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Feline dysautonomia in the Midwestern United States: a retrospective study of nine cases

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Dysautonomia of domestic animals is pathologically characterized by chromatolytic degeneration of the neurons in the autonomic nervous ganglia that results in clinical signs related to dysfunction or failure of the sympathetic and parasympathetic nervous systems. The exact cause is unknown. It has a poor prognosis among all species reported and no definitive treatment is available currently. To date, most reported feline cases have occurred in the United Kingdom and Scandinavia. The cases reported here highlight the clinical signs, physical examination findings, and results of autonomic nervous system function testing in nine cats with dysautonomia in the US. Feline dysautonomia is uncommon in the US, but may have a regional prevalence, as is seen in dogs with most cases reported in Missouri and Kansas.

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Dysautonomia of domestic animals is pathologically characterized by chromatolytic degeneration of the neurons in the autonomic nervous ganglia that results in clinical signs related to dysfunction or failure of the sympathetic and parasympathetic nervous systems. Having been first described in the early 1900s in horses in Scotland, the disease was not described in another animal species until 1982 when Key and Gaskell reported five cats from the United Kingdom with clinical signs of autonomic nervous system dysfunction (Greig 1928, Key and Gaskell 1982). Since the 1980s dysautonomia has been reported worldwide in horses, cats, dogs, hares, and a llama (Rochlitz and Bennett 1982, Gaskell and Edney 1985, Pollin and Sullivan 1986, Prethus and Bjerkas 1987, Edney et al 1987, Edney and Gaskell 1988, Schrauwen et al 1991, Pollin and Griffiths 1992, Griffiths and Whitewell 1993, Longshore et al 1996, Schulze et al 1997, Kik and van der Hage 1999). To date, most reported feline cases have occurred in the United Kingdom and Scandinavia (Gaskell and Edney 1985, Edney and Gaskell 1988). Degeneration of autonomic ganglia, including a marked reduction in neuronal numbers in the ganglia is observed in all cases of dysautonomia, regardless of species (Pollin and Griffiths 1992, Griffiths and Whitewell 1993, Kik and van der Hage 1999). No etiology is known for this disease in any species although a neurotoxin or an infectious agent has been postulated (Pollin and Griffiths 1992, Nunn et al 2004).

Common reported clinical findings in feline dysautonomia include depression, reduced appetite or anorexia, dysphagia, regurgitation or vomiting, constipation, dilated unresponsive pupils, prolapsed nictitating membranes, dry nose and mouth, reduced lacrimation, bradycardia, and megaesophagus (Rochlitz 1984). While the disease is typically seen in cats less than 3 years old, it has

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been recorded in felines between 2 months of age and 11 years old (Edney et al 1987). Clinical signs develop in less than 48 h in most cases and prognosis is poor with a reported 70% mortality rate (Sharp et al 1984).

The purpose of this study is to describe feline dysautonomia as it occurs in the Midwestern United States and compare these findings to reports of feline dysautonomia outside the US and to reports of canine dysautonomia in the Midwestern United States.

Methods and materials

Hospital records from June 2001 through September 2006 were reviewed in which a diagnosis of feline dysautonomia was made in cats presenting to the University of Missouri Veterinary Medical Teaching Hospital (VMTH) (four cats), the Kansas State University VMTH (four cats), or the Veterinary Specialty and Emergency Center of Kansas City (one cat). All nine cats were included in the study based on the following criteria: a complete history was available and there was either histological confirmation of the disease or cats evaluated had clinical signs consistent with dysautonomia and autonomic nervous system function testing supportive of feline dysautonomia (Table 1).

Data recorded for all cases included month of diagnosis; signalment; environment, such as multi-cat or single-cat household and indoor exclusive or free roaming; history; clinical findings; results of routine laboratory diagnostics, radiography, and ultrasonography; results of physiological and pharmacological testing for dysautonomia; treatment; outcome; and results of post-mortem evaluation.

Autonomic nervous system function testing

Some or all of the autonomic nervous system function tests were performed in eight of nine

Table 1. Historical and physical examination abnormalities noted at presentation to the veterinary referral hospital in the nine cats

Clinical finding	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 6	Cat 7	Cat 8	Cat 9
Lethargy	+	+	+	+	+	+	+	+	+
Anorexia/inappetence	+	+	+	+	+	+	+	+	+
Vomiting/regurgitation	+	−	+	+	+	+	+	+	+
Weight loss	1.8 kg	1.8 kg	−	−	U/K	−	−	−	−
Dysphagia	+	+	+	−	−	−	−	−	−
Sneezing	+	+	−	−	+	−	+	−	−
Stranguria/dysuria	−	−	−	+	−	+	+	−	−
Tenesmus/constipation	+	−	+	−	−	−	−	−	−
Diarrhea	−	−	−	−	−	−	−	−	+
Stertorous breathing	−	−	+	−	+	−	−	−	−
Abnormal gait	−	−	−	−	−	−	−	+	−
Dehydration	+	−	+	−	+	+	−	−	+
Mydriasis	+	+	+	+	+	+	+	Anisocoria	+
Pupillary light reflex	−	−	−	−	−	−	−	+	−
Prolapsed nictitans	+	-	+	+	+	+	+	+	+
Dry mucous membranes	+	+	+	+	+	+	−	−	+
Nasal discharge/ crusted nares	+	−	+	−	+	+	+	−	−
Ocular discharge	−	−	+	−	−	−	−	−	+
Heart rate	126 bpm	150 bpm	120 bpm	U/K	128 bpm	120 bpm	140 bpm	140 bpm	140 bpm
Megaesophagus	−	−	−	+	−	−	−	+	−
Distended, easily expressed urinary bladder	−	−	−	+	−	+	−	−	−
Decreased anal tone	−	−	−	−	−	+	−	−	+
Stertorous respirations	−	−	+	−	+	−	+	−	−
Ventroflexion	+	−	−	−	−	−	−	−	−

U/K = unknown.

cats. The Schirmer tear test was performed with a standard tear test strip in seven cats. Eight cats underwent pilocarpine testing in which one drop of 0.1% (four cats) and 0.01% (one of the four previous cats), or 0.05% (five cats, one also received 0.1%) pilocarpine ophthalmic solution was placed in one eye and each cat was monitored for up to 60 min for development of miosis. Test solutions were prepared by diluting 1% pilocarpine 1:10, 1:100, or 1:20 with ophthalmic irrigating solution. Atropine (0.04 mg/kg) was administered subcutaneously to two cats and 0.06 mg/kg SQ to one cat followed by heart rate assessment every 15 min (up to 60 min). A histamine response test was performed in one cat by intradermal 0.05 ml injections of histamine (1:10,000) and 0.9% saline. Anticipated responses from a healthy cat would be a Schirmer tear test result of >10 mm/min, no change in pupil size with the application of 0.1%, 0.05% or 0.01% pilocarpine, an increase in heart rate of >20 beats/minute (bpm) with SQ atropine (0.04 mg/kg or 0.06 mg/kg) and formation of a visible wheal and flare in response to histamine.

Results

Time of evaluation, signalment, and environment

Two cats were presented in the month of June (2001 and 2002), three in September (2001, 2002, and 2006), and two in January (2003 and 2006). One cat was presented in March (2006) and one in April (2003). Cats were between the ages of 10 months and 5 years (median age = 1 year). The breeds represented were domestic shorthair (seven cats), Himalayan (one cat), and Oriental Shorthair (one cat). There were six castrated males, two spayed females, and one intact female cat. Four cats were kept exclusively indoors, four were considered indoor/outdoor, and lifestyle information was not available for one cat. Six cats were from multi-cat households and were the only animal affected. Two cats were from single-cat households (one was kept exclusively indoors). It was unknown if one of the cats was from a multi- or single-cat household. One cat had been fed raw venison several times in the month prior to becoming ill, and one cat was allowed smoked salmon in addition to a dry maintenance diet; time association to illness was not recorded. All cats were native to either Missouri or Kansas and none of the cats had traveled outside these two states.

Clinical signs and physical examination findings

The duration of illness prior to examination at a referral hospital ranged from 3 days to 2 weeks. Eight cats had been examined by the primary care veterinarian prior to their presentation to one of the three referral centers. Therapies prior to referral were non-specific and included administration of subcutaneous fluids (four cats), various antibiotic therapies [amoxycillin (three cats), amoxycillin–clavulinate and enrofloxacin (one cat), ceftiofur and penicillin (one cat)], corticosteroids (two cats), vitamin B_{12} supplementation (two cats), intravenous diazepam (one cat), and intravenous famotidine and metoclopramide (one cat). Two cats received no therapy prior to referral. Therapy was associated with little or no improvement in the six cats for which information was available.

All affected cats had a history of lethargy and inappetence. Eight cats had experienced at least one episode of vomiting or regurgitation; only one had diarrhea. Other reported signs included sneezing (four cats), dysphagia (three cats), stranguria (three cats), tenesmus (two cats), open-mouthed breathing (one cat), abnormal gait (one cat), and cervical ventroflexion (one cat). Two cats had recorded weight loss (1.8 kg in each) prior to presentation.

Physical examination revealed numerous abnormalities and involvement of multiple systems. Eight cats exhibited bilateral mydriasis that was non-responsive to light. Mydriasis was accompanied by bilateral prolapse of the nictitans in seven cats. One cat, which initially had anisocoria with bilateral prolapsed nictitans, developed mydraisis 4 days after presentation to the referral hospital. Dry mucous membranes (seven cats) and dry, crusted nasal secretions (five cats) were observed in most cats. Stertorous breathing due to obstruction of the nares with crusted nasal secretions was noted in two cats. Seven cats ($n = 8$; heart rate information was unavailable for one cat) had heart rates that were less than 150 bpm (range 120–150 bpm; median 136 bpm) despite apparent nervousness and/or dehydration in some. The urinary bladder was distended and large and urine was easily expressed in two cats; in one of these cats, anal tone was also decreased. Decreased anal tone was noted in one additional cat.

Diagnostic evaluation

A complete blood count and serum chemistry panel were performed in six of nine cats. No important abnormalities were recorded. Six cats

were tested with a standard feline leukemia virus and feline immunodefficiency virus (FeLV/FIV) enzyme-linked immunosorbent assay (ELISA) snap test and were negative. Urinalysis was performed on samples obtained from four cats, and three had markedly concentrated urine (specific gravity > 1.055). Thoracic radiography was performed on four of the nine cats at initial presentation to the referral hospital and was unremarkable in two, and showed esophageal dilation that was characterized as mild in one cat and pronounced in the other. Abdominal radiographs performed in three cats showed splenomegaly in one cat and evidence of ileus in the other two cats. Abdominal ultrasonography performed in the latter two cats revealed a fluid filled stomach and duodenum with no evident peristaltic contractions in both cats, a thickened ileum with loss of layering in one cat as well as evidence of pancreatitis observed as a hypoechoic pancreas surrounded by hyperechoic fat, and evidence of gastrointestinal parasites observed as parallel linear structures within the lumen of the duodenum and stomach in the other cat.

Schirmer tear testing, performed in seven cats, indicated decreased tear production (<5 mm/min in each eye (oculus uterque, OU)) in all seven cats. In one cat tear production was normal at presentation and was decreased (2 mm/min OU) 3 days later. Seven of eight cats responded with the development of miosis when dilute pilocarpine was placed in one eye. Time to development of miosis with dilute pilocarpine was ≤ 35 min in all seven cats. One cat which did not respond to 0.05% pilocarpine in one eye developed miosis with 0.1% pilocarpine placed in the other eye. No miosis was noted in the eye of one cat tested with a 0.01% dilution of pilocarpine; this cat developed miosis in the eye in which 0.1% pilocarpine was placed. The one cat that did not develop miosis was administered a 0.05% diluted solution only. An atropine response test was performed in three cats (0.04 mg/kg SQ to two cats and 0.06 mg/kg SQ to one cat). Heart rates in all three cats varied <20 bpm from the starting heart rate during the test period. A histamine response test was performed in one cat by intradermal 0.05 ml injections of histamine (1:10,000) and 0.9% saline. Only a mild wheal response was noted.

Clinical course and outcome

Four cats were euthanased within 48 h of presentation to the referral center. Five cats received various supportive therapies including hospitalization and intravenous fluids (four cats), lubricating ophthalmic ointment (four cats), 1% pilocarpine ophthalmic solution (four cats), metoclopramide (two cats), famotidine (two cats), cyproheptadine (two cats), cisapride (one cat), lactulose (one cat), thiamine supplementation (one cat after developing cervical ventroflexion in the face of normokalemia), and percutaneous endoscopic gastrostomy (PEG) tube placement (one cat). One cat was euthanased after 4 days of hospitalization, and another after 5 days. In each case euthanasia was due to persistent vomiting and regurgitation, ongoing weight loss (0.3 kg), and profound inappetence. Three cats were discharged from the referral hospital. One cat returned 3 days after discharge for humane euthanasia because of profound regurgitation, dysuria, and dyschezia, signs that had not been recorded during previous hospitalization, as well as a 0.5 kg weight loss. One cat returned to the referral hospital several hours after discharge with respiratory distress. Pulmonary edema was identified via thoracic radiographs and an echocardiogram performed on this cat revealed an enlarged left atrium and increased fractional shortening (55.4%). Mitral regurgitation was not recorded. This cat was again hospitalized, treated with furosemide (1 mg/kg IV q 24 h), and discharged 3 days later. The cat was sent home with oral furosemide (3.125 mg PO q 24 h) for approximately 2 weeks. At 6 months after diagnosis, the heart rate was recorded to be 200 bpm and at 1 year after diagnosis the cat had gained 1 kg in body weight; unresponsive bilateral pupil dilation remained, however. This cat was lost to follow-up after 1 year. The third cat discharged from the hospital received a PEG tube 2 weeks after initial diagnosis due to a 2 kg weight loss. This cat was maintained with tube feedings for approximately 11 months before dying at home of an undetermined cause (via communications with the referring veterinarian).

Histopathologic findings

Four cats had post-mortem examinations performed. In all cases necropsy findings were consistent with feline dysautonomia. Autonomic ganglia that were sectioned for histology were depleted of neurons, containing few vacuolated, eosinophilic ganglion cells. Nuclei of affected neurons were shrunken and pyknotic. Inflammation was absent except in one cat with scant aggregates of lymphocytes and plasma cells observed in several autonomic ganglia. Two cats

had neuronal degeneration present in the myenteric plexus, and one of these cats also had neuronal loss and degeneration with mild gliosis in the motor nucleus of the vagus nerve. The other had spinal nerve roots affected with normal nerve cell bodies mixed with neurons that were swollen with a loss of cytoplasmic basophilia and pyknotic nuclei.

Discussion

Although numerous cases of canine dysautonomia have been reported in the US (Longshore et al 1996, Harkin et al 2002) only four confirmed cases of feline dyautonomia were reported in the US during the years 1986–1994 (Bromberg and Cabaniss 1988, Canton et al 1988, Levy et al 1994, Guilford et al 1998). The low numbers of US feline cases stand in stark contrast to the hundreds of feline cases recorded in Europe during that same period of time (Gaskell and Edney 1985, Edney and Gaskell 1988). Interestingly, one cat was native of Kansas (Guilford et al 1998) and two of the four US feline cases are known to have spent time in countries where feline dysautonomia is more common (Bromberg and Cabaniss 1988, Canton et al 1988). This study describes nine cases of feline dysautonomia in the US cats.

The findings of the current study are consistent with previous reports that young cats are most often affected. An average age of 2.25 years was reported in one British study (Sharp et al 1984). Feline dysautonomia has been reported to affect multiple cats in the same household, although it is more common to have only one cat affected (Rochlitz 1984, Sharp et al 1984, Symonds et al 1995, Cave et al 2003). Five cats in the present study came from multi-cat households; however, these cats were the only ones affected in their respective households. Signs of autonomic dysfunction usually progress over a period of 48 h; however, Sharp et al (1984) in a series of 40 cases of feline dysautonomia reported 28% of cases having a more slowly progressive course of disease with signs developing over up to a 7-day period. For one cat in the present study, the time course of progression is known with signs of autonomic dysfunction progressing over an 8-day period. The remaining cats were sick for 1–2 weeks before their presentation to the referral center, and information about the progression of clinical signs/autonomic system dysfunction was not available.

Dysautonomia typically occurs in cats with routine access to the outdoors (Edney et al 1987) and an indoor lifestyle might suggest lower risk for developing the disease. In this study, four cats were determined to have at least some access to the outdoors and four were described as exclusively indoor cats by their owners. Thus, as 50% of the affected cats in the study group were housed exclusively indoors and dysautonomia has been previously recognized in indoor cats (Rochlitz 1984, Sharp et al 1984), the patient's housing conditions may not significantly modulate the risk for developing dysautonomia.

The most common signs and physical examination findings in this group of cats included lethargy, decreased appetite or anorexia, dilation of the pupils with absent pupillary light reflexes, regurgitation or vomiting, dry mucous membranes, dried nasal secretions, sneezing, reduced tear production, prolapse of the nictitating membrane, and bradycardia. Less common clinical features include dysuria, dysphagia, decreased anal tone, ocular discharge, diarrhea, megaesophagus, ataxia, and ventroflexion of the neck with the forehead touching the ground when sleeping. These findings are consistent with previous reports (Rochlitz 1984, Sharp et al 1984). However, dysphagia (45/46 cats) and megaesophagus (32/36 cats) were reported more frequently and bradycardia (6/26) less frequently in one study (Rochlitz 1984) and constipation was also noted more frequently in two studies evaluating feline dysautonomia in the UK (Sharp et al 1984, Rochlitz 1984). Given the limited numbers of cases in this study frequency of clinical signs may not be representative. Other than bradycardia, no cardiac abnormalities have been directly associated with dysautonomia in cats. The cause of the left atrial enlargement and pulmonary congestion in one cat in this study is unknown but might have been due to fluid overload. Common clinical features of canine dysautonomia reported in the US are similar to those reported in cats of this series; however, reduced or absent anal tone, dysuria, and diarrhea occur more commonly in dogs and dilation of pupils less commonly (Longshore et al 1996, Harkin et al 2002).

Of particular significance is the regional clustering of cases of dysautonomia seen in both the US and Europe (Gaskell and Edney 1985, Edney and Gaskell 1988, Pollin and Griffiths 1992) among various species. The vast majority of canine dysautonomia has been reported in dogs inhabiting eastern Kansas and western and southern Missouri (Longshore et al 1996, Berghaus et al 2001, Harkin et al 2002). All nine cats reported in the present study were from either eastern Kansas or western Missouri. Although the cause of the

disease is unknown, the regional prevalence of dysautonomia should raise suspicion of a common etiology and perhaps a relation with specific climatic requirements.

A presumptive diagnosis of dysautonomia can be made based upon clinical signs and physical examination findings. Subsequent pharmacological testing can be used to confirm loss of autonomic function. Agents that have been used to test autonomic nervous system function via their action on heart rate and blood pressure in anesthetized cats include physostigmine, phenylepherine, epinephrine, nitroprusside, ephedrine, tyramine, propranolol, methacholine, neostigmine, and edrophonium (Edney et al 1987, Guilford et al 1998). However, tests that employ these substances are not useful in the clinical setting, may be detrimental to patients, and are not recommended. Pharmacologic agents used for testing autonomic function in the cats in this series included the administration of dilute pilocarpine ophthalmic solution, subcutaneous injection of atropine, and intradermal administration of histamine. Miosis after instillation of dilute pilocarpine is consistent with dysautonomia and reflects denervation-induced hypersensitivity of the iris ciliary muscle to parasympathetic agonists. Not all of the cats in this series that were evaluated with the pilocarpine-response test exhibited a positive response despite clinical signs of dysautonomia. A negative response to pilocarpine does not rule out dysautonomia in cats, however, as dysautonomia was subsequently confirmed at necropsy in one non-responder. Likewise, the results of Harkin et al (2002) indicate that 10–15% of dogs with histologically confirmed dysautonomia do not respond to dilute pilocarpine. The pupil's sensitivity to pilocarpine likely depends on numerous factors, such as the timing of the testing with respect to the onset or stage of the disease or the severity of autonomic damage. Failure to respond to lower dilutions of pilocarpine may be a result of technical error, resulting in no administration of pilocarpine. Subcutaneous administration of atropine, a parasympatholytic drug, failed to increase the heart rate in the four cats with dysautonomia in which the test was performed and indicates damage to sympathetic nervous system or lack of parasympathetic input. Likewise, Harkin et al (2002) reported a change in heart rate of $\leq$20 bpm in the majority (27/28) of confirmed dysautonomic dogs tested with the atropine response test.

The intradermal histamine test has been used in the diagnosis of dysautonomia in humans and dogs and has been described by Guilford et al in one cat (Smith and Dancis 1963, Wise and Lappin 1990, Guilford et al 1998, Harkin et al 2002). The flare response is dependent on a sympathetic neuron reflex, and the single cat tested in this series did not develop a flare at the site of histamine injection and only a mild wheal. The histamine test may not be useful in the evaluation of cats with suspected dysautonomia as Guilford et al (1998) observed no differences in the histamine responses between the cat with dysautonomia and four unaffected control cats. The infrequent use of the histamine response test to evaluate the cats in our study group (only one cat was tested using histamine) might reflect clinicians' decision not to incorporate histamine testing into the dysautonomia work-up in light of the results of Guilford et al (1998).

The unusual constellation of clinical signs and abnormal results from autonomic testing is sufficient to justify a clinical diagnosis of dysautonomia in most cases. However, definitive diagnosis of feline dysautonomia is based upon demonstration of characteristic histological lesions in the autonomic ganglia. Descriptions of the gross and microscopic pathology of dysautonomia have been extensively reviewed elsewhere (Sharp et al 1984, Griffiths et al 1985, Edney et al 1987, Pollin and Griffiths 1992). Generally, both parasympathetic and sympathetic ganglia are usually affected to the same degree, although disease chronicity may alter the pattern and degree of neuronal loss. Dorsal root ganglia and the ganglia of cranial nerves may also be affected. Enteric and central nervous system lesions have been reported in cats, as well as in dogs and horses, with dysautonomia (Sharp et al 1984, Griffiths et al 1985, Pollin and Sullivan 1986, Prethus and Bjerkas 1987, Edney et al 1987, Pollin and Griffiths 1992, Longshore et al 1996, Schulze et al 1997, Harkin et al 2002). Two of the cats examined in this study had neuronal degeneration seen in the myenteric plexus. The cat that exhibited ventroflexion in the face of normokalemia did have a necropsy performed; no abnormality in the nucleus of the accessory nerve or in the lower motor nucleus in the cervical spinal cord was recorded. No necropsy was performed in the aforementioned cat with ultrasonographic evidence of pancreatitis.

Previous studies indicate that feline dysautonomia is associated with a poor prognosis. No definitive treatment is currently available. In a large case series of 40 cats with dysautonomia, Sharp and colleagues reported nearly 50% of cats

were euthanased or died less than 2 months after the onset of disease. By 18 months, 70% of cats had died or were euthanased. Complete resolution occurred in only about 25% of affected cats and partial recovery was noted in some cats (Sharp et al 1984). Only one of the cats in this study could be classified as making a recovery. The cat was able to maintain body weight with oral consumption and fecal and urinary incontinence were not seen in this cat. These factors likely played a role in survival. Although prognostic factors have not been thoroughly evaluated for dysautonomic cats, Rochlitz reported that cats with prolonged anorexia, frequent regurgitation or vomiting, severe megaesophagus or non-responsive fecal or urinary retention were more likely to be euthanased; and, that cats which survived showed a response to therapy within 7–10 days (Rochlitz 1984). Cats showing mild clinical signs or signs limited to a particular organ system (eg, ocular abnormalities) have the best chance for long-term survival. However, as aptly demonstrated in the present study signs of progressive autonomic damage may continue and often lead to euthanasia or death within weeks to months following diagnosis.

In summary feline dysautonomia, although uncommon, is a devastating disease with a grave prognosis and should be suspected in any cat presenting with the combination of vomiting, anorexia, elevated third eyelids, dilated pupils, and decreased pupillary light responses.

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