Risk factors for development of dysautonomia in dogs

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Objective—To identify risk factors associated with dysautonomia in dogs.

Design—Case-control study.

Animals—42 dogs with dysautonomia examined between October 1988 and January 2000 and 132 control dogs examined during the same period for an unrelated problem.

Procedure—Information was gathered from medical records and surveys mailed to owners of case and control dogs.

Results—42 case and 132 control dogs were included; completed surveys were returned by owners of 30 case and 103 control dogs. Dogs with dysautonomia were significantly younger (median, 18 months) than control dogs (median, 60 months) and more likely to come from rural areas and to spend ≥ 50% of their time outdoors. Compared with rural control dogs that spent at least some time outdoors, affected dogs were more likely to have access to pasture land, farm ponds, and cattle, and to have consumed wildlife, at least occasionally. The largest numbers of dogs with dysautonomia were identified during February and April, with relatively few dogs identified during the summer and early fall.

Conclusion and Clinical Relevance—Although the cause of dysautonomia is unknown, results suggest that dogs with dysautonomia were significantly more likely to live in rural areas and spend ≥ 50% of their time outdoors than were control dogs examined for unrelated diseases. (*J Am Vet Med Assoc* 2001;218:1285–1290)

Dysautonomia was first identified in horses in Scotland early in the twentieth century.[1] Local residents attributed the disease to certain pastures and observed that horses placed on those pastures at certain times of the year were at increased risk of developing dysautonomia, giving the disease its common name, "grass sickness." A similar, if not identical disease, mal seco, has been recognized in South American horses since at least the mid 1950s.[2] Dysautonomia was not identified in other domestic animals until 1982, when it was first described in cats.[3] The first description of dysautonomia in a dog was published in 1983.[4]

Several hundred cases of dysautonomia involving cats across Europe have been reported,[5] with a peak in prevalence between 1982 and 1986.[6] Several case reports describing dysautonomia in European dogs have also been published,[7-9] but the disease appears to be less common in dogs than in cats in Europe.

Clinical abnormalities in dogs with dysautonomia typically include an acute onset of signs relating to loss of autonomic nervous function. Vomiting and regurgitation are often the first signs prompting owners to have their dogs examined. Most dogs also develop dysuria, dry mucous membranes, and decreased anal sphincter tone.[10] Ocular abnormalities usually include elevated third eyelids and mydriatic nonresponsive pupils. Most dogs with dysautonomia become progressively ill and are euthanatized within a few days after initial examination. Megaesophagus is a frequent gross finding at necropsy and is occasionally accompanied by aspiration pneumonia. Histologic evaluation of autonomic ganglia from affected dogs consistently reveals degenerative changes.[10,11]

Despite the large number of reported cases, the cause of dysautonomia in animals is still unknown. In a previous case-control study, Wood et al[12] found that young horses grazing on pastures where grass sickness had recently occurred and those that had been moved to a new pasture in the previous 2 weeks were at increased risk for developing dysautonomia. The purpose of the study reported here was to determine risk factors for dysautonomia in dogs. The study was constructed as a case-control study, and factors related to signalment, home environment, geographic location, and preventive veterinary care were investigated.

Materials and Methods

Selection of case dogs—Records of the University of Missouri veterinary teaching hospital and the University of Missouri diagnostic laboratory were searched to identify dogs in which a diagnosis of dysautonomia was made between October 1988 and January 2000. Dogs were considered to have dysautonomia if they had at least 4 of the following 6 signs: dysuria with distention of the urinary bladder; mydriasis or midrange pupils without a pupillary light reflex; elevation of the third eyelids; dry mucous membranes; dysphagia, regurgitation, or vomiting; and decreased anal reflex. If fixed tissues were available, histologic evidence of autonomic degeneration was also required. Lesions considered consistent with a diagnosis of dysautonomia included a loss of nerve cell bodies resulting in reduced neuron density in multiple autonomic ganglia, along with various degrees of gliosis and minimal or no inflammation. Pharmacologic testing was not required; however, if pharmacologic testing was carried out, results had to be consistent with those expected for dogs with dysautonomia.[10] Briefly, dogs with dysautonomia are expected to develop miosis in response to ocular instillation of 1 to 2 drops of a dilute (0.05 to 0.1%) pilocarpine solution

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(clinically normal dogs do not typically respond to pilocarpine solutions this dilute, although some can respond within 45 to 60 minutes) and are expected to show an improved ability to urinate in response to SC administration of a low dose of bethanechol (0.04 mg/kg [0.018 mg/lb] of body weight). Although neither of these pharmacologic tests is specific for dysautonomia, positive responses are suggestive of denervation hypersensitivity and rule out an inability to contract the iris and detrusor muscles.

Selection of control dogs—Three control dogs were selected for each case dog included in the study. Control dogs were selected by use of a random number generator from among all dogs referred to the University of Missouri veterinary teaching hospital during the study period for examination of a problem unrelated to dysautonomia. Control and case dogs were matched with respect to year of examination at the veterinary teaching hospital.

Data collection—Signalment, including month of examination, age, sex, and breed, was obtained from the medical records. Populations of towns where owners of case and control dogs resided were obtained from the 1990 US census data. A survey was mailed to owners of case and control dogs soliciting information on lifestyles of the dogs, exposure to various environmental factors, and previous veterinary care. Surveys were mailed with a cover letter and self-addressed stamped return envelope. Individuals who had not responded after 30 days were sent a second copy of the survey with a reminder letter.

Data analysis—Histogram analysis was used to determine whether results for continuous variables were normally distributed. Normally distributed variables were summarized as mean ± SD; continuous variables that were not normally distributed were summarized as median and **interquartile range** (**IQR**; 25th to 75th percentile).

Because many case dogs were found to live in rural areas and to spend at least part of their time outdoors, values for case dogs were compared with values for all control dogs and with values for a subset of control dogs that lived in rural areas and spent at least some time outdoors. Body weights of the case dogs and the rural subset of the control dogs were approximately normally distributed and were compared by use of a 2-tailed unpaired *t*-test. Town populations, body weights of the overall control group, and ages of the case and control dogs were not normally distributed, and the Mann-Whitney rank sum test was used to compare values between case and control dogs. The χ^2 test was used to test for differences in proportions of individuals exposed to various risk factors; analyses with 1 *df* were performed with the Yates correction for continuity.[13] Unadjusted **odds ratios (OR)** and **95% confidence intervals (95% CI)** were calculated for individual risk factors. Statistical calculations were performed with commercially available software.[a,b] For all analyses, values of $P < 0.05$ were considered significant.

Results

Forty-four case and 132 control dogs were initially considered for inclusion in the study. However, 2 case dogs were removed, because clinical examination and histologic findings were inconsistent with the case definition. Thirty-two control dogs were included in the rural subset of control dogs. Detailed information on 11 of the case dogs has been published previously.[10]

Valid addresses were available for owners of 33 of the 42 case dogs and 116 of the 132 control dogs. Owners of 30 of the 33 case dogs and 103 of the 116 control dogs that received surveys completed and returned them.

Signalment—Age of the case dogs at the time of initial examination ranged from 3 months to 12 years (age of 1 case dog was not recorded). The age distribution was highly skewed, and median age of the case dogs (median, 18 months; IQR, 10.5 to 48.3 months) was significantly less than median age of all control dogs (median, 60 months; IQR, 24.5 to 103 months; n = 131; $P < 0.001$) and median age of the rural subset of control dogs (median, 60 months; IQR, 23 to 85 months; n = 32; $P = 0.009$).

Mean body weight of the case dogs (mean ± SD, 20.6 ± 9.4 kg [46.1 ± 21.1 lb]; n = 34) was significantly ($P = 0.044$) less than mean weight of the rural subset of control dogs (27.3 ± 15.9 kg [61.2 ± 35.7 lb]; n = 27). Body weight of the overall control group had a bimodal distribution, with a median weight of 20.3 kg (45.5 lb; IQR, 7.6 to 29.7 kg [17 to 66.5 lb]; n = 100). Median body weight of the case dogs was not significantly ($P = 0.933$) different from median body weight of all control dogs.

Twenty-two case dogs were female (11 spayed) and 20 were male (7 castrated). Sixty-seven control dogs were female (52 spayed) and 65 were male (28 castrated). For the rural subset of the control group, 12 were female (8 spayed) and 20 were male (6 castrated). Sex distribution of the case dogs was not significantly different from sex distribution of all control dogs or of the rural subset of the control dogs.

Case dogs represented a wide variety of breeds, with Labrador Retrievers the most common (9/42 [21%]). Labrador Retrievers were over-represented in the case group, compared with the overall control group (11/132 [8%]; $P = 0.041$), but not compared with the rural subset of the control group (4/32 [13%]; $P = 0.489$). None of the case dogs were toy breeds, whereas 19 of the 132 (14%) control dogs were. Toy breeds were significantly ($P = 0.020$) over-represented in the overall control group but not in the rural subset of the control group (2/32 [6%]; $P = 0.184$).

Clinical findings—Clinical abnormalities in dogs with dysautonomia were similar to those reported previously.[10] Fixed tissues were available from 35 case dogs and revealed typical histologic abnormalities. Pharmacologic testing had been performed in 4 of the case dogs that did not have fixed tissues available for examination.

Seasonal and annual distribution—Only 1 dog with dysautonomia was identified during 1988, 1991, and 1993. The number of dogs identified with the disease then increased dramatically (**Fig 1**). Dogs with dysautonomia were identified during every month of the year; the largest numbers of dogs with the disease were identified during February and April, with relatively few dogs identified during the summer and early fall (**Fig 2**).

Geographic distribution—The geographic distribution of case dogs was more restricted than that of control dogs. Case dogs were mostly from the southwestern and west-central parts of Missouri, whereas control

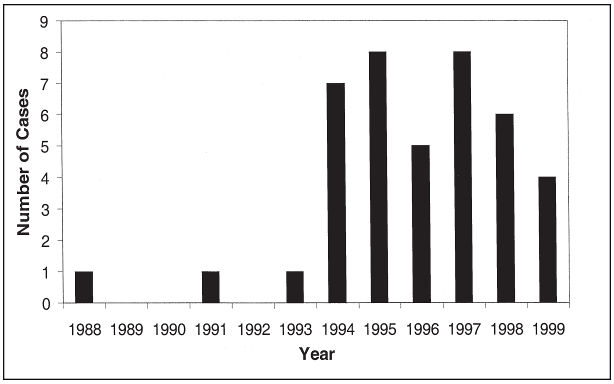

Figure 1—Yearly distribution of numbers of dogs identified with dysautonomia at the University of Missouri veterinary teaching hospital and diagnostic laboratory between 1988 and 1999.

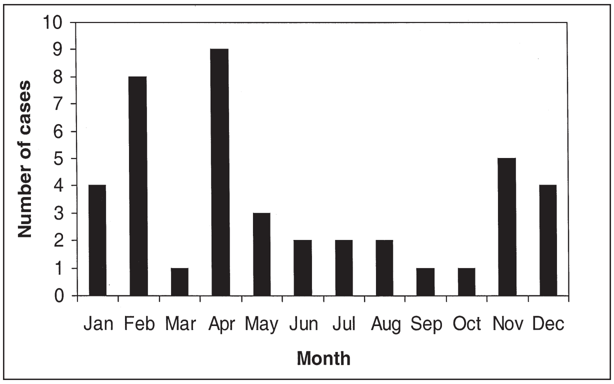

Figure 2—Monthly distribution of numbers of dogs identified with dysautonomia at the University of Missouri veterinary teaching hospital and diagnostic laboratory between 1988 and 1999.

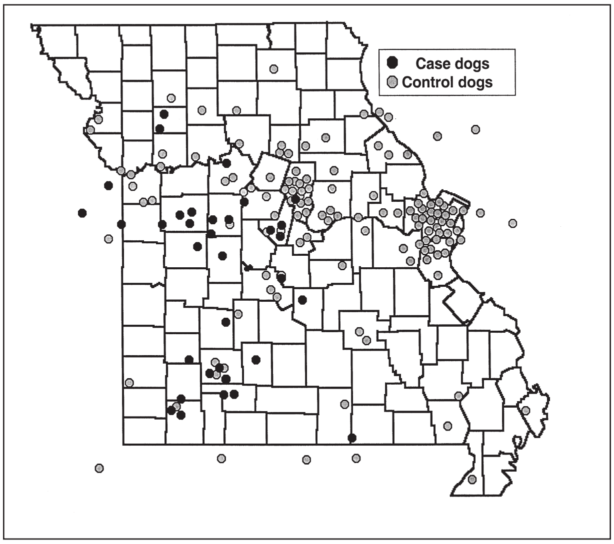

Figure 3—Geographic distribution of dogs identified with dysautonomia at the University of Missouri veterinary teaching hospital and diagnostic laboratory between 1988 and 1999.

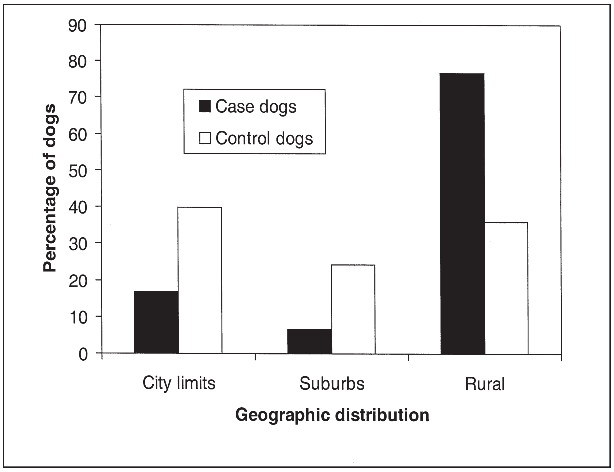

Figure 4—Percentages of dogs with dysautonomia (case dogs; n = 30) and control dogs (103) living in urban, suburban, and rural areas.

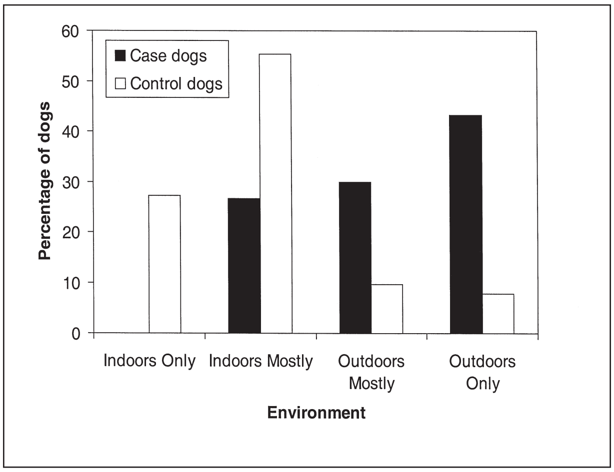

Figure 5—Percentages of dogs with dysautonomia (case dogs; n = 30) and control dogs (103) that were categorized by their owners as "indoors only" (went outside only for elimination), "indoors mostly" (< 50% of time spent outdoors), "outdoors mostly" (≥ 50% of time spent outdoors), or "outdoors only" (always stayed outdoors).

dogs were from across the state and tended to cluster near metropolitan areas (**Fig 3**).

Owners of case dogs were significantly more likely to live in small towns than were owners of all control dogs ($P < 0.001$) but were not significantly more likely to live in small towns than were owners of the rural subset of control dogs ($P = 0.439$). For owners of case dogs, median town population was 2,961 (IQR, 672 to 10,721; n = 33), whereas for owners of control dogs, median town population was 18,902 (IQR, 2,821 to 69,133; 132), and for owners of the rural subset of control dogs, median town population was 2,230 (IQR, 775 to 4,198; 32).

Owners of case dogs were significantly ($P < 0.001$) more likely than owners of control dogs to report that they lived in a rural area, rather than in an urban or suburban area. Twenty-three of 30 (77%) owners of case dogs lived in rural areas, compared with 37 of 103 (36%) owners of control dogs (**Fig 4**).

Environment—Owners were asked to identify the amount of time their dogs spent outside on an ordinal scale. Case dogs were significantly ($P < 0.001$) more likely than control dogs to be classified by their owners as spending ≥ 50% of their time outdoors ("outdoors only" or "outdoors mostly"); 22 of 30 (73%) case dogs spent ≥ 50% of their time outdoors versus 18 of 103 (17%) control dogs (**Fig 5**). Case dogs were also significantly ($P = 0.01$) more likely than the rural subset of control dogs to spend ≥ 50% of their time outdoors, even though dogs that were categorized as "indoors only" (those that went outside only for purposes of elimination) were specifically excluded from the rural subset of control dogs. Twelve of 32 (38%) of the rural subset of control dogs spent ≥ 50% of their time outdoors. Case dogs were also significantly ($P < 0.001$) more likely than control dogs to have an opportunity to roam (26/30 [87%] case dogs vs 43/103 [42%] control dogs) but were not significantly ($P = 0.102$) more likely to roam than the rural subset of control dogs (21/32 [66%]).

Diet—For most case dogs (29/30 [97%]), diet consisted primarily of commercial dog food. This was also true for the control dogs (100/103 [97%]) and the rural subset of control dogs (32/32 [100%]). Owners of case dogs reported use of products from 12 manufacturers, and owners of control dogs reported use of products from 19 manufacturers. Ten of the 30 (33%) case dogs were fed foods from a variety of manufacturers, as were 13 of the 103 (13%) control dogs ($P = 0.018$) and 6 of the 32 (19%) dogs that made up the rural subset of the control group ($P = 0.307$). When responses from owners who said they fed a single brand of food were analyzed, the same brand was most popular among owners of case and control dogs.

Owners reported that 16 of 30 (53%) case dogs had eaten wildlife such as rabbits or birds at least occasionally. This was in contrast with the 16 of 103 (16%) control dogs ($P < 0.001$) and 8 of 32 (25%) dogs that made up the rural subset of the control group ($P = 0.008$). Owners of 7 of 30 (23%) case dogs, 77 of 103 (75%) control dogs, and 20 of 32 (63%) dogs that made up the rural subset of the control group reported that their dogs never consumed wildlife. Owners of 7 (23%) case dogs, 10 (10%) control dogs, and 4 (13%) dogs that made up the rural subset of the control group said they were uncertain whether their dogs ever consumed wildlife.

Well water was listed as a source of drinking water for 18 of 30 (60%) case dogs, and treated water was listed as a source for 11 (37%). Many case dogs (20 [67%]) were also likely to drink from ponds or other sources of standing water. Control dogs were significantly ($P < 0.001$) more likely to have treated water as a water source (79/103 [77%]) and significantly ($P < 0.001$) less likely to have well water as a water source (25/103 [24%]). Control dogs were also significantly ($P < 0.001$) less likely to drink from ponds or other sources of standing water. The rural subset of control dogs, however, was not significantly more or less likely to have well water (19/32 [59%]; $P = 0.835$) or treated water (11/32 [34%]; $P = 0.939$) as a water source, compared with case dogs, and were as likely to drink from ponds or other sources of standing water (14/32 [44%]; $P = 0.120$).

Animal contact—Of the 30 case dogs for which information was provided, 22 (73%) were exposed to other dogs, 20 (67%) were exposed to cats, 4 (13%) were exposed to swine, 10 (33%) were exposed to horses, 1 (3%) was exposed to sheep, and 19 (63%) were exposed to cattle. By comparison, of the 103 control dogs for which information was provided, 55 (53%) were exposed to other dogs ($P = 0.083$), 58 (56%) were exposed to cats ($P = 0.422$), 4 (4%) were exposed to swine ($P = 0.139$), 14 (14%) were exposed to horses ($P = 0.027$), 1 (1%) was exposed to sheep ($P = 0.934$), and 11 (11%) were exposed to cattle ($P < 0.001$). Of the 32 dogs that made up the rural subset of the control group, 22 (69%) were exposed to other dogs ($P = 0.907$), 25 (78%) were exposed to cats ($P = 0.468$), 3 (9%) were exposed to swine ($P = 0.703$), 9 (28%) were exposed to horses ($P = 0.866$), 1 (3%) was exposed to sheep ($P = 1.0$), and 9 (28%) were exposed to cattle ($P = 0.011$).

Land exposures—Of the 30 case dogs for which information was provided, 25 (83%) had access to pasture land, 11 (37%) had access to land used for row crops, and 18 (60%) had access to undeveloped land (defined as wooded areas, wetlands, and similar areas), but none had access to land used for mining or industrial purposes. By comparison, of the 103 control dogs for which information was provided, 23 (22%) had access to pasture land ($P < 0.001$), 14 (14%) had access to land used for row crops ($P = 0.010$), 41 (40%) had access to undeveloped land ($P = 0.080$), and 3 (3%) had access to land used for mining or industrial purposes ($P = 0.805$). Of the 32 dogs that made up the rural subset of the control group, 15 (47%) had access to pasture land ($P = 0.006$), 9 (28%) had access to land used for row crops ($P = 0.655$), 20 (63%) had access to undeveloped land ($P = 0.953$), and 2 (6%) had access to land used for mining and industrial purposes ($P = 0.492$). The proportion of case dogs with access to farm ponds (22/30 [73%]) was significantly higher than the proportion of control dogs that did (17/103 [17%]; $P < 0.001$) and the proportion of dogs that made up the rural subset of the control group that did (13/32 [41%]; $P = 0.019$).

Exposure to potential toxins—Seventeen of 30 (57%) owners of case dogs used lawn fertilizer, as did 47 of 103 (46%) owners of control dogs ($P = 0.391$) and 11 of 32 (34%) owners of dogs that made up the rural subset of the control group ($P = 0.132$). Eight of 30 (27%) case dogs were exposed to herbicides, compared with 39 of 103 (38%) control dogs ($P = 0.362$) and 9 of 32 (28%) dogs that made up the rural subset of the control group ($P = 0.876$). Eight of 30 (27%) case dogs were exposed to pesticides, compared with 25 of 103 (24%) control dogs ($P = 0.978$) and 9 of 32 (28%) dogs that made up the rural subset of the control group ($P = 0.876$).

Preventive veterinary medical care—Twenty-six of 30 (87%) case dogs were vaccinated regularly, as were 96 of 103 (93%) control dogs ($P = 0.443$) and 28 of 32 (88%) dogs that made up the rural subset of the control group ($P = 1.0$). Twenty-one of 30 (70%) case dogs received heartworm preventative, as did 81 of 103 (79%) control dogs ($P = 0.459$) and 26 of 32 (81%) dogs that made up the rural subset of the control group ($P = 0.461$). Ten of 30 (33%) case dogs were treated with spot-on flea and tick products, as were 54 of 103 (52%) control dogs ($P = 0.102$) and 17 of 32 (53%)

dogs that made up the rural subset of the control group ($P = 0.189$). Six of 30 (20%) case dogs were given flea control products orally, as were 17 of 103 (17%) control dogs ($P = 0.864$) and 4 of 32 (13%) dogs that made up the rural subset of the control group ($P = 0.502$).

Travel—The proportion of case dogs that had traveled > 50 miles away from home (8/30 [27%]) was significantly less than the proportion of control dogs (64/103 [62%]; $P < 0.001$) and the proportion of dogs that made up the rural subset of the control group (20/32 [63%]; $P = 0.010$) that had.

Odds ratios—Unadjusted OR and 95% CI were calculated for all risk factors evaluated (**Table 1**). When case dogs were compared with all control dogs, risk factors significantly associated with dysautonomia were age < 36 months, sexually intact female, Labrador Retriever, town population < 5,000, living in a rural area, spending ≥ 50% of time outdoors, roaming, exposure to pasture land, exposure to row crops, exposure to farm ponds, consumption of wildlife or a variety of dog food brands, drinking pond or well water, and exposure to horses and cattle. When comparisons were limited to the more similar rural subset of controls, significant associations that remained were age < 36 months, spending ≥ 50% of time outdoors, exposure to pasture land or farm ponds, consumption of wildlife, and exposure to cattle. Although the use of adjusted OR would have been preferable, our ability to eliminate bias or confounding, using multivariate approaches, was precluded by the limited number of cases with complete information (n = 30) and the large number of risk factor categories examined (14).

Table 1—Odds ratios for various factors potentially associated with development of dysautonomia in dogs

Risk factor	Category	Odds ratio (95% confidence interval)	
		Control group*	Rural subset†
Age			
	< 36 mo	3.95 (1.88–8.27)	3.21 (1.23–8.41)
	≥ 36 mo	0.25 (0.12–0.53)	0.31 (0.12–0.81)
Sex			
	Sexually intact male	1.41 (0.50–3.98)	1.24 (0.31–4.92)
	Castrated male	0.71 (0.25–2.01)	0.81 (0.20–3.21)
	Sexually intact female	3.47 (1.26–9.54)	2.00 (0.47–8.61)
	Spayed female	0.29 (0.11–0.79)	0.50 (0.12–2.15)
Breed			
	Labrador Retriever	3.00 (1.15–7.83)	1.91 (0.53–6.86)
	Toy breed	NC	NC
Town population			
	< 5,000	4.00 (1.78–8.97)	0.46 (0.15–1.45)
	≥ 5,000	0.25 (0.11–0.56)	2.17 (0.69–6.80)
Rural versus urban			
	Rural area	5.86 (2.30–14.93)	NA
	City limits/suburbs	0.17 (0.07–0.44)	NA
Time spent outdoors			
	< 50%	0.08 (0.03–0.20)	0.29 (0.08–1.05)
	≥ 50%	12.99 (5.00–33.71)	4.58 (1.56–13.47)
Roaming			
	Roam occasionally	9.07 (2.96–27.82)	3.41 (0.95–12.22)
	Strictly confined	0.11 (0.04–0.34)	0.29 (0.08–1.05)
Land exposures			
	Pasture	17.39 (6.00–50.41)	5.67 (1.74–18.49)
	Row crops	3.68 (1.45–9.33)	1.48 (0.51–4.31)
	Farm ponds	13.91 (5.33–36.34)	4.02 (1.38–11.73)
	Undeveloped (ie, woodlands)	2.27 (0.99–5.19)	0.90 (0.32–2.50)
	Mining and industry	NC	NC
Diet			
	Eats most popular brand food	0.56 (0.19–1.53)	0.60 (0.17–2.09)
	Eats variety of brands	3.46 (1.33–8.99)	2.17 (0.68–6.95)
	Eats wildlife	6.21 (2.55–15.16)	5.71 (1.71–19.09)
Drinking water			
	Treated water	0.18 (0.07–0.42)	1.11 (0.39–3.12)
	Well water	4.68 (1.99–11.02)	1.03 (0.37–2.83)
	Ponds, puddles, etc	6.58 (2.72–15.94)	2.57 (0.92–7.20)
Animal contact			
	Other dogs	2.40 (0.98–5.88)	1.25 (0.42–3.75)
	Cats	1.55 (0.66–3.64)	0.56 (0.18–1.73)
	Swine	3.81 (0.89–16.21)	1.49 (0.31–7.25)
	Horses	3.18 (1.24–8.17)	1.28 (0.43–3.76)
	Sheep	3.52 (0.22–57.65)	1.07 (0.06–17.79)
	Cattle	14.45 (5.48–38.06)	4.41 (1.52–12.84)
Lawn chemicals			
	Fertilizer	1.56 (0.69–3.53)	2.50 (0.90–6.95)
	Herbicides	0.60 (0.24–1.47)	0.93 (0.31–2.83)
	Pesticides	1.14 (0.45–2.86)	0.93 (0.31–2.83)
Preventive veterinary care			
	Regular vaccinations	0.47 (0.13–1.74)	0.93 (0.21–4.09)
	Heartworm prevention	0.63 (0.26–1.58)	0.54 (0.17–1.23)
	Spot-on (flea and tick prevention)	0.45 (0.19–1.06)	0.44 (0.16–1.23)
	Oral flea prevention	1.27 (0.45–3.56)	1.75 (0.44–6.92)
History of travel			
	Travel > 50 miles from home	0.22 (0.09–0.56)	0.22 (0.07–0.64)

*Odds ratios represent odds that a dog with dysautonomia was exposed divided by the odds that a control dog was exposed; control dogs consisted of randomly selected dogs examined for an unrelated reason. †Odds ratios represent odds that a dog with dysautonomia was exposed divided by the odds that a dog from a subset of the control dogs was exposed; the subset of dogs consisted of dogs that lived in rural areas and spent at least some time outdoors.

NC = Not calculated; odds ratio could not be calculated because none of the case dogs were toy breeds or were exposed to lands used for mining or industrial purposes. NA = Not applicable; all dogs in this subset lived in rural areas.

Discussion

Although the cause of dysautonomia is unknown, results of the present study suggest that dogs with dysautonomia were significantly more likely to live in rural areas and spend a majority of their time outdoors than were control dogs examined for unrelated diseases. Even when dogs with dysautonomia were compared only with control dogs that lived in rural areas, dogs with dysautonomia were significantly more likely to spend all or most of their time outdoors. This may help explain why dogs with dysautonomia were significantly more likely to have consumed wildlife than were control dogs and could also be involved in why dogs with dysautonomia were significantly more likely to have been exposed to pasture land, farm ponds, and cattle. However, dogs with dysautonomia were not significantly more likely to have been exposed to other types of land or other types of domestic animals, compared with control dogs.

The geographic distribution of case dogs in the present study was more restricted than that of the control dogs. Although this provides some evidence for a regional distribution of dysautonomia in Missouri, it also causes some concern for the validity of analyses that involved comparing dogs from the western part of the state with dogs that were more widely dispersed. Several control dogs came from the St. Louis metropolitan area, whereas none of the case dogs did. However, when χ^2 analyses were used to compare control dogs from an area circumscribed by lines connecting dysautonomia cases with control dogs from outside this area, we did not detect any significant differences in regard to age (< 3 years vs ≥ 3 years), sex, breed, town population ($< 5{,}000$ vs $\geq 5{,}000$), environment (rural vs urban), time spent outdoors ($< 50\%$ vs $\geq 50\%$), opportunity to roam, exposure to various types of land, diet, source of drinking water, exposure to other domestic animals, exposure to various lawn chemicals, preventive veterinary care, or history of travel.

The present study could have been improved by selecting control dogs that were more closely matched to the case dogs. A more ideal control group for future studies would consist of rural, mostly outdoor dogs from the areas where dysautonomia is common. For the present study, we chose to use only dogs for which the diagnosis had been made or confirmed at the University of Missouri, but cooperative work with practitioners in areas where this disease is common might allow for identification of a larger number of cases. Unfortunately, because free-roaming outdoor dogs are typically unsupervised, identifying risk factors may be difficult. It should be pointed out that this disease is not limited to Missouri and that dogs with dysautonomia had been identified in eastern Kansas,[c] Oklahoma,[d] Colorado,[e] Wyoming,[e] and, in the experience of 1 of the authors (DPO), North Dakota and western Tennessee.

Our finding that most dogs with dysautonomia were young is similar to findings for horses and cats with dysautonomia.[14,15] Labrador Retrievers were over-represented, compared with control dogs, but this was less apparent when comparisons were made to the rural subset of control dogs. Hence, the popularity of Labrador Retrievers as rural outdoor dogs may explain their apparent propensity for the disease. Likewise, it is probable that toy breeds were under-represented, because they tend to be indoor dogs even when they live in a rural area.

In the present study, dogs with dysautonomia were identified most often during February and April, and relatively few dogs were identified during the summer and early fall. A seasonal pattern of dysautonomia among horses in the United Kingdom has been reported, with affected horses identified most commonly in late spring and early summer.[14]

In the present study, dysautonomia was not associated with feeding any particular diet; case and control dogs ate a wide variety of commercial dog foods. This does not exclude the possibility that dogs with an indiscriminate appetite may be exposing themselves to this disease by consuming something besides regular dog food. Dysautonomia has not been identified in North American wildlife; however, wild hares with dysautonomia have been identified in the United Kingdom.[16,17] It is interesting to consider whether rabbits or other wildlife may be a link between opportunistic carnivores and what has historically been a disease of herbivores.

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[a] SigmaStat, version 2.03, SPSS Inc, Chicago, Ill.

[b] SAS, version 8.0, SAS Institute Inc, Cary, NC.

[c] Harkin K, Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, Kan: Personal communication, 2000.

[d] Lorenz MD, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Oklahoma State University, Stillwater, Okla: Personal communication, 2000.

[e] Veterinary Medical Data Base, Purdue University, West Lafayette, Ind.

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