Cofactors associated with Sudden Acquired Retinal Degeneration Syndrome: 151 dogs within a reference population

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Abstract

Objective To determine factors associated with sudden acquired retinal degeneration syndrome (SARDS) diagnosed within one referral population.

Animals Studied 151 dogs diagnosed with SARDS.

Procedures Breed, age, sex, and body weight were compared between dogs with electroretinogram-confirmed SARDS and dogs presented to the UC Davis Veterinary Medical Teaching Hospital (UCD-VMTH) from 1991 to 2014.

Results SARDS was diagnosed in 151 dogs, representing 1.3% of dogs presented to the UCD-VMTH for ophthalmic disease. Although dogs of 36 breeds were affected, the Dachshund (n = 31, 21%), Schnauzer (16, 11%), Pug (11, 7%), and Brittany (5, 3%) were significantly overrepresented, and the Labrador Retriever (3, 2%) was significantly underrepresented vs. the reference population ($P < 0.001$). Median (range) age and body weight of affected vs. reference dogs were 8.9 (3–20) vs. 6.8 (0.1–26) years and 12.4 (2.8–52.7) vs. 22.3 (0.1–60) kg, respectively. Dogs 6–10 years of age and between 10–20 kg in body weight were significantly overrepresented in the SARDS population, while dogs <6 years of age were significantly underrepresented ($P < 0.01$). Spayed females (59% of affected dogs) were significantly overrepresented compared to the reference population, whereas intact females (1% of affected dogs) were significantly underrepresented.

Conclusions Consistent with previous studies, smaller, middle-aged, spayed female dogs may be at increased risk of developing SARDS. Unlike previous studies, this is the first study comparing a variety of SARDS-affected breeds to a reference population. Potentially increased risk of SARDS in several breeds, particularly Dachshunds, suggests a familial factor that warrants further investigation using genetic techniques.

Key Words: Brittany, Dachshund, electroretinogram, Pug, Schnauzer, sudden acquired retinal degeneration

INTRODUCTION

Sudden acquired retinal degeneration syndrome (SARDS) is a common cause of irreversible blindness in dogs. However, its etiopathogenesis is currently poorly defined and understood.[1–6] Dogs are usually presented with acute, bilateral blindness in the absence of marked funduscopic abnormalities, and the diagnosis is confirmed if an electroretinogram (ERG) reveals no recordable retinal activity.[1,4,7,8] Sudden acquired retinal degeneration syndrome is frequently diagnosed in middle-aged, spayed female dogs.[2,6,7,9] A wide range of concurrent systemic signs including polyuria, polydipsia, polyphagia; lethargy, or weight gain is also reported.[1,4,6–9] Serum biochemical abnormalities are often seen in dogs with SARDS and include elevated serum concentrations of alkaline phosphatase, alanine aminotransferase, and cholesterol. A stress leukogram and thrombocytosis are also reported but are inconsistent findings.[1,4,6–11] Currently, there are no peer-reviewed, placebo-controlled studies describing effective

treatment of dogs with SARDS. However, most owners report that affected pet dogs maintain a good quality of life.[4]

Histopathological evaluation of retinas from dogs with SARDS reveals apoptosis of rod and cone photoreceptors in approximately equal number.[12] The inner retina appears to be spared in the early stages of disease. Others have suggested that defects in the retinal ganglion cells cause subsequent damage to the nerve fiber layer.[10] There is also evidence that autoimmunity may be an important component of the disease with serum antiretinal or neuron-specific enolase antibodies detected in small numbers of dogs diagnosed with SARDS but not in healthy, unaffected dogs.[9,13] However, others have failed to identify antiretinal autoantibodies in SARDS-affected dogs.[3]

Several studies have shown that dogs of certain breed, sex, age, and weight may be predisposed to SARDS and that there may be some seasonality to disease occurrence.[1–4,6–9,14–17] However, to the authors' knowledge, no studies have compared a population of dogs affected by SARDS with a reference population to determine if such differences are significant. In addition, uniform inclusion criteria for the diagnosis of SARDS are sometimes lacking. Therefore, the purposes of this study were to provide epidemiologic data regarding a population of dogs diagnosed with SARDS at one institution over 23 years using consistent diagnostic criteria and to use data from the same hospital's general admissions as a reference population so as to develop evidence suggesting possible risk factors for this disease with a particular emphasis on breed.

MATERIALS AND METHODS

Medical record review

Medical records were searched for dogs diagnosed with SARDS at the UC Davis Veterinary Medical Teaching Hospital (UCD-VMTH) between April 1, 1991 and December 31, 2014. Entry criteria included examination and diagnosis by a board certified veterinary ophthalmologist or ophthalmology resident in training, sudden and complete vision loss, a completely extinguished ERG, and fundic examination findings inconsistent with the extent of vision loss. Dogs were excluded if they had ambiguous ERG results, notable regions of retinal degeneration evident on fundic examination, or intraocular abnormalities impeding adequate visualization of the ocular fundus. Color pupillometry may also be a helpful tool to diagnose dogs with SARDS[10]; however, color pupillometry was unavailable for testing dogs included in this study. For all dogs meeting entry criteria, the date of presentation, time from onset of blindness to presentation at UCD-VMTH, age at time of diagnosis, breed, gender, and neuter status were recorded. Date of presentation was used to assign season of presentation with winter defined as December through February, spring as March through May, summer as June through August, and fall as September through November. For the original and all follow-up visits, ophthalmic examination findings, signs of systemic disease, and results of all testing performed were also recorded for each dog. In particular, conjunctival hyperemia, episcleral injection, retinal vascular attenuation, and tapetal hyperreflectivity were marked as absent, mild, moderate, or severe.

Statistical analysis

The reference population against which the study population was compared comprised all dogs presented to the UCD-VMTH during the same period as dogs in the study population. Proportions of dogs by breed, sex, and weight, and by month, season, and year of presentation were each compared between the study and reference populations using Pearson's chi-squared test with Stata/IC 13.1 (StataCorp LP, College Station, Texas, USA). For all analyses, Standard and Miniature Dachshunds with short, long, or wire hair coats were grouped together under the category 'Dachshund', and Miniature, Standard and Giant Schnauzers were grouped together under the category 'Schnauzer'. The Kruskal–Wallis test was used to compare age and body weight between the study and reference populations. To compare ages between the study and reference populations, dogs were assigned to one of the following five groups: < 1, 1–5, 6–10, 11–15, or > 15 years of age. To compare body weights between populations, dogs were assigned to one of the following five groups: < 10, 10–20, 21–30, 31–40, or > 40 kg. Body weight was rounded to the nearest kilogram. To compare sex status between populations, dogs were assigned to one of the following four groups: intact male, neutered male, intact female, or spayed female. Dogs of unknown age, weight, or sex were excluded from the analyses for which data were missing. The presence of fundic abnormalities, such as retinal vascular attenuation and tapetal hyper-reflectivity, was also evaluated and compared to the onset of blindness using a Pearson's chi-squared test.[18] For all analyses, a P value of < 0.05 was considered significant.

RESULTS

Signalment

The entire hospital reference population comprised 470,362 dogs of 200 different breeds or of mixed breed. Of these dogs, 11,570 were presented to the UCD-VMTH Ophthalmology Service. A total of 151 dogs were diagnosed with SARDS during the 23-year study period, and comprised 0.03% of all dogs presented to the UCD-VMTH, and 1.3% of all dogs presented to the Ophthalmology Service. Dogs diagnosed with SARDS represented 36 breeds or were of mixed breed. Nine breeds were significantly overrepresented, and the Labrador retriever was significantly underrepresented in comparison to the reference population ($P < 0.001$; Table 1).

Table 1. Breed distribution for 151 dogs diagnosed with sudden acquired retinal degeneration syndrome (SARDS) at a single referral hospital between April 1, 1991 and December 30, 2014. The SARDS-affected population was compared with the 470,211 dogs presented to the same referral hospital during the same period and for which breed was recorded

Breed	Number of dogs with SARDS	Number of dogs in reference population	O:E ratio
Dachshund	31	11 747	8.16*
Mixed Breed Dog	29	116 151	0.78
Schnauzer	16	7 303	6.96*
Pug	11	4 811	7.33*
Brittany	5	2 205	7.14*
Cocker Spaniel	5	11 446	1.35
Golden Retriever	5	26 211	0.59
Lhasa Apso	4	2 982	4.00*
Pomeranian	3	3 754	2.50
Chihuahua	3	8 431	1.11
German Shepherd	3	17 861	0.53
Labrador Retriever	3	44 245	0.21*
Alaskan Malamute	2	1 436	4.00*
Shar Pei	2	2 274	2.86
Maltese	2	3 982	1.54
Australian Cattle Dog	2	3 918	1.54
Bichon Frise	2	3 032	1.53
Jack Russell Terrier	2	4 674	1.33
Poodle	2	5 635	1.11
Shih Tzu	2	6 521	0.95
Red Bone Hound	1	120	>10.00*
Bearded Collie	1	280	10.00*
Saluki	1	476	5.00*
Fox Terrier	1	742	5.00
Havanese	1	558	5.00
Papillon	1	692	5.00
Schipperke	1	703	5.00
Tibetan Terrier	1	1 063	3.33
American Eskimo Dog	1	1 084	3.33
Australian Shepherd	1	7 301	0.43
Scottish Terrier	1	1 797	1.67
Chow	1	1 901	1.67
West Highland White Terrier	1	3 063	1.00
Boston Terrier	1	4 022	0.77
Boxer	1	8 688	0.36
Yorkshire Terrier	1	6 949	0.45
Rottweiler	1	12 602	0.25
Other Pure-breed Dogs	0	129 580	0
TOTAL	**151**	**470 211**	

O:E = observed:expected.
*P,<,0.05.

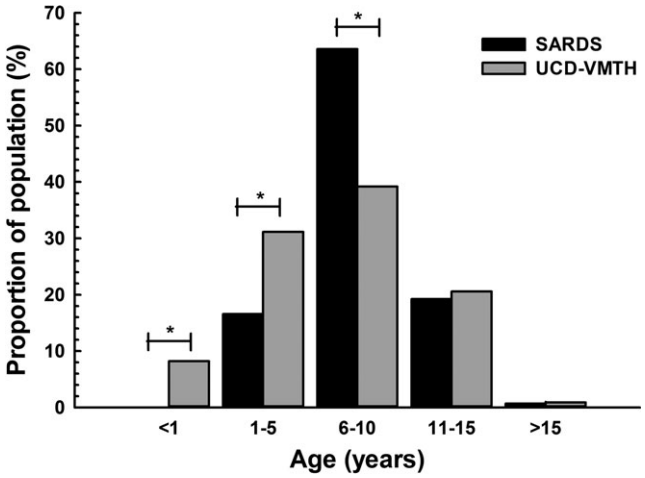

Figure 1. Age distribution of 151 dogs diagnosed with sudden acquired retinal degeneration syndrome (SARDS) at a single referral hospital between April 1, 1991 and December 30, 2014. The SARDS-affected population was compared with the 455 688 dogs presented to the same referral hospital during the same period and for which age or date of birth was recorded. *$P < 0.05$.

Median (range) age of affected dogs was 8.9 (3–20) years vs. 6.8 (0.1–26) years for the reference population with 64% of affected dogs being between 6 and 10 years of age at presentation. In the hospital reference population, 14,506 dogs did not have age or date of birth recorded in the medical record and these dogs were excluded from the age comparison; age data were available for all SARDS-affected dogs. Relative to the reference population, dogs 6–10 years of age were significantly overrepresented, and dogs < 6 years of age were significantly underrepresented in the SARDS population ($P < 0.001$; Fig. 1). Likewise, spayed females were significantly overrepresented, and intact females were significantly underrepresented in the SARDS population ($P = 0.002$; Fig. 2). In the hospital reference population, 939 dogs did not have sex recorded in the medical record and were excluded from the gender comparison; gender data were available for all SARDS-affected dogs. Median (range) body weight of affected dogs was 12.4 (2.9–52.7) kg vs. 22.3 (0.1–60) kg for the reference population. The distribution of body weights of SARDS-affected dogs were < 10 kg = 32%, 10–20 kg = 33%, 21–30 kg = 15%, 30–40 kg = 14%, and > 40 kg = 6%. Dogs between 10 and 20 kg were significantly overrepresented in the SARDS population ($P = 0.006$; Fig. 3). A total of 3,524 dogs in the reference population and 70 SARDS-affected dogs did not have their body weight recorded and were excluded from this analysis.

Dogs diagnosed with SARDS were presented in every month of the year. The most common month of presentation was August ($n = 19$; 13%), followed by April and September ($n = 17$; 11%), June and December ($n = 15$;

10%), October (n = 13; 9%), July (n = 10; 7%), May and November (n = 9; 6%), January (n = 8; 5%) and March (n = 6; 4%). Summer was the most common season of presentation (29.1%) followed by fall (25.8%), winter (23.8%), and spring (21.1%). A significant difference was not detected between the study and reference population for month (P = 0.1) or season (P = 0.6) of presentation.

History and concurrent disease

A total of 84 (56%) dogs diagnosed with SARDS had at least one of the following concurrent systemic signs: polyuria, polydipsia, polyphagia, lethargy, or weight gain; 11 (13%) of these dogs had all five clinical signs (Fig. 4). Fifty-five (37%) dogs had no clinical signs; data were not available for the remaining 12 dogs. Eight SARDS-affected dogs (5%) had been diagnosed with hyperadrenocorticism prior to the diagnosis of SARDS; and five of these were receiving lysodren (n = 2) or trilostane (n = 3). Twenty SARDS-affected dogs (13%) were diagnosed with hypothyroidism prior to the onset of SARDs, and 16 were receiving treatment with levothyroxine. Eight SARDS-affected dogs (5%) were receiving prednisone at presentation or had received prednisone within 1 week prior to diagnosis of SARDs. Prednisone was initiated in these dogs for immune-mediated thrombocytopenia (n = 1), allergic skin disease (n = 1), or reasons not stated in the patient history (n = 6). Five (3%) of the SARDS-affected dogs had a history of allergic skin disease at the time of SARDS diagnosis. In addition, SARDS-affected dogs were concurrently affected with seizures (n = 2), immune-mediated polyarthritis (n = 2), cardiac disease (n = 2), systemic hypertension (n = 2) or inflammatory bowel disease, renal disease, intermittent pancreatitis, lumbosacral disease, or hepatopathy (n = 1 each). No SARDS-affected dogs had concurrent diabetes mellitus.

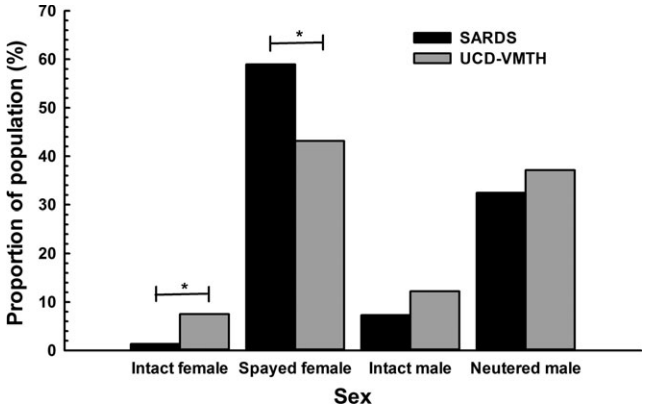

Figure 2. Gender distribution of 151 dogs diagnosed with sudden acquired retinal degeneration syndrome (SARDS) at a single referral hospital between April 1, 1991 and December 30, 2014. The SARDS-affected population was compared with the 469,264 dogs presented to the same referral hospital during the same period and for which gender was recorded. *P < 0.05.

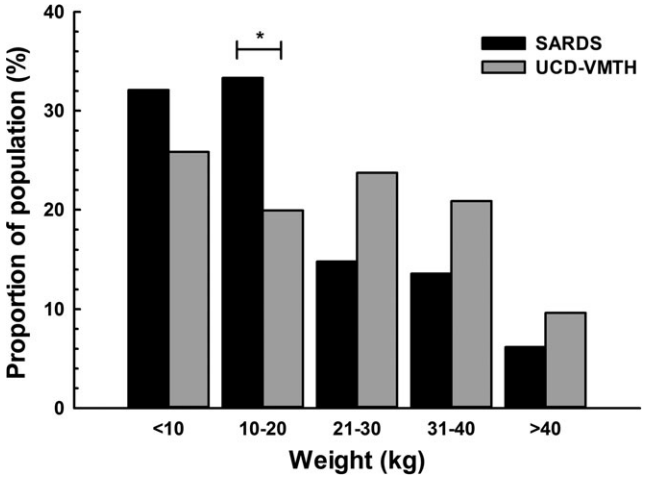

Figure 3. Body weight distribution of 81 dogs diagnosed with sudden acquired retinal degeneration syndrome (SARDS) at a single referral hospital between April 1, 1991 and December 30, 2014; body weight was not recorded for 70 SARDS-affected dogs. The SARDS-affected population was compared with the 295,148 dogs presented to the same referral hospital during the same period and for which body weight was recorded. *P < 0.05.

Ophthalmic signs

Median (range) time from onset of blindness to presentation was 17 (1-168) days in 149 SARDS-affected dogs; data were not available for the remaining 2 dogs. Of the 151 SARDS-affected dogs, 149 (99%) had absent menace response in both eyes and two (1%) had an equivocal response in one or both eyes at the time of presentation. A dazzle reflex was elicited in both eyes in 71 dogs (47%) and in one eye of 3 dogs (2%); 77 dogs (51%) did not demonstrate a dazzle reflex in either eye. Fifty-seven (38%) SARDS-affected dogs exhibited a normal pupillary

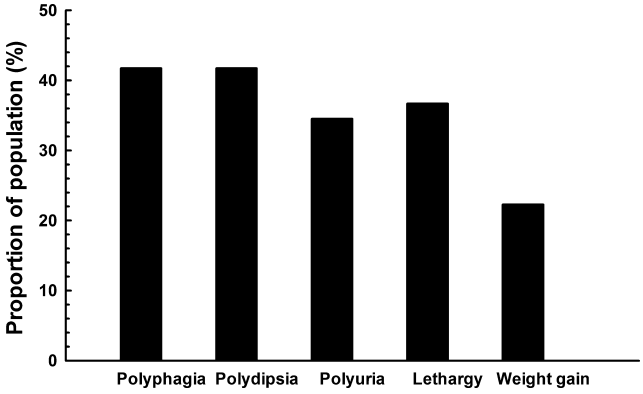

Figure 4. Proportion (%) of 139 dogs with sudden acquired retinal degeneration syndrome (SARDS) and in which one or more of polyphagia, polydipsia, polyuria, lethargy, and/or weight gain were reported; data were not available for 12 SARDS-affected dogs. All dogs were seen at a single referral hospital between April 1, 1991 and December 30, 2014 and were diagnosed with SARDS using consistent criteria.

light reflex (PLR), 84 (56%) of dogs had an incomplete PLR, and 10 (6%) of dogs did not demonstrate a PLR in either eye.

Conjunctival hyperemia was not observed in either eye of 103 dogs (68%). Bilateral conjunctival hyperemia was mild in 25 dogs (17%), moderate in nine dogs (6%), and severe in one dog. Unilateral hyperemia was detected in 13 dogs (9%) in which it was mild ($n = 11$) or moderate ($n = 2$). Episcleral injection was not observed in 114 (75%) of affected dogs. Bilateral episcleral injection was mild in 22 dogs (15%), moderate in eight dogs (5%), and severe in one dog (< 1%). Episcleral injection was unilateral in six dogs (4%) in which it was mild ($n = 5$) or moderate ($n = 1$).

Intraocular findings included cataracts, retinal vascular attenuation, tapetal hyper-reflectivity, and optic nerve head pallor. Cataracts were detected in neither eye of 81 dogs (54%), at least one eye of 20 dogs (13%), and in both eyes of 50 dogs (33%). The cataracts were primarily incipient ($n = 67$ dogs); however, early immature cataract was found bilaterally in two dogs (1%). Retinal vascular attenuation was considered mild in 32 dogs (21%) or moderate in one dog (1%); it was absent in the remaining 118 dogs. Tapetal reflectivity was normal in both eyes of 99 dogs (66%). Mild tapetal hyper-reflectivity was noted bilaterally in 41 dogs (27%) and unilaterally in 10 dogs (7%). Moderate tapetal hyper-reflectivity was noted bilaterally in one dog (< 1%). Bilateral optic nerve head pallor was noted in two dogs (1%). Tapetal hyper-reflectivity and/or retinal vascular attenuation was identified in 42 of 111 dogs (38%) presenting after ≤ 5 weeks of blindness vs. 23 of 34 dogs (68%) presenting after > 5 weeks of blindness; this difference was significant ($P = 0.002$).

Clinical pathology

Serum biochemical analysis was performed at the UCD-VMTH in 73 (48%) of SARDS-affected dogs. Elevated serum alkaline phosphatase, alanine transferase, gamma-glutamyltransferase, cholesterol, and blood urea nitrogen concentrations were relatively common findings in SARDS-affected dogs (Table 2). Creatinine was not elevated in any of the 73 SARDS-affected dogs where a serum biochemical analysis was performed. A complete blood count was performed in 71 (47%) of affected dogs. Eight (11%) of the dogs had an increased white blood cell count with a median (range) value of 18 000 (16 230–45 940)/μL (reference range: 6000–13 000/μL). The remaining values were unremarkable in the 71 SARDS-affected dogs in which a complete blood count was performed. A urinalysis was performed in 43 dogs (28%). Twenty dogs (47%) had concentrated urine (USG > 1030), 13 dogs (30%) had moderately concentrated urine (USG = 1.013–1.029), seven dogs (16%) had isosthenuria (USG = 1.009–1.012), and three dogs (7%) had hyposthenuria (USG ≤ 1.008).

Table 2. Median (range) serum concentration and number of dogs with elevated serum concentrations of alkaline phosphatase (ALP), alanine transferase (ALT), gamma-glutamyltransferase (GGT), cholesterol, and blood urea nitrogen (BUN). Data are from 73 SARDS- affected dogs presented to at a single referral hospital between April 1, 1991 and December 30, 2014 and for which data were available

Serum biochemical parameter	Median (range) elevated serum concentration in SARDS-affected dogs	Reference range and units of measurement	Number of SARDS-affected dogs with elevated serum concentration (% of the 73 dogs tested)
ALT	125 (73–401)	19–67 IU/L	35 (48%)
ALP	628 (173–3954)	21–170 IU/L	30 (41%)
GGT	9 (7–15)	0–5 IU/L	15 (21%)
Cholesterol	433 (364–570)	135–361 mg/dL	7 (10%)
BUN	39 (34–49)	11–33 mg/dL	4 (5%)

Endocrine testing was performed at the UCD-VMTH or by the referring veterinarian in 30 dogs (20%) and included an ACTH stimulation test ($n = 19$ dogs), low-dose dexamethasone suppression test ($n = 9$), or thyroid hormone testing ($n = 9$); more than one test was conducted in five (17%) dogs. The ACTH stimulation test results were consistent with a diagnosis of hyperadrenocorticism in two of 19 dogs (11%), not supportive of hyperadrenocorticism in 15 dogs (79%), and equivocal in two dogs (11%). Low-dose dexamethasone suppression test results supported a diagnosis of hyperadrenocorticism in three dogs and was unsupportive of ($n = 4$) or equivocal ($n = 2$) for hyperadrenocorticism in six dogs. Thyroid hormone testing included total thyroxine concentration only ($n = 6$), free thyroxine concentration only ($n = 1$), or a panel of tests which included total and free thyroxine and thyroid stimulating hormone ($n = 2$). Total thyroxine concentration was within normal limits in five dogs and decreased in one dog. Free thyroxine concentration was normal in the one dog tested. In the two dogs that had a thyroid panel performed, one panel was normal and the other was inconclusive.

Arterial blood pressure was recorded in 20 (13%) SARDS-affected dogs. Median (range) systolic arterial blood pressure in these dogs was 141.5 (95–230) mmHg. Fourteen dogs (66%) were normotensive (systolic blood pressure < 150 mmHg). Systolic blood pressure was between 150 and 159 mmHg in two dogs (10%), between 160 and 179 mmHg in three dogs (14%), and > 180 mmHg in one dog (5%).

Thirty-nine dogs (26%) underwent thoracic radiography ($n = 25$), abdominal ultrasonography ($n = 34$), or magnetic resonance imaging of the brain ($n = 6$). Thoracic radiographs were considered unremarkable in 19 of 25 (76%) dogs. Abnormal thoracic radiographic findings in the remaining six dogs included diffuse bronchointerstitial pattern ($n = 2$ dogs), increased cardiac silhouette ($n = 2$),

suspected collapsed lung lobe (n = 1), left atrial enlargement (n = 3), or pulmonary edema (n = 1). Results of abdominal ultrasonography were considered unremarkable in 12 of 34 (35%) dogs. Abnormal abdominal ultrasound findings in the remaining 22 dogs included hepatomegaly (n = 10 dogs), adrenomegaly (n = 4), splenomegaly (n = 3), splenic nodules (n = 3), urinary tract calcification (n = 2), renal disease (n = 2), or pancreatitis (n = 1). One patient that underwent magnetic resonance imaging of the brain had a chronic infarct in the rostral left thalamic region; the remaining five patients had unremarkable magnetic resonance imaging results.

Treatment and follow-up

Treatment for SARDS was initiated in two dogs (< 1%). Both dogs received prednisone (1 mg/kg PO BID); one dog also received doxycycline (5 mg/kg PO BID). Medications were prescribed for other systemic or ophthalmic conditions in 14 dogs (9%) including corneal ulceration or keratoconjunctivitis sicca (n = 3 each); anterior uveitis, otitis media, or severe dental disease (n = 2 each); or cough, joint disease, systemic hypertension, or suspected tick-borne disease (n = 1 each). Three dogs diagnosed with hyperadrenocorticism were started on therapy with lysodren (n = 2) or trilostane (n = 1). Levothyroxine was initiated in the dog with the low total thyroxine.

Seventeen dogs (11%) were presented to the UCD-VMTH for follow-up ophthalmic examination at a median (range) of 32 (7–1236) days following initial examination. Eleven dogs presented for recheck examination of other ocular conditions in addition to SARDS. Three dogs presented for recheck examination for SARDS exclusively, and three dogs were admitted to other services and had a recheck examination for SARDS while at the university. Owners of all 17 dogs reported that their dogs were doing well with nine owners specifically reporting that their dogs were adjusting well to vision loss. Fifteen of the seventeen dogs (88%) exhibited no systemic clinical signs at the time of follow-up examination. Four of the seventeen dogs (24%) had no systemic clinical signs at the time of the initial exam and in 11 of 17 dogs (65%) clinical signs had resolved at the follow-up exam. Ophthalmic findings on the follow-up examination were largely unchanged from those noted at initial presentation; the menace response was absent in all dogs, dazzle reflex was no longer present in two dogs (12%) in which it had been present at presentation, one dog that had normal PLRs on initial examination had absent PLRs on follow-up examination. The other dog that had slow and incomplete PLRs initially was judged to have a normal PLR on follow-up examination. In addition, one dog had developed incipient cataracts by the follow-up examination at 44 days. Retinal vascular attenuation had progressed from absent to mild in three dogs examined 23, 34, and 1,236 days, respectively after the initial examination, and from mild to moderate in one dog followed up 32 days after initial examination. Tapetal reflectivity progressed from normal to mild hyper-reflectivity in two dogs examined 35 and 44 days, respectively, after the initial examination.

DISCUSSION

To the authors' knowledge, the present study is the first to identify through direct comparison to a reference population from the same hospital multiple breeds that appear to be predisposed to SARDS and to quantify the magnitude of that predisposition. The present study is also the first to provide evidence that some dog breeds (specifically Labrador Retrievers) were significantly less likely to be diagnosed with SARDS. The present study confirms suggestions from previous studies that lacked reference populations that Dachshunds, Schnauzers, Pugs, and Brittanys are predisposed breeds.[2–4,6,8,14–17] These four breeds comprised 42% of the UCD-VMTH SARDS population and were approximately 7- to 8.5-fold overrepresented. Dachshunds alone in the present study accounted for 21% of the SARDS population, and this breed was eight-fold overrepresented when compared to the reference population. These findings are consistent with a previous study by van der Woerdt and colleagues in which Dachshunds comprised 22% of the SARDS-affected dogs vs. 1.6% in their reference population.[6] This information, in combination with data from previous studies, suggests that a heritable component for this disease may exist. Detailed pedigree analyses or genome-wide association studies should be performed in these breeds as they may elucidate etiopathogenic mechanisms, permit development of earlier diagnostic tests for SARDS, and inform breeding programs. Five other breeds overrepresented in the UCD-VMTH SARDS population (the Lhasa Apso, Alaskan Malamute, Bearded Collie, Red Bone Hound, and Saluki) had not been previously identified as predisposed. Only a single dog was diagnosed with SARDS for the Bearded Collie, Red Bone Hound, and Saluki, and only two for Alaskan Malamute suggesting that the statistically demonstrated association with SARDS is likely due to the relative paucity of individuals for these three breeds within the reference population (280, 120, 476, and 1436 dogs, respectively). Previous studies have suggested that the Bichon Frise, Maltese, American Cocker Spaniel, Pomeranian, and Shih Tzu are breeds commonly affected by SARDS.[4,8,17] Although at least two of each of these breeds were diagnosed with SARDS in the present study, none was significantly overrepresented in comparison to the reference population. Additionally, we determined that mixed-breed dogs comprised 19% of the SARDS population but were not significantly overrepresented when compared to the reference population. This highlights the value of comparing the study population against a reference population from the same geographic area. However, it is also possible that regional differences in breed popularity or genetics within breeds affect generalization of

findings from one location. Multicenter retrospective studies of SARDS across broad geographic areas and using large reference populations are recommended to better elucidate the relative risk of SARDS, especially in these five breeds (Bichon Frise, Maltese, American Cocker Spaniel, Pomeranian, and Shih Tzu).

Dogs in the present study were diagnosed with SARDS in all months of the year, and we were unable to demonstrate a seasonal distribution of onset based upon the presentation dates of affected dogs. This finding mirrors data from another study, but contrasts with observations from a second study in which the incidence of SARDS diagnosis was highest in December and January.[1,4] However, data from the present study did reveal apparent associations between the development of SARDS and body weight, age, and gender and neuter status. Specifically, dogs weighing 10–20 kg, 6–10 years of age and spayed females were overrepresented in the SARDS-affected population, while dogs < 6 years of age and female intact dogs were significantly underrepresented. These data may represent a causal relationship between SARDS and body weight, age, or gender, but more likely they may be confounded associations. For example, the body weight association may reflect the observation that predisposed breeds tend to be of lower body weight than nonpredisposed breeds. Likewise, it is possible that middle-aged dogs are not directly at more risk of being affected by SARDS, but are in an age group when endocrinopathies tend to develop spontaneously.[19] Similarly, although gender may be a direct causal factor with various sex hormones being involved in the development of SARDS, it is also possible that some adrenal sex hormones are exerting their effects via their glucocorticoid activity. For example, other studies have suggested that a female predisposition exists in the development of SARD[1,2,4,6,7,9,14,15] and shown that > 90% of SARDS-affected dogs have elevated 17-hydroxyprogesterone and progesterone.[7] The glucocorticoid activity of these sex hormones may explain the polyuria, polydipsia, polyphagia, panting, and weight gain commonly exhibited by SARDS-affected dogs. Indeed, a direct causal connection between SARDS and hyperadrenocorticism has been proposed due to the similar clinical signs and laboratory data seen in many dogs with SARDS and those with Cushing's disease.[1,2,5–9,11,14] Likewise, an association between hypertension and SARDS has also been proposed as 40% of SARDS-affected dogs in one study were considered hypertensive.[7] Again, it is unclear whether this represents a direct causal relationship because hyperadrenocorticism can be associated with hypertension. In the current study, four of 20 SARDS-affected dogs (30%) that had blood pressure recorded were hypertensive with systolic arterial blood pressure measuring greater than 160 mmHg,[20] and five dogs were definitively diagnosed with hyperadrenocorticism by either a low-dose dexamethasone test or an ACTH stimulation test. However, relatively few dogs in the present study were tested for hyperadrenocorticism and had blood pressure measurements taken, and this study may underreport SARDS-affected dogs with coincident hyperadrenocorticism or hypertension. Taken together, data from the present and previous studies suggest that dogs newly diagnosed with SARDS should have blood pressure measured and, if the patient exhibits clinical signs suggestive of hyperadrenocorticism, appropriate hormonal testing should be performed.

In the present study, tapetal hyper-reflectivity and/or retinal vascular attenuation was identified in 38% of dogs presenting with a 5 week or less history of blindness compared to 68% of dogs with a greater than 5-week history of blindness. This observation suggests that clinical signs of mild retinal degeneration can be observed in the majority of SARDS with a greater than 5-week history of blindness and is consistent with a previous study where similar fundic lesions were identified.[8] Similarly, conjunctival hyperemia was identified in 32% of dogs in the present study consistent with a previous study where 27% of SARDS patients presented with this clinical finding.[8] While conjunctival hyperemia is a nonspecific sign that can accompany many ocular pathologies, it was identified significantly more commonly in SARDS vs. optic neuritis affected patients in a previous study.[8] In aggregate, subtle fundic lesions and/or conjunctival hyperemia in acutely blind patients may be associated with SARDS but an ERG is still recommended to definitively diagnose SARDS and rule out neurologic causes of acute blindness.

Sudden acquired retinal degeneration of dogs and cancer-associated retinopathy (CAR) and autoimmune retinopathy of humans share many features such as acute onset of blindness, extinguished ERG, and a lack of marked funduscopic abnormalities.[21–33] Additionally, autoimmune retinopathy and SARDS more commonly manifest in females than in males.[22,24,26,27,34,35] However, some contrasts are also evident. For example, CAR is a paraneoplastic syndrome whereas concurrent neoplasia was not diagnosed in any dogs in the present study; however, only 26% of SARDS-affected dogs had diagnostic imaging performed.[34,36–39] This is supported by data from other studies which reveal that 0.8% of dogs with SARDS had neoplasia, which is similar to the prevalence of neoplasia reported for a general canine population, and SARDS-affected dogs do not show evidence of neoplasia on diagnostic imaging nor do they demonstrate specific retinal protein-antibody interactions.[2,8,40] Taken together, data from the present and previous studies do not support a causal association between neoplasia and SARDS in dogs, as is the case for CAR.

In conclusion, we provide evidence that spayed female dogs, dogs between 6 and 10 years of age, dogs weighing 10–20 kg, and dogs of four breeds (Dachshunds, Pugs, Brittanys, and Schnauzers) may be more likely to develop SARDS, whereas intact female dogs, Labrador Retrievers and dogs less than 6 years of age may be less likely to develop SARDS than dogs in our reference population.

Although previous studies have identified similar findings, this is the first study comparing a variety of SARDS-affected breeds to a reference population. Identifying at-risk breeds is a step toward future studies to help determine the underlying mechanisms that cause SARDS. Furthermore, a thorough history, physical and ophthalmic examination and complete diagnostic workup should be performed to definitively diagnose SARDS, assess for other diseases, and to ensure accurate genotypic and phenotypic data for these future studies.

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