Dysautonomia in dogs: 65 cases (1993–2000)

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Objective—To determine signalment, history, clinical findings, results of autonomic function testing and other antemortem diagnostic tests, and pathologic findings in dogs with dysautonomia.

Design—Retrospective study.

Animals—65 dogs with dysautonomia.

Procedure—Case records of 68 dogs with a diagnosis of dysautonomia were reviewed; inclusion criteria included histologic confirmation of dysautonomia or clinical signs and results of pharmacologic testing consistent with dysautonomia.

Results—65 dogs fulfilled all criteria for dysautonomia. Dogs from rural environments were overrepresented, and cases of dysautonomia were reported for every month, although the highest number of cases was reported in February and March. Vomiting was the most common clinical sign, followed by diarrhea, signs of anorexia and depression, weight loss, and dysuria. The most common physical examination finding was decreased or absent anal tone, followed by absent pupillary light reflexes and elevated nictitating membrane. Results of pharmacologic testing were consistent with dysautonomia, although no single test was 100% sensitive. Histologic lesions consistent with dysautonomia were found in the autonomic ganglia, brainstem nuclei, and ventral horns of the spinal cord.

Conclusions and Clinical Relevance—Dysautonomia is an endemic disease in Kansas, and a high index of suspicion of the disease can be made by combining clinical signs, physical examination findings, and results of pharmacologic testing. (*J Am Vet Med Assoc* 2002;220:633–639)

Primary dysautonomia of dogs, cats, horses, and rabbits is described as an idiopathic rare neurodegenerative disorder characterized by chromatolytic degeneration of neurons in autonomic ganglia, which results in clinical signs referable to failure of the sympathetic and parasympathetic nervous systems. The disease was first reported in horses in Scotland in the early 1900s and has also been reported in horses from South America.[1-3] Subsequently, the disease was reported in the 1980s in cats from the United Kingdom and has since been reported in cats from other parts of the world,[4-10] hares, dogs, and a llama.[11-13] Canine dysautonomia was first reported in the United Kingdom in 1983, and isolated cases have been reported throughout Europe.[14-19] The first suspected case of canine dysautonomia in the United States was reported in 1991 in a dog from Wyoming.[20] However, there was no histologic confirmation of the disease in that dog. Longshore et al[12] reported 11 cases of dysautonomia in dogs from Missouri, dating from 1988 through 1995, all of which were confirmed histologically. One additional isolated case of canine dysautonomia was reported in 1997 in a dog from Tennessee.[21] Berghaus et al[22] reported on 42 dogs from Missouri with dysautonomia between August 1988 and January 2000 (including the 11 dogs reported by Longshore et al) in evaluating potential risk factors for the disease.

Clinical signs and physical examination findings in canine dysautonomia reflect the severity of autonomic nervous system damage. Dysuria with a distended urinary bladder, mydriasis with absent pupillary light reflexes, xerostomia, decreased tear production, decreased anal tone, and vomiting or regurgitation were reported most commonly in dogs with dysautonomia.[12] The disease typically affects young dogs, with a reported median age of 14 months in 1 study.[12] The clinical course is relatively brief, with a reported median duration of clinical signs of 14 days in the same study, and the prognosis is typically grave. Although some horses and cats may survive and even partially recover, there is only 1 reported case of long-term survival and apparent recovery in a dog.[23]

Gross necropsy findings in dogs with dysautonomia are nonspecific but often reflect the severity of digestive tract hypomotility. Findings may include megaesophagus, fecal impaction of the distal portion of the small intestine or large intestine, and aspiration pneumonia resulting from megaesophagus or chronic vomiting.[12,23] Light microscopic findings are described as chromatolytic degeneration of autonomic ganglia and a marked reduction in neuronal numbers in ganglia.[12,24] Additionally, similar chromatolytic degeneration has been described in the brainstem nuclei of 1 dog and the lateral and ventral horns of the spinal cord in 4 dogs.[12,16]

The purpose of the study reported here was to determine signalment, history, clinical findings, results of autonomic function testing and other antemortem diagnostic tests, and pathologic findings in dogs with dysautonomia.

Criteria for Selection of Cases

All hospital records in which a diagnosis of dysautonomia was made at the **Kansas State University Veterinary Medical Teaching Hospital** (**KSUVMTH**; n = 68 dogs) were reviewed. Dogs were included in the study on the basis of the following criteria: dogs were submitted by a referring veterinarian to the Department of Diagnostic Medicine/Pathobiology for necropsy, a complete history was available, and there was histologic confirmation of the disease (n = 10

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dogs); dogs were evaluated at the KSUVMTH and were confirmed to have dysautonomia at necropsy (37); or dogs evaluated at the KSUVMTH had clinical signs consistent with dysautonomia and fulfilled all diagnostic criteria for the disease (18). Diagnostic criteria that had to be fulfilled for inclusion in the study without histologic confirmation were as follows: absent or diminished pupillary light reflex, miosis with the topical application of 1 drop of 0.1% pilocarpine, diminished Schirmer tear test results (< 5 mm/min) in both eyes, no change in heart rate during a 60-minute period after administration of atropine (0.02 mg/kg [0.009 mg/lb], IV, or 0.04 mg/kg [0.018 mg/lb], SC), and the absence of a flare response to intradermally administered histamine (0.05 ml of 1:10,000 histamine). Three dogs with a clinical diagnosis of dysautonomia did not fulfill all inclusion criteria for this study.

Procedures

Physiologic and pharmacologic testing—Some or all of the physiologic or pharmacologic tests were performed in 50 of 65 dogs. The Schirmer tear test was performed with a standard tear test strip in 41 dogs, and tear production was classified as < 5 mm/min, 5 to 10 mm/min, > 10 to 15 mm/min, and > 15 to 20 mm/min. One drop of a 0.1% solution of pilocarpine (1% pilocarpine diluted 1:10 with irrigating solution) was applied to 1 eye in 38 of 65 dogs, and each dog was monitored for 60 minutes for the development of miosis. In 27 dogs, atropine was administered IV (0.02 mg/kg), and heart rate was measured prior to administration and every 5 to 10 minutes for up to 60 minutes. In 1 dog, atropine was administered SC (0.04 mg/kg), and heart rate was monitored every 15 minutes for 60 minutes. The maximum change in heart rate during the observation period was used in data analysis and classified as < 10 beat increase, 10 to 20 beat increase, > 20 to 40 beat increase, and > 40 beat increase. Anticipated responses from a healthy dog would be a Schirmer tear test result of 15 to 20 mm/min, no change in pupil size with the application of 0.1% pilocarpine, and an increase in heart rate of > 40 **beats/min (bpm)** or end-test heart rate of > 140 bpm. Heart rates prior to and after atropine administration were compared by use of a paired *t*-test.[a]

An ID histamine test was performed in 30 dogs. An area of hair on the lateral thorax of the dog was clipped, and 0.05 ml of histamine (1:10,000) was injected alongside an equal quantity of saline (0.9% NaCl) solution, which served as a control. The injection sites were monitored for 30 minutes for the development of a wheal and flare response. A healthy dog would be expected to have a visible wheal and flare response. In 1 dog, a bethanechol challenge was performed (0.0375 mg of bethanechol chloride/kg [0.0170 mg/lb], SC), and subjective evaluation of the dog's ability to evacuate the urinary bladder was made 30 minutes after injection. Determination of the effects of body position on blood pressure was made in 3 conscious dogs. Indirect blood pressure measurements were taken simultaneously of the forelimb and hind limb with the dog in lateral recumbency and then with the dog tilted at 30 degrees, with the forelimbs above the hind limbs (orthostatic hypotension test).

Additional information obtained from the medical record included results of CBC, serum biochemistry profile, urinalysis, fecal flotation, and other diagnostic tests. For 46 dogs, some or all of the tests were performed; for 19 dogs, no additional diagnostic tests were performed. Necropsies were performed on 47 dogs, and the results of gross and microscopic examination were reviewed. Climate reports for the northeastern Kansas region were evaluated for the years 1996 through 2000 and compared to dates of dog evaluations. Separate dot density maps of the geographic distribution of dogs with dysautonomia and of all dogs referred to the KSUVMTH during the last 6-month period (March through September, 2001) were generated for comparison.[b]

Results

Signalment, time of evaluation, and environment—Twenty-eight breeds were represented by the 65 dogs. The radiographic findings in 24 of these dogs have been reported.[25] The most frequently represented breeds included Labrador Retriever (n = 8), German Shorthaired Pointer (7), German Shepherd Dog (6), Australian Shepherd and Australian Shepherd-mixed breed (5), Brittany Spaniel (4), Border Collie (3), Golden Retriever (3), Siberian Husky (3), English Pointer (3), Boxer (3), Dalmatian (2), Rottweiler (2), Australian Blue Heeler (2), Chow-mixed breed (2), and other mixed-breed dogs (3). There was 1 dog each of the following breeds: Welsh Corgi, Collie, Miniature Schnauzer, American Eskimo, Cocker Spaniel, Toy Poodle, Cairn Terrier, Doberman Pinscher, and Dachshund. Five of the German Shorthaired Pointers were related (the dam and 4 puppies) and developed dysautonomia within a week of each other; findings in these dogs have been reported.[26] Two of the Brittany Spaniels were 4-year-old female littermates that were housed together and developed dysautonomia on the same day.

There were 19 sexually intact male dogs, 7 neutered male dogs, 20 sexually intact female dogs, and 19 neutered female dogs. Ages ranged from 5 weeks to 15 years (median, 18 months). Thirty-four dogs were < 24 months of age, 16 dogs were 24 to 36 months old, and 15 dogs were older than 36 months. Weights of the dogs were grouped as < 5 kg (< 11 lb; n = 6 dogs), 5 to 10 kg (11 to 22 lb; 8), > 10 to 20 kg (> 22 to 44 lb; 17), and > 20 to 40 kg (> 44 to 88 lb; 34).

The first diagnosis was made in July of 1993 and was the only case of dysautonomia identified that year. There were 5 cases in 1994, 7 cases in 1995, 6 cases in 1996, 6 cases in 1997, 11 cases in 1998, 16 cases in 1999, and 13 cases in 2000.

Evaluation of distribution of cases by month revealed that February and March had the highest number of cases (10 each month), followed by May (8), April and July (6 each), September and October (5 each), June and November (4 each), January and December (3 each), and August (1). Excluding 1993, evalaution of distribution of cases within each year revealed periods of no reported cases for 3 months or longer at the following times: in 1994 from April through June and from October through February of

1995, in 1995 from June through October, in 1996 from June through August, in 1997 from January through April, in 1998 from August through December, and in 2000 from June through August. Evaluation of climatology reports failed to reveal consistent patterns for rainfall, mean temperature, snowfall, or deviation from normal temperature and precipitation that correlated with date of evaluation of the dogs. Dogs with dysautonomia were referred predominantly from the eastern half of Kansas, compared with the population dogs without dysautonomia, which were referred from a more widespread distribution.

The environment in which the dogs were maintained was reported as rural or farm (n = 56 dogs), city (8), and military base (1). Dogs were included in the rural or farm category if livestock or crops were maintained on the property or a neighboring property. For the dogs that lived in a rural or farm setting, direct contact with other animals was reported as following: cattle (n = 8 dogs), horses (4), sheep (1), goats (1), pheasants (1), and chickens (1). Except for 3 of the rural or farm dogs that were routinely kenneled except for hunting and the 4 puppies that were housed and too young to roam, 49 dogs were free roaming. Of the city dogs, 7 participated in outdoor activity regularly, particularly hunting and hiking. Indiscriminate eating behavior was reported in 21 of the 65 dogs. Known items that were ingested in the week prior to the onset of clinical signs of disease included dead birds (n = 4 dogs), rabbit carcass (2), deer carcass, cow placenta, pine oil, compost, toads, spoiled meat, spoiled peppers, moldy dog food, and mice (1 each).

Clinical signs and physical examination findings—Duration of clinical signs prior to evaluation varied from 0 to 28 days (median, 5 days). Vomiting was the most frequent clinical complaint and was reported in 51 dogs. Vomiting was the first clinical sign noticed in 34 dogs and was the sole clinical sign in 4 dogs. Diarrhea and anorexia were the next most frequent clinical signs and were present in 33 dogs each. Diarrhea was the first clinical sign noticed in 21 dogs but was never the sole clinical sign. Anorexia was the first clinical sign noticed in 21 dogs and was the sole clinical sign in 1 dog (except for signs of depression).

Other clinical signs reported by clients included lethargy and signs of depression (n = 19 dogs), weight loss (15), dysuria (13), inspiratory dyspnea (11), nasal discharge (7), tenesmus (6), constipation (5), photophobia (5), severe muscle weakness (4, 1 of which was nonambulatory for > 1 day), regurgitation (3), coughing (3), sneezing (2), ocular discharge (1), dilated pupils (1), seizures (1), and dysphagia and dysphonia (1). Weight loss was described as severe in 9 dogs. In 8 of these 9 dogs, weights had been recorded by the primary care veterinarian when the dog was reportedly healthy < 4 months previously and were available for review. Percentage weight loss in these 8 dogs ranged from 1.2 to 5.6%/d from first day of reported illness (median, 2.45%/d). Maximum weight loss was 39% during a 25-day period.

The most frequent physical examination finding recorded at time of evaluation was decreased or absent anal tone (34 dogs). The next most common findings were absent pupillary light reflex and elevated nictitating membrane (32 dogs each). Twenty-eight dogs were reportedly dehydrated, 27 dogs had distended and expressible urinary bladders, and 26 dogs had xerostomia. Mydriasis was reported in 19 dogs.

Signs referable to the upper or lower respiratory tract included a dry crusty nasal discharge (n = 11 dogs), increased respiratory sounds (11), mucopurulent nasal discharge (10), inspiratory dyspnea (10), pulmonary crackles (3), nasal congestion (2), and labored breathing (2).

Several dogs had physical examination findings suggestive of lesions of the central or peripheral nervous systems or a myopathic syndrome. Severe muscle weakness was detected in 7 dogs, and 3 dogs were nonambulatory at the time of evaluation. One of the dogs that was nonambulatory had severe hind limb paresis but normal forelimb function. Other physical examination findings included diminished conscious proprioception in forelimbs and hind limbs (n = 3 dogs), anisocoria (2), marked ptyalism suggestive of pharyngeal dysfunction (1), absent gag reflex (1), diminished patellar reflexes (1), exaggerated patellar reflexes (1), and whole-body muscle tremors (1).

Less frequently recorded physical examination findings included ocular discharge (n = 5 dogs), weak pulses (4), fever (6), hypothermia (3), generalized muscle wasting (2), signs of obtundation or recumbent (6), tense abdomen (4), conjunctivitis (1), abdominal distension (1), and rectal prolapse (1).

Heart rate at time of evaluation was recorded in 50 dogs and was 60 to 80 bpm in 3 dogs, > 80 to 120 bpm in 30 dogs, > 120 to 140 bpm in 12 dogs, and > 140 bpm in 5 dogs.

Diagnostic evaluation—A CBC and serum biochemistry profile were performed on 27 of 65 dogs; no important abnormalities were identified. An ELISA for parvovirus was performed on 5 dogs, and results were positive in 3 dogs. The 3 dogs with positive test results were littermates and did not have histologic evidence of parvovirus infection at necropsy. Two dogs had whipworm infestation identified via fecal flotation, and 1 dog had coccidiosis. Plasma lead concentrations were measured in 2 dogs and were within reference ranges.

Schirmer tear testing was performed on 41 dogs. Tear production was < 5 mm/min in 22 dogs, 5 to 10 mm/min in 10 dogs, > 10 to 15 mm/min in 6 dogs, and > 15 to 20 mm/min in 3 dogs. Dilute pilocarpine (0.1%) was instilled in 1 eye in 38 dogs, and miosis developed in 33 dogs. Time for development of miosis was 15 to 30 minutes in 6 dogs, > 30 to 45 minutes in 7 dogs, > 45 minutes in 2 dogs, and was not reported in 18 dogs. An atropine response test was performed in 28 dogs (27 by IV administration and 1 with SC administration). Mean heart rate prior to atropine administration was 108.7 bpm (SD, 18.4), and mean heart rate after atropine administration (taken as the highest recorded heart rate at any time point) was 113.8 bpm (SD, 24.1). There was no significant difference ($P = 0.16$) between heart rates determined before and after administration of atropine. There was either

no change or a decrease in heart rate in 24 dogs, an increase in heart rate of 10 to 20 bpm in 3 dogs, or an increase in heart rate of > 40 bpm in 1 dog (actual increase of 90 bpm). Before administration of atropine, 2 dogs had heart rate > 140 bpm. In 1 of these dogs heart rate decreased from 142 to 131 bpm, and in the other dog heart rate did not change from 143 bpm. Only 3 dogs had heart rate > 140 bpm after atropine administration. The ID histamine test was performed in 30 dogs. A wheal response developed in 15 dogs and did not develop in 15 dogs. A flare response developed in 1 dog and did not develop in 29 dogs. Bethanechol administration in 1 dog did not induce a subjective improvement in urination. The orthostatic hypotension test was performed in 3 dogs, and no conclusive or repeatable results were obtained.

Clinical course and outcome—The progression and development of clinical signs were recorded in 16 dogs that were not euthanatized within the first 48 hours of admission to the KSUVMTH. In 4 dogs, exploratory laparotomies were performed for suspected intestinal foreign bodies. Two of these dogs had midjejunal or ileocecal impactions with dry feces, and no evidence of obstruction was found in the other 2 dogs. In 7 dogs, anal tone became absent 2 to 6 days (median, 2 days) after hospitalization. Dysuria, urine retention, or both, with urine dribbling, developed in 6 dogs 2 to 3 days after hospitalization. Absent or diminished pupillary light reflex with mydriasis developed in 5 dogs 2 to 5 days (median, 3 days) after hospitalization. Aspiration pneumonia was identified in 3 dogs 2 to 10 days after hospitalization. One dog developed seizures on the third day of hospitalization. Three dogs had normal or inconclusive results of testing for dysautonomia initially but had results consistent with the disease 2 days later. One dog developed a lower motor neuron paralysis of all limbs on the third day.

Ten dogs were discharged from the hospital. Six of these dogs had dysuria as the only major clinical sign, which was improved or controlled by oral administration of bethanechol. One dog that was vomiting was sent home and treated with cisapride, which subjectively reduced the number of vomiting episodes. The outcome of 3 other dogs was unknown; however, these dogs had severe clinical signs and were likely euthanatized or died. Fifty-five dogs were euthanatized or died at the KSUVMTH or another veterinary hospital.

Histopathologic findings—Autonomic ganglia that were evaluated histologically in these dogs included the periadrenal (n = 38 dogs), cervicothoracic (25), celiacomesenteric (24), cranial mesenteric (15), caudal mesenteric (8), cranial and middle cervical (4 each), pterygopalatine and trigeminal (3 each), ciliary (2), and cranial thoracic and nodose ganglia (1 each). Additionally, the myenteric plexus of the small or large intestine was evaluated in 11 and 3 dogs, respectively, and the pelvic plexus was evaluated in 2 dogs. There was substantial neuronal degeneration in all ganglia examined, with a variable loss of neuron numbers, although usually there was a substantial reduction in neurons. Occasional neurons were swollen, and others were shrunken and hypereosinophilic with pyknotic or karyorrhectic nuclei. The cytoplasm was hypereosinophilic in most neurons and either lacked Nissl granules or contained only a thin peripheral rim of Nissl granules (ie, central chromatolysis). The cytoplasm of many neurons contained vacuoles that were either peripherally located or diffuse throughout the cytoplasm, and some vacuoles contained an eosinophilic material. Nuclei were pyknotic and peripherally located in most affected neurons. A mild infiltration of lymphocytes, plasma cells, glial cells, and macrophages was described in a few ganglia.

Brainstem nuclei were examined in a small number of dogs. These nuclei included the dorsal motor nucleus of the vagus nerve (n = 7 dogs), hypoglossal nucleus (6), facial nucleus (4), oculomotor nucleus (4), motor nucleus of the trigeminal nerve (3), unspecified brainstem nuclei (2), and the nucleus ambiguous (1). An identical neuronal degeneration with chromatolysis as seen in peripheral autonomic ganglia was seen in all of the brainstem nuclei that were examined. The degenerate neurons were typically irregularly shaped and shrunken with karyolytic nuclei, whereas a few neurons had a hypereosinophilic cytoplasm with pyknotic nuclei.

The spinal cord was examined histologically in 6 dogs. In 5 of these dogs, most lesions were localized to the ventral horns. The neurons in these ventral horns had the same chromatolytic degeneration as the autonomic ganglia. No lesions were identified in the cerebellum (n = 7 dogs), cerebrum (6), hippocampus (2), midbrain (1), vagal sympathetic trunk (3), hypogastric nerves (2), vagus nerve (2), thoracic sympathetic trunk (1), or pterygopalatine trunk (1).

Gross necropsy findings included evidence of bronchopneumonia that was confirmed histologically in 26 dogs and megaesophagus in 12 dogs. Five dogs had histologic evidence of esophagitis, 2 of which also had megaesophagus.

Discussion

Canine dysautonomia was diagnosed definitively in 47 dogs on the basis of histologic confirmation of the clinical diagnosis, and the disease was strongly suspected in 18 dogs on the basis of clinical signs and results of pharmacologic testing. Labrador Retrievers, German Shorthaired Pointers, and German Shepherd Dogs were the breeds most commonly affected with dysautonomia. In 2 previous studies[12,22] an apparent breed predisposition for dysautonomia in Labrador Retrievers has been reported. Because dogs raised and housed in rural environments appeared to be at greater risk (56/65 dogs) for dysautonomia than dogs from the city, this may influence the apparent breed predisposition, because the most commonly reported breeds in our study are popular farm dogs in Kansas. Berghaus et al[22] also noted that Labrador Retrievers were not at risk, compared with the rural population of dogs.

In our study, as in previous studies, we did not find a significant association between sex and dysautonomia. As in previous studies, results of our study also confirm that canine dysautonomia is predominantly seen in younger dogs. The median age in our study was 18 months, whereas in other studies[12,22] mean ages of

14 and 18 months were reported. More than half (34/65) of the dogs were < 2 years of age, and 77% (50/65) were < 3 years of age. The young age of affected dogs may reflect a more indiscriminate scavenging behavior of younger dogs that potentially exposes them to the causative agent or a variable susceptibility to the causative agent.

Cases of dysautonomia were reported for every month, although February and March had the highest concentration (20/65) of cases. Berghaus et al[22] similarly reported that February and April had the highest number of cases in their study. Nevertheless, the number of cases per year was too low to make meaningful conclusions regarding any apparent high-risk seasons for canine dysautonomia. The clinical impression is that more cases are seen when the weather begins to warm up in the spring or cool down in the fall, especially associated with increased rainfall. However, evaluation of the climatology reports failed to confirm that clinical impression. The period from June through August of the year 2000 was 1 of the hottest and driest on record in Kansas, and no cases of dysautonomia were reported during that period. That finding does corroborate the clinical impression that cases of canine dysautonomia are rare in those climate conditions; however, the number of cases reported in our study was too small to confirm that impression.

In this study, apparent risk factors included habitation in a rural environment (56/65 [86%] dogs) and freedom to roam in that rural environment. Berghaus et al[22] reported similar risk factors, with 77% of the dogs from rural environments and 73% of those dogs spending more than 50% of their time outdoors. In our study, clients were not routinely questioned regarding contact their dog may have had with other animals or whether their dogs had indiscriminate eating behavior. However, several clients offered such information without being prompted, particularly a history of the dog having eaten dead wildlife. Exposure to livestock and wildlife are unavoidable in free-roaming rural dogs. Dogs with dysautonomia were clustered geographically in eastern Kansas to some degree, whereas the referral population was more widespread over Kansas and Nebraska. Because Missouri is the only other state to report a large number of dogs with dysautonomia, this clustering may indicate a similar cause of dysautonomia in Kansas and Missouri.

The duration of clinical signs of disease of dogs in our study compared favorably with that reported by Longshore et al,[12] with a range of 0 to 28 days. Mean duration of clinical signs of dogs in our study was less (5 vs 14 days), likely reflecting a more timely referral for evaluation and not a difference in severity of disease or progression of clinical signs.

The dogs in our study had clinical signs similar to those reported by Longshore et al[12]; however, vomiting and diarrhea were reported more often, and dysuria and weight loss were reported less often. Although weight loss was reported less often in our study, this may reflect the shorter median duration of signs prior to referral. Severity of weight loss was not reported by Longshore et al; however, it was severe in 9 of 15 dogs in our study with reported weight loss, with a mean percentage weight loss of 2.45%/d. The reason for this severe weight loss is unclear. Similar severe weight loss was described in a cat with dysautonomia; however, the time period during which that cat lost 25% of its body weight was not defined.[4] Likewise, Doxey et al[27] reported a median weight loss of 4.9% in horses with dysautonomia, with a maximum daily loss of 0.5% and maximum total loss of 21.5% of body weight. Within the autonomic nervous system, parasympathetic nerves are responsible for stimulating insulin secretion, whereas sympathetic nerves serve the opposing function, and it is possible that the regulation of glucose and fat metabolism may be influenced by disruptions of the autonomic nervous system.[28] However, in our study, there were no dogs that were hyperglycemic, hypoglycemic, or glucosuric.

Clinical signs and physical examination findings in dogs with dysautonomia in our study that have not been reported previously included seizures, dysphonia, paresis, absent gag reflex, conscious proprioceptive deficits, hyper- and hyporeflexia, and muscle tremors. These findings suggest that the causative agent affects aspects of the nervous system beyond the autonomic nervous system. Tremors have been described in horses with dysautonomia but not in dogs.[29] Although weakness was reported in 2 dogs by Longshore et al,[12] and 4 dogs had lesions in the lateral and ventral horns of the spinal cord, no dog was described as paretic, nor were proprioceptive deficits and hyper- or hyporeflexia reported. Sharp et al[8] reported paresis in 18% and proprioceptive deficits in 14% of their cats with dysautonomia.

In our study, confirmation of the diagnosis required that there were characteristic histologic findings or that the dogs responded to all pharmacologic testing as predicted or described for dysautonomia. For pharmacologic testing, response to topical ocular administration of dilute pilocarpine, IV or SC administration of atropine, and ID administration of histamine was evaluated. Longshore et al[12] reported results of administration of dilute pilocarpine in 11 dogs but did not perform or report the response to atropine and histamine.

The response to dilute pilocarpine is dependent on damage to the postganglionic parasympathetic neuron that results in supersensitivity of the iris muscle. As anticipated, 33 of 38 (87%) dogs developed miosis in response to administration of dilute pilocarpine. The 5 dogs in this study that failed to respond had histologically confirmed dysautonomia, and it is important that not all dogs will respond, contrary to the 100% response rate reported in a previous study.[12]

Previous reports[12,23] suggest that the failure of dogs to respond to atropine (a parasympatholytic) with an increase in heart rate may be an indication that there is damage to the sympathetic innervation of the heart. Because heart rate is dependent on baseline parasympathetic and sympathetic tone, it should also be considered that damage to the parasympathetic nervous system is also responsible for the lack of response to atropine. If parasympathetic tone is already abolished, administration of a parasympatholytic will fail to effect any change in heart rate. Heart rate at time of evalua-

tion was > 120 bpm in 17 dogs and < 80 bpm in only 3 dogs, supporting destruction of the parasympathetic innervation as the primary defect. In our study, the atropine response test was performed in 28 dogs, and only 1 dog had a substantial increase in heart rate. This dog had histologically confirmed dysautonomia. No dogs in this study had adverse reactions to atropine administration, in contrast to the potentially life-threatening effects of epinephrine administration.[12]

The ID histamine test has been described as a simple diagnostic test for human familial dysautonomia.[30] In that study, patients developed a wheal but failed to develop a flare response. Wise and Lappin[20] reported 2 dogs that failed to develop a wheal or flare in response to ID administration of histamine, and O'Brien and Longshore[31] suggested that the response should be abnormal but stated that this has not been fully evaluated. In our study, the ID histamine test was performed in 30 dogs. As predicted on the basis of the response in humans, the flare response did not develop in 29 of 30 (97%) dogs. A wheal, however, developed in 15 of 30 (50%) dogs, suggesting that response is not completely blunted in dogs with dysautonomia. Development of a wheal is dependent on the direct actions of histamine on blood vessels and should be intact in dogs with dysautonomia, whereas the flare response is dependent on a sympathetic neuron reflex.[30] One possible explanation for lack of development of a wheal in 50% of the dogs in our study is that intensification of the wheal response may also depend on a similar sympathetic neuron reflex, so subtle wheal responses are missed.

The histologic lesions identified in the autonomic ganglia in the dogs in this study were characteristic of the chromatolytic degeneration described in dogs, horses, cats, and rabbits with dysautonomia.[24] Additionally, similar chromatolytic degenerative changes were identified in multiple brainstem nuclei and ventral horns of the spinal cord. Lesions of the brainstem nuclei have been described in 1 dog, and lesions of the ventral and lateral horns have been described in 5 dogs.[12,16] Similar brainstem and spinal cord lesions are well described in cats and horses.[8,24,32,33,c] These lesions, particularly of the ventral horns (containing efferent lower motor neurons), suggest that neuronal destruction in dysautonomia is not restricted to the autonomic nervous system.

Although this study did not attempt to identify a causative agent of dysautonomia, several findings in this study suggest an acute insult such as infection or toxicosis. Development of dysautonomia in the 5 German Shorthaired Pointers and the Brittany Spaniels that were littermates and kennel mates at identical times would be unusual for a chronic degenerative process. In addition, 16 dogs had progressive involvement of the autonomic nervous system during a short period, suggesting an acute insult and progressive destruction. Hunter et al[34] suggested that *Clostridium botulinum* type C may be the causative agent of equine dysautonomia and that toxin production and subsequent absorption from the intestinal tract was responsible for the disease. *Clostridium botulinum* type C neurotoxin prevents neurotransmitter release by selective proteolysis of syntaxin, resulting in neuronal degeneration, which is unique for a *C botulinum* toxin.[34] No attempt was made in our study to assay for clostridial toxins, and we are unaware of similar studies in canine dysautonomia.

Dysautonomia was seen in a substantial number of dogs at the KSUVMTH during a 7-year period, suggesting that this disease is endemic in Kansas, as it is in Missouri. The clinical signs and physical examination findings are not pathognomonic, although an antemortem diagnosis can be made with a high degree of certainty when these are combined with pharmacologic testing. The ID histamine and atropine response tests had the fewest number of results that were inconsistent with dysautonomia (3 and 4%, respectively) and should be included with the dilute pilocarpine test, which was a less reliable test in our study. As in previous studies, the prognosis is typically grave unless dogs are mildly affected with dysuria and do not have digestive tract signs. Histopathologic findings are characteristic and confirmatory of dysautonomia, and the cause of this disease remains unknown, although evidence supports a toxicosis or infection.

[a]Kwikstat, version 2.11, TexaSoft, Cedar Hill, Tex.
[b]ArcGIS 8.1, Environmental Systems Research Institute, Redlands, Calif.
[c]Hahn CN, Mayhey IG. Equine dysautonomia—a misnomer? (abstr) *J Vet Intern Med* 2001;15:78.

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