogs in this study the diagnosis could have been incorrect and the dogs could actually have had other congenital or acquired heart diseases that resulted in volume overload and mimicked the diagnosis of dilated cardiomyopathy. The severity of the systolic dysfunction in these dogs was more consistent with a primary myocardial disease, but without the benefit of histologic examination of cardiac tissues, it is impossible to know with certainty. Additionally, it is often difficult with retrospective studies to gain reliable information on response to treatment, survival time, and rate of progression, because data obtained are dependent on the owner's memory. Therefore, we did not attempt to evaluate these issues in the present study. Instead, we limited the information to items that had been evaluated during examination at the veterinary teaching hospital. It is hoped that future prospective studies would attempt to address additional issues about the cause and progression of DCM in Great Danes.

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Correction: Nonenteric *Escherichia coli* isolates from dogs: 674 cases (1990–1998)

In the article "Nonenteric *Escherichia coli* isolates from dogs: 674 cases (1990–1998)" (*J Am Vet Med Assoc*, Feb 1, 2001, pp 381–384), Dr. Thomas Burke was inadvertently identified as a diplomate of the American College of Veterinary Internal Medicine.