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Ventricular arrhythmias in Rhodesian Ridgebacks with a family history of sudden death and results of a pedigree analysis for potential inheritance patterns

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Abstract

Objective—To evaluate a group of related Rhodesian Ridgebacks with a family history of sudden death for the presence of arrhythmia and to identify possible patterns of disease inheritance among these dogs.

Design—Prospective case series and pedigree investigation.

Animals—25 Rhodesian Ridgebacks with shared bloodlines.

Procedures—Pedigrees of 4 young dogs (1 female and 3 males; age, 7 to 12 months) that died suddenly were evaluated, and owners of closely related dogs were asked to participate in the study. Dogs were evaluated by 24-hour Holter monitoring, standard ECG, echocardiography, or some combination of these to assess cardiac status. Necropsy reports, if available, were reviewed.

Results—31 close relatives of the 4 deceased dogs were Identified. Of 21 dogs available for examination, 8 (2 males and 6 females) had ventricular tachyarrhythmias (90 to 8,700 ventricular premature complexes [VPCs]/24 h). No dogs had clinical signs of cardiac disease reported. Echocardiographic or necropsy evaluation for 7 of 12 dogs deemed affected (ie, with frequent or complex VPCs or sudden death) did not identify structural lesions. Five of 6 screened parents of affected dogs had 0 to 5 VPCs/24 h (all singlets), consistent with a normal reading. Pedigree evaluation suggested an autosomal recessive pattern of inheritance, but autosomal dominant inheritance with incomplete penetrance could not be ruled out.

Conclusions and Clinical Relevance—Holter monitoring of Rhodesian Ridgebacks with a family history of an arrhythmia or sudden death is recommended for early diagnosis of disease. An autosomal recessive pattern of inheritance in the studied dogs was likely, and inbreeding should be strongly discouraged.

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Sudden death has been previously reported to be associated with ventricular arrhythmias in young German Shepherd Dogs and English Springer Spaniels.[1,2] In people, sudden cardiac arrest is a leading cause of deaths not attributed to external trauma in young individuals and is frequently the result of a genetic disorder that predisposes to life-threatening arrhythmias including ventricular tachycardia and ventricular fibrillation.[3] Cardiomyopathies, congenital heart diseases, and channelopathies are common causes of these arrhythmias in young people. These disorders can be Identified in the presence (eg, cardiomyopathies and congenital heart disease) or absence of structural heart disease.[4,5] A channelopathy such as long QT syndrome, a familial disorder characterized by ventricular arrhythmias with a prolonged QT interval, is an important example of a disease that can lead to sudden death in the absence of structural heart disease.[2]

To the authors' knowledge, there have been no reports of sudden death associated with arrhythmic disorders in Rhodesian Ridgebacks; however, we recently Identified 4 related young Rhodesian Ridgebacks that were reported to have died suddenly between 7 and 12 months of age. None had a history that suggested a systemic disease, traumatic injury, or other event likely to have caused death; thus, sudden cardiac arrest was suspected. The objective of the study reported here was to evaluate a group of related Rhodesian Ridgebacks for the presence of an arrhythmic disorder that could be associated with sudden cardiac death and to identify possible patterns of disease inheritance among these dogs.

Materials and Methods

Identification of cases

In February 2014, the authors were contacted by a Rhodesian Ridgeback breeder who was aware of the sudden deaths of 4 related Rhodesian Ridgebacks < 2 years of age. The subsequent investigation focused on identification of related dogs, evaluation of these dogs for the presence of functional cardiac abnormalities, and examination of pedigrees to determine potential modes of inheritance for these conditions. The study was conducted in accordance with the guidelines of the North Carolina State University Institutional Animal Care and Use Committee.

Procedures

Pedigrees of dogs that died suddenly were collected from the owners of these dogs. The records were analyzed to identify dogs that appeared in the pedigrees of > 1 of these deceased dogs. When available, necropsy reports of dogs that died were collected and evaluated for evidence of structural heart disease or other causes of death.

Owners of dogs that were closely related to the dogs that died suddenly (ie, siblings, parents, and grandparents) were contacted and asked to have their dogs clinically evaluated, which included completion of a questionnaire requesting information about any episodes of collapse and any family history of sudden death as well as a 24-hour Holter monitor evaluation as described.[6] Identified dogs resided in various parts of the country; Holter monitoring was performed with a monitor by one of the investigators (KMM) or by a commercial Holter monitoring company. All of the monitor data were interpreted by

retrospective data analysis.[a,b] Holter monitor data was evaluated for presence of abnormal pauses, bradyarrhythmias, or tachyarrhythmias that could be associated with a fatal cardiac event. The number of VPCs/24 hours and their complexity (eg, single, monomorphic VPCs [singlets]; bigeminy; trigeminy; couplets; triplets; R-on-T phenomenon; or ventricular tachycardia) were tabulated. If a ventricular arrhythmia was present, it was interpreted as a normal finding if there were < 50 VPCs/24 hours and all were single beats.[6] Echocardiographic information about myocardial size and function was obtained when possible.

Pedigrees were then examined to identify relationships among dogs with cardiac abnormalities and those Identified as having died suddenly. Possible modes of inheritance for the abnormalities and the potential relationships of these conditions with sudden death were assessed.

Results

The 4 young Rhodesian Ridgebacks that died suddenly included a female (age, 7 months) and 3 males (age, 7, 9, and 12 months). The 3 male dogs underwent necropsy examination, and no structural lesions or other abnormalities were detected that indicated a likely cause of the sudden death. Myocardial tissue from the 7-month-old male dog was tested by PCR assay for *Bartonella*, *Ehrlichia*, and *Rickettsia* infections with negative results. Examination of pedigrees revealed that the 4 dogs that died suddenly were linked to 2 distinct branches of 1 family, connected by 2 sibling dogs (a male and a female; Figure 1). Thirty-one related dogs were Identified, and 21 were available for evaluation. No other sudden deaths were Identified in the investigation.

Two of the 4 deceased dogs were littermates (a male and a female) that died suddenly within 11 days of each other; the male dog died while resting after exercise, and the female died while sleeping. Seven of 8 closely related dogs in this branch of the family (the dam and 6/6 littermates) were evaluated by 24-hour Holter monitoring. Three littermates (2 males and 1 female) were found to have frequent ventricular ectopy by Holter monitoring (1,240 VPCs/24 hours [singlets]; 5,335 VPCs/24 hours [singlets and couplets]; and 8,700 VPCs/24 hours [singlets with ventricular tachycardia]) at 8 months of age. The remaining 3 littermates (all males) had no VPCs identified on Holter monitoring at the same age. The dam was 6 years of age and had 90 VPCs/24 hours (singlets with ventricular tachycardia). Clinical signs associated with cardiac disease, including syncope or exercise intolerance, were not reported for any of the dogs, and no other abnormalities were reported. The dam, 1 affected male littermate, and 1 unaffected male littermate were available for echocardiography. All 3 dogs had appropriate cardiac size for the body size, normal left ventricular function, and an absence of structural lesions on echocardiographic examination. One adult female dog, a half-sibling to the dam of the affected puppies, had frequent VPCs identified by ECG; Holter monitoring was not performed, but approximately 5 to 6 VPCs/min were identified on 1-minute lead II ECGs at annual examinations from the time that arrhythmia was detected (2

[a]Trillium 5000 Holter recorder, Forest Medical, East Syracuse, NY.
[b]Alba Medical, Hyde Park, NY.

years of age) until the dog's death (not attributed to cardiac abnormality) at 13 years of age. This dog had undergone echocardiography at 2 years of age, with no structural lesions found, and did not develop clinical signs of cardiac disease. The sire of the dogs that died suddenly in this branch of the family was unavailable for evaluation.

The second branch of the family included the 2 male dogs that died suddenly at 9 and 12 months of age (Figure 1). One dog died while sleeping, and the other died shortly after a brief period of excitement associated with greeting its owner. Thirteen closely related dogs, including the parents of both deceased dogs and siblings (including littermates) of one, were evaluated by Holter monitoring. Three of these dogs (all females) were Identified as affected on the basis of frequent ventricular ectopy. These dogs had 803 VPCs/24 hours (singlets), 792 VPCs/24 hours (singlets with 1 triplet), and 3,913 VPCs/24 hours (singlets, couplets, triplets, and ventricular tachycardia) at 10, 27, and 13 months of age, respectively (Figure 2). Clinical signs consistent with cardiac disease, including syncope or exercise intolerance, and signs of other diseases were not reported for any of the dogs. Evaluated parents of affected dogs in this branch of the family ranged in age from 36 to 120 months and were deemed unaffected, with 0 to 5 (singlet) VPCs/24 hours. Echocardiography of 1 unaffected dog (the 36-month-old sire of one deceased male) and 1 affected dog (a 13-month-old female half-sibling to the other deceased male) revealed an appropriate cardiac size, normal left ventricular function, and an absence of structural lesions. One unaffected female with 0 VPCs detected was the dam of 2 affected dogs and the granddam of 3. Four of the 5 affected dogs in this branch of the family had 1 sire, an unaffected dog with 1 singlet VPC recorded in 24 hours, in common.

Overall, 12 dogs (7 females and 5 males) related by pedigree were Identified as affected with frequent ventricular ectopy (n = 8) or sudden death (4). On the basis of history, age, and familial associations of the 4 deceased dogs; evidence of ventricular ectopy in several dogs; and failure to identify another cause of death for the 3 dogs that were necropsied, these dogs were deemed likely to have died from sudden cardiac arrest. On the basis of pedigree analysis, the pattern of inheritance was most consistent with an autosomal recessive pattern, considering that both males and females appeared to be similarly affected and that multiple affected dogs with unaffected parents were Identified.[7] However, an autosomal dominant mode of inheritance with incomplete disease penetrance could not be completely ruled out.

Discussion

To the authors' knowledge, this is the first report of death attributed to sudden cardiac arrest and familial ventricular arrhythmias in Rhodesian Ridgebacks. Echocardiography (n = 4) or necropsy examination (3) of 7 of the 12 affected dogs did not identify any evidence of structural cardiac disease. Investigators have reported that approximately 30% of young human patients with sudden cardiac death do not have a structural cardiac lesion Identified.[8] Many such cases are eventually attributed to primary arrhythmic disorders that are often the result of an abnormality in a cardiac channel gene (eg, long and short QT syndrome and catecholaminergic polymorphic ventricular tachycardia).[3,4,8] The etiopathogenesis of the arrhythmia in the Rhodesian Ridgebacks of the present report remained unknown, but additional exploration to identify a genetic cause is warranted.

Pedigree evaluation of the dogs described in this report confirmed a familial relationship and suggested an autosomal recessive mode of inheritance for ventricular arrhythmias and the likely associated sudden deaths. Autosomal recessive traits are carried on autosomal chromosomes and are not generally evident unless an individual carries 2 copies of the genetic variant responsible for the trait (ie, is homozygous). An autosomal recessive mode of inheritance can be characterized by fairly equal distribution between sexes and the ability of phenotypically unaffected parents (heterozygous individuals carrying 1 copy of the genetic variant) to produce affected offspring. In our investigation, males and females appeared to be similarly affected and in 1 branch of the family, all 5 affected dogs (3 with frequent VPCs and 2 that died suddenly) had parents with 0 to 5 [singlet] VPCs identified in 24 hours, which was considered a normal finding[6] and suggested that the parents could be unaffected carriers of a genetic cause for ventricular arrhythmias. These findings were consistent with an autosomal recessive mode of inheritance; however, we could not rule out the possibility of an autosomal dominant trait with incomplete penetrance. In that scenario, the parents that were deemed phenotypically unaffected in this analysis would have had a mild form of the disease, which may have become less evident as they matured. Because none of the parents were evaluated by Holter monitoring or ECG at the age of the affected dogs of this report (which ranged from 7 to 27 months), we could not ascertain that that they did not have clinical evidence of disease at a younger age.

The 4 dogs in which sudden death was attributed to cardiac arrest died at 7 months to 1 year of age. The 8 living dogs Identified as having frequent ventricular ectopy ranged from 8 months to 10 years of age and were free of clinical signs, with what was considered relatively small numbers of VPCs in a 24-hour period. This variability of disease severity is consistent with the variability of disease penetrance and expression observed in human patients with familial arrhythmias.[9] Although the factors that impact variation in penetrance and expression are poorly understood, it is likely that other genetic factors as well as age and sex may be involved. Interestingly, in the family of dogs of this report, 3 of the 5 Identified affected male dogs died suddenly, whereas only 1 of the 7 Identified affected females died suddenly. This could suggest an influence of sex on the risk of sudden death; however, the numbers of dogs studied was very small and this finding could be attributable to chance alone.

This study had several limitations. First, 5 of the dogs Identified as affected (4 living with confirmed VPCs and 1 deceased) were not evaluated by echocardiography or necropsy; therefore, we could not completely rule out the presence of structural heart disease in some dogs. Second, although it appeared that many of the parents of these affected dogs were unaffected, we could not completely rule out that the parents expressed the disease at a younger age and that it was not apparent at the time of evaluation. Annual Holter monitoring of the remaining affected dogs might help to determine if the arrhythmia becomes less apparent with age. Finally, the study could not identify the mechanism that resulted in sudden death. The presence of the ventricular arrhythmias in a substantial proportion of the living dogs in this study (8/21 [38%] assessed by Holter monitoring, including 3 littermates of deceased dogs) suggested that the 4 young dogs identified at the start of the investigation developed ventricular fibrillation and died; however, cardiac arrhythmias or signs referable

to cardiac abnormalities had not been reported in any of these 4 dogs, so we cannot state this conclusively.

Our findings indicate that, even in the absence of clinical signs or physical examination abnormalities that suggest heart disease (eg, heart murmur), it may be worthwhile to consider Holter monitoring in Rhodesian Ridgebacks with a family history of an arrhythmia or sudden death. An autosomal recessive pattern of inheritance was considered likely, and inbreeding should be strongly discouraged.

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Abbreviations

VPC Ventricular premature complex

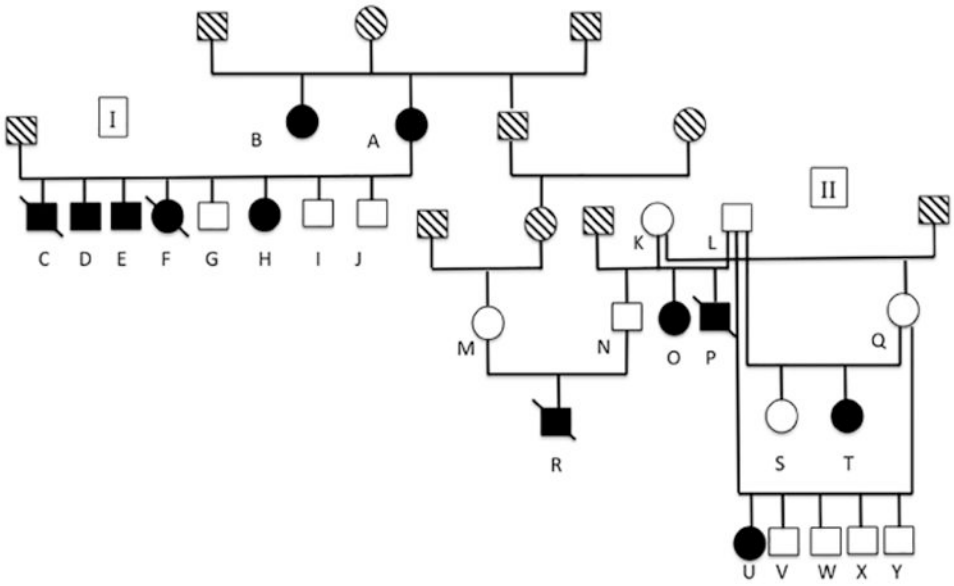

Figure 1.

Pedigree data for a family of Rhodesian Ridgebacks in which 4 young dogs (C, F, R, and P) had deaths attributed to sudden cardiac arrest. Circles indicate females, squares indicate males, and a single diagonal line though a symbol indicates death. Solid white symbols represent dogs that were deemed to have normal cardiac electrical function via 24-hour Holter monitoring (ie, unaffected); solid black symbols represent dogs Identified as affected (ie, those that had frequent or complex VPCs, or both, detected by 24-hour Holter monitoring [dogs A, D, E, H, O, T, and U] or by 1-minute ECG tracings [dog B] and the 4 dogs with sudden death). In addition to ECG or Holter monitoring, 6 dogs (A, B, E, J, N, and T) underwent echocardiography with no abnormalities Identified; 3 of the 4 dogs with sudden death (C, R, and P) underwent complete necropsy, and none had evidence of structural lesions or other abnormalities that indicated a cause of death. Diagonally shaded symbols represent dogs that were not available for evaluation and for which disease status was unknown.

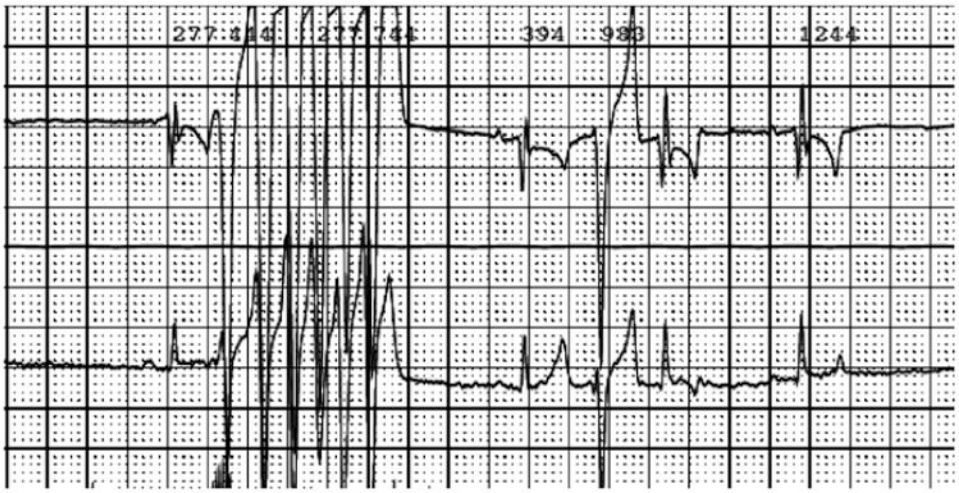

Figure 2.

Representative ECG tracings (leads II and III) obtained from a 13-month-old Rhodesian Ridgeback with VPCs. Notice the short run of ventricular tachycardia and a single VPC. Paper speed, 25 mm/s; 1 cm = 1 mV.