Dysautonomia in 53 cats and dogs: A retrospective review of clinical data and outcome

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Abstract

Background

Dysautonomia is a disease characterised by degeneration of autonomic neurons.

Methods

The aim of this study was to perform a retrospective multicentre review of clinical data relating to cats and dogs diagnosed with dysautonomia and to evaluate their outcome.

Results

Cats (n=34) and dogs (n=19) with clinical signs consistent with dysautonomia were considered for this retrospective study. Reported clinical findings included oesophageal and gastrointestinal dysmotility and distension, urinary retention, reduced or absent tear production, third eyelid protrusion and inappropriate mydriasis. Treatment was supportive, and included gastrointestinal prokinetics, feeding tube placement (oesophageal and percutaneous endoscopic gastrostomy tubes) and medications to treat urinary retention. The survival to discharge was 29% in cats and 47% in dogs. The overall survival in cats was 21% and 32% in dogs. Survival of greater than two years was seen in six cats and three dogs.

Conclusion

This paper illustrates that some individuals are able to survive this disease and can have a good long-term prognosis, which is an infrequently reported finding for this disease.

Introduction

Dysautonomia is a term used to describe dysfunction of the autonomic nervous system (ANS). Pathologically, dysautonomia is characterised by neuronal degeneration.

Dysautonomia has been reported worldwide in a variety of species including horses[1], cats[2 3], dogs[4], hares[5] and a llama[6]. The aetiology of dysautonomia in veterinary species remains uncertain, although a possible association with *Clostridium botulinum* (type C/D) neurotoxin has been described in horses and cats[1 7 8]. McGorum *et al.* (2017)[9] reported that dysautonomic cats were deficient in sulpha-containing amino acids (methionine and cysteine/ cystine) despite an adequate dietary intake. They hypothesised this deficiency was due to consumption of an unidentified dietary neurotoxic mycotoxin or xenobiotic that resulted in the signs of dysautonomia as well as the deficiency in sulpha-containing amino acids [9]. Outbreaks have been reported in

both cats[10] and dogs[11 12] indicating possible contagion or interaction with/ ingestion of contaminated food, an environmental toxin or infectious pathogen (e.g. *Clostridium botulinum* type C neurotoxin).

In both feline and canine dysautonomia commonly reported clinical signs include depression, anorexia or hyporexia, dysphagia, dysuria, regurgitation, vomiting, constipation, dilated and unresponsive pupils, third eyelid protrusion, dry nares and mucosae, reduced lacrimation, orthostatic hypotension, and bradycardia[13 14 15]. Reduced anal tone has also been described, although less commonly, likely caused by denervation of the internal anal sphincter which is autonomically innervated. Non-autonomic nervous system signs such as ataxia and proprioceptive deficits have also been described in both cats and dogs[13 16].

Definitive diagnosis can be confirmed by *post mortem* identification of pathognomonic lesions in the ventral horns of the spinal cord, the autonomic ganglia and/or the brainstem nuclei[4, 16]. A histopathological *ante mortem* diagnosis can sometimes be made on full thickness intestinal biopsies. Findings in acute cases include neuronal chromatolytic degeneration and nuclear pyknosis, while neuronal loss and proliferation of satellite cells are seen in more chronic cases[17].

The aim of this study was to perform a retrospective multicentre review of clinical data relating to cats and dogs diagnosed with dysautonomia, and to evaluate the outcome in those patients. This is the first large scale study on feline and canine dysautonomia in the United Kingdom (UK) for over 30 years. Given improvements in veterinary practice, we wanted to evaluate whether previously reported high mortality rates persist. We also aim to describe patient characteristics, incidence of multiple-pet households being affected, diagnostic tests, rural or urban location and therapeutic interventions.

Methods and materials

Hospital records from the author's referral clinics, between 2007 and 2016, were searched for cats and dogs with a clinical diagnosis of dysautonomia. Data were extracted and collated in a spreadsheet; data collected included presenting signs, physical examination findings, clinicopathological findings, results of pharmacological testing results, outcome, management and details of husbandry. Address details were obtained to ascertain if location rural (i.e. primarily countryside), urban (i.e. city centre, minimal 'green' spaces) or semi-urban (i.e. relatively densely developed but with ready access to 'green' spaces), based on map examinations of the areas.

Medical records were reviewed for presenting signs and physical examination findings consistent with dysautonomia, including gastrointestinal signs, urinary retention and respiratory signs, protrusion of the third

eyelids, mydriasis, absent or delayed pupillary light response (PLR), bradycardia (defined as a heart rate less than 120 in cats and less than 70 in dogs[18]), altered anal tone, and excessively dry mucous membranes or nares.

Pharmacological testing was performed as described by O'Brien and Johnson (2002)[19] and Harkin *et al.* (2002)[4]. The pharmacological test used and results were extracted from the medical records when available.

Cases were included when dysautonomia was considered the most plausible diagnosis for the clinical findings and when other possible differential diagnoses had been eliminated to the satisfaction of the attending clinician. A definitive *post mortem* diagnosis was available in some instances.

Results

A total of 53 cases were included; 34 cats and 19 dogs –

Cats

There were 19 male neutered, two male entire, eight neutered female and five entire female cats. Their median age was 3.9 years (range 17 weeks to 13 years and 4 months). There were 19 domestic shorthair cats, four Siamese, two Bengal, two Maine Coon, two Burmese and one each of Norwegian Forest cat, British Shorthair, British Blue, Burmilla and Ragdoll cat.

Dogs

There were seven male neutered, two male entire, three female neutered and seven female entire dogs. The median age was 3.3 years (range 7 months to 9 years and 3 months). There were three crossbreed dogs, three Labrador retrievers, two Cocker spaniels, two Jack Russell terriers, two border collies, and one each of Great Dane, West Highland White terrier, Japanese Shiba Inu, German Shepherd dog, Border terrier, Siberian Husky and Springer spaniel.

Travel history was available for 24 cases; none had travelled outside the United Kingdom.

Location

A total of 13 cats and six dogs lived in a predominately urban environment; 14 cats and eight dogs lived predominately in a rural environment and seven cats and five dogs lived in a semi-urban environment.

Multi-pet households

A total of 19 animals were from multi-pet households. Nine cats were from multi-cat households where all in-contacts were unaffected. One cat and one dog each lived with an unaffected dog. There were four instances where two individuals of the same species were affected in a single household (Table 1). Sixteen animals came from single pet households. Information regarding other pets in the household was not available for 18 cases.

Table 1: Instances where more than one animal were affected by dysautonomia within the same household.

Signalment	Clinical signs	Time lapse	Treatment	Outcome
Two 11 year old Burmese cats, both neutered, one male and one female.	Bilateral third eyelid protrusion, mydriasis, anorexia, lethargy, dehydration	Male cat developed clinical signs two weeks prior to the female	Supportive and symptomatic including oesophageal feeding tube placement	Both cases euthanised. *Post mortem* examinations; the male had changes consistent with dysautonomia, whereas insufficient ganglia were examined for a definitive diagnosis in the female.
Two Siamese cats, both were neutered females, one five years old, one 11 years old.	Vomiting, anorexia, dry nares, bilateral mydriasis with third eyelid protrusion	Developed clinical signs concurrently	Gastrointestinal prokinetics, PEG tube placement and antiemetics	The younger cat was euthanised after eight days; no *post mortem* examination was performed. The older cat was euthanised 186 days later due to an unrelated disease, all dysautonomia signs resolved.
Two one year old male neutered domestic short haired cats	Constipation, dehydration, xerostomia, third eyelid protrusion, anorexia, vomiting and regurgitation	Developed clinical signs concurrently	None	Both were euthanised on the day of presentation and post mortem examinations confirmed dysautonomia.
Two year old female Border terrier and a two year 6 month old female Labradoodle	Vomiting, diarrhoea, lethargy, anorexia, altered anal tone, ulcerative keratitis secondary to absent tear production and pollakiuria	Developed clinical signs concurrently	Bethanecol, metoclopramide and ocular ulcer management. The labradoodle also received metronidazole.	Border terrier failed to respond to treatment and was euthanised after five days. The Labradoodle made a progressive return to normality; this case is still alive one year and one month following discharge.

Duration of illness prior to referral

Information regarding duration of illness prior to referral was available for all but two cats and one dog. The median time to referral after the onset of clinical signs was 13.5 days (range 0-60 days) for cats and 32.3 days (range 2-365 days) for dogs.

Presenting signs, physical examination findings, pharmacological testing and diagnostic imaging results

Reported presenting signs are detailed in Table 2 (cats) and Table 3 (dogs), while reported ocular signs are detailed in Table 4.

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155 Table 2: Presenting signs recorded for cats with dysautonomia

Presenting sign	Number of cats affected (total 34) [%]	Data not available (no. of cats)
Anorexia or hyporexia	24 [92]	8
Vomiting or regurgitation	29 [85]	0
Constipation	17 [55]	3
Nasal discharge or crusting	13 [46]	6
Lower urinary tract signs	13 [43]	4
Respiratory signs	11 [37]	4
Bradycardia	10 [30]	1
Altered anal tone	4 [20]	14
Diarrhoea	5 [16]	3

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158 Table 3: Presenting signs recorded for dogs with dysautonomia

Presenting sign	Number of dogs affected (total 19) [%]	Data not available (no. of dogs)
Anorexia or hyporexia	10 [100]	9
Vomiting or regurgitation	17 [94]	1
Lower urinary tract signs	14 [82]	2
Altered anal tone	8 [73]	8
Diarrhoea	12 [67]	1
Nasal discharge or crusting	9 [56]	3
Respiratory signs	8 [44]	1
Bradycardia	1 [6]	1
Constipation	1 [6]	3

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161 Table 4: Specific ocular signs in dogs and cats

162 Key: PLR - pupillary light response; STT – Schirmer tear test

Ocular sign	Number of cats affected (total 34) [%]	Result not available (no. of cats)	Number of dogs affected (total 19) [%]	Result not available (no. of dogs)
Abnormal STT	26 [90]	5	12 [86]	5
Absent or delayed PLR	15 [88]	17	8 [73]	8

Pilocarpine response test	19 [86]	12	8 [73]	8
Mydriasis	22 [81]	7	6 [55]	8
Third eyelid protrusion	20 [77]	8	9 [60]	4

Cats and dogs presented with broadly similar signs, with vomiting or regurgitation (85% cats; 94% dogs) and hyporexia (92% cats; 100% dogs) common in both species. Urinary tract signs were reported in both species, but were more common in dogs than cats (43% cats; 82% dogs).

The Schirmer Tear Test (STT) was commonly utilised. It was found to be abnormal (<15mm in 60 seconds), in at least one eye, in 90% of cats and 86% of dogs tested. An ocular pilocarpine response test was used as a diagnostic aid in 22 cats, and was reported to be consistent with dysautonomia by the attending clinician in 19 cases (86%), and 11 dogs, with a result consistent with dysautonomia in 8 cases (73%). An atropine response test was performed in three cats, one with a resting heart rate of 52 thus meeting the bradycardia inclusion criteria, and two with a rate greater than 120 beats per minute but considered to be inappropriately bradycardic by the attending clinician (136 and 140 beats per minute). There was no response to atropine in all three cats, indicating a lack of appropriate sympathetic input to the heart. A histamine response test has been described in the literature[4 12 19 20] but was not utilised in any of the cases. Additionally, acetylcholine receptor antibodies were not measured in any of the cases reviewed.

Diagnostic imaging modalities employed included thoracic radiography (cats n=25, dogs n=12), abdominal radiography (cats n=11, dogs n=8), abdominal ultrasound (cats n=20, dogs n=9) and, less commonly, computerised tomography (cats n=6, dogs n=1). Aspiration pneumonia was identified using thoracic imaging in 13% cats (n=4) and 31% of dogs (n=4), while megaoesophagus was identified in 65% of cats (n=20) and 23% of dogs (n=3). Abdominal imaging identified gastrointestinal dilation with gas or fluid in nine cats and five dogs, excess faeces consistent with colonic hypomotility in three cats and one dog, and urinary bladder distension in three cats and one dog.

Treatment

Various treatments and medications were utilised to help manage the clinical signs associated with dysautonomia in this study. Non-specific supportive treatments such as intravenous fluid therapy and ocular lubrication were not specifically recorded.

Hospitalisation

Overall, cases were hospitalised for a median of three days (range 0-29). Cases that survived and experienced a resolution of their clinical signs were hospitalised for a longer median period (median six days, range 0-11)

compared with those cases that died (median 2.9 days, range 0-29). Additionally, 50% of the cases that survived were hospitalised for seven days or more compared to only 16% of the cases that died. Information regarding the duration of hospitalisation was not available for five cases.

Gastrointestinal dysmotility

Gastrointestinal prokinetic medications were commonly prescribed to animals with gastrointestinal dysmotility. Cisapride (Cisapride®; Summit Veterinary Pharmaceuticals) was given to 10 cats and one dog, metoclopramide (Emeprid®; Ceva) prescribed to 12 cats and nine dogs, and ranitidine (Zantac®; GlaxoSmithKline) prescribed to 10 cats and four dogs. Two dogs and 10 cats received multiple gastrointestinal prokinetic medications.

Maropitant (Cerenia®; Zoetis) was prescribed to reduce nausea/ vomiting in four cats and four dogs. Omeprazole (Losec®; AstraZeneca) was employed as a gastric protectant in six cats and one dog.

Lactulose (Lactulose; Sandoz) was administered to three cats and one dog to manage constipation and in one cat for suspected hepatic encephalopathy secondary to hepatic lipidosis.

Urinary retention

Bethanecol (Myotonine®; Glenwood GMBH) was prescribed in nine cats and five dogs, prazosin (Hypovase®; Pfizer) in two cats and two dogs, and phenoxybenazmine (Dibenyline®; Dales Pharmaceuticals Ltd) to one cat.

Other medications and management strategies

Antimicrobials were administered to nine cats and 11 dogs most commonly to treat suspected or confirmed aspiration pneumonia. Prednisolone (Prednidale®; Dechra) was prescribed to two dogs; one due to concurrent immune mediated haemolytic anaemia, the reason was not recorded in the second patient. Feeding tubes, either percutaneous endoscopic gastrostomy (PEG) tubes or oesophageal tubes, were placed in 18 cats (of which five survived to discharge) and three dogs (of which two survived to discharge). Feeding tube complications were only reported in one cat; failure of stoma formation following PEG tube removal contributed to the decision for euthanasia in this case. Long term (minimum of 186 days) resolution of clinical signs was seen in four cases in which feeding tubes were placed (PEG n= 3, oesophageal n=1).

Of the cats which survived to discharge three were euthanised within eight days due to signs consistent with dysautonomia/ poor response to treatment. The remaining two had long-term resolution of their clinical signs (at least seven month follow up in both cats). Of the dogs which survived to discharge clinical signs resolved in one case who survived at least three years and 11 months post discharge. Follow up information is not available for the other dog.

Exploratory laparotomies were performed in four dogs and one cat prior to referral. In all instances the small intestinal/ gastric dilation seen on diagnostic imaging was considered compatible with an intestinal obstruction prior to surgery. No evidence of underlying gross pathology was identified during these surgeries. Of these patients, only one dog survived to discharge, the rest were euthanised due to clinical signs consistent with dysautonomia. Aspiration pneumonia was diagnosed in one of these dogs; PEG tubes were placed in two of these dogs.

Survival

Cats

Of the 34 cats included in this study, 10 survived to discharge (29%). Three of these 10 cats were euthanised within eight days of discharge due to progressive signs consistent with dysautonomia. One case was euthanised 186 days following discharge from hospital due to suspected triaditis, with the dysautonomia having resolved. There was complete and long-term (greater than two years) resolution of dysautonomia in six cases, which are discussed below.

Dogs

Of the 19 dogs included in this study, nine dogs survived to discharge (47%). Two cases were euthanised the week following discharge due to progressive clinical signs consistent with dysautonomia. One dog was euthanised seven months after discharge due to progressive clinical signs. One dog had resolution of clinical signs within two months of presentation and this case is still alive with no clinical signs 11 months following discharge. One dog had resolution of clinical signs within seven days of discharge but was lost to follow up. Long-term survival (greater than two years) was seen in three patients who are discussed below. Follow up information was not available for the remaining case.

Long Term Survivors

Survival longer than two years was seen in six cats and three dogs (Table 5). One dog required on-going ocular lubricants as tear production never recovered. All other cases had complete resolution of their presenting signs and did not require any long-term treatments.

Table 5: Long term survivors of canine and feline dysautonomia

Key: STT - Schirmer tear test; DSH – domestic short hair; PLR - pupillary light response; PEG – percutaneously placed gastrostomy tube

Signalment	**Clinical Signs**	**Diagnostic imaging**	**STT**	**Pilocarpine response test**	**Treatment**	**Outcome**
One year old,	Vomiting, regurgitation, lethargy, coughing, mydriasis, absent PLR,	Thoracic radiographs and abdominal	R 4mm/min L 11mm/min	No ocular response (% dilution and the	Postural feeding from a height and ranitidine.	Improvement over months until complete resolution

neutered female DSH	protrusion of the third eyelid, constipation and crusty/dry nares.	ultrasound were within normal limits		time taken not recorded).		of clinical signs. Patient alive at the time of publication four years after discharge.
Four year old, neutered male DSH	Vomiting, lethargy, inappetence, dysuria, pollakiuria, bilateral mydriasis, third eyelid protrusion, dysphagia and absent PLRs.	Abdominal/ thoracic radiography: distended bladder, otherwise unremarkable. Abdominal ultrasound unremarkable.	R 0mm/min L 0mm/min	Not performed	Gastrointestinal signs self-resolved. Bethanecol, phenoxybenzamine and alprazolam for urinary signs.	Normal micturition returned over the proceeding weeks. PLR started to return eight months later. Patient is alive and asymptomatic six years and three months later.
Nine month old, female neutered DSH	Hyporexia, dysphagia, tenesmus, coughing, sneezing, weakness, xerostomia, tachypnoea, reduced anal tone, third eyelid protrusion and marked mydriasis.	Thoracic radiographs: megaoesophagus. Abdominal ultrasound unremarkable.	R 0mm/min L 0mm/min	Miosis within nine minutes (% not recorded).	Ranitidine, cisapride, antimicrobials, PEG tube placement.	Clinical signs gradually resolved. Patient was euthanised three years and seven months after diagnosis due to development of arterial thromboembolism of unknown aetiology.
Four year old, male neutered Bengal cat	Hyporexia, third eyelid protrusion, lethargy, sneezing, bradycardia (heart rate 100 beats per minute) and a bilateral, clear nasal discharge.	Abdominal ultrasound unremarkable.	Not performed	Not performed	Extremely fractious patient; owner unable to medicate, consequently no treatment prescribed.	Recovered over a few months until all clinical signs fully resolved. Clinically well four years and three months following discharge
18 month old, male neutered DSH	Anorexia, lethargy, weight loss, mydriasis, dry nares, absent PLRs and dehydration.	Thoracic radiography and abdominal ultrasound were both unremarkable. Fluoroscopy; reduced oesophageal motility	R 0mm/min L 0mm/min	Miosis achieved (% dilution and the time taken not recorded).	Oesophageal feeding tube placement, cisapride and ocular lubricant	Hospitalised for 11 days. Cisapride continued for six months. Case lost to follow up three years and seven months later; at this time clinical signs had resolved.
Four year old, male neutered DSH	Two month history of faecal incontinence, third eyelid protrusion, bradycardia (heart rate 96-116 beats per minute), occasional vomiting and diarrhoea	None performed	R 0mm/min L 0mm/min	Not performed	Ocular lubrication alone	Clinical signs resolved over approximately a six month period. This individual is still alive at the time of publication, five years

						and six months following discharge.
Eight month old, female Labrador	Initially only dysuria, stranguria, urinary retention, then developed xerostomia, vomiting, regurgitation, diarrhoea, hyporexia, lethargy, corneal ulceration, bilateral purulent ocular and nasal discharge and mild generalised ataxia.	None performed	Noted to be "reduced" but values not recorded	Not performed	Prazosin and ocular ulcer management.	Alive two years following discharge, resolution of urinary signs, dry-eye management on-going.
Seven months old, female Labrador	Diarrhoea, vomiting, coughing, pollakiuria. Tachypnoea, harsh lung sounds on auscultation, bilateral third eyelid protrusion, absent PLRs and a reduced gag reflex.	Thoracic radiographs unremarkable.	Not performed	Miosis within 30 minutes (% not recorded).	Metoclopramide constant rate infusion, amoxicillin clavulanate, maropitant and omeprazole. PEG tube placement	Five days of hospitalisation. PEG tube removed after 7 weeks, clinical signs had resolved. Still alive and asymptomatic three years and 11 months following the initial presentation.
Five year old, female neutered Border collie	Lethargy, hyporexia, dysuria, stranguria, urinary incontinence, coughing, dysphagia, increased upper respiratory tract noise, bilateral third eyelid protrusion and decreased anal tone.	Abdominal ultrasound was unremarkable, mild aspiration pneumonia was identified on computerised tomography.	Not performed	Not performed	Oxygen therapy and broad spectrum antimicrobials.	Alive three years following discharge but third eyelid protrusion, decreased anal tone and dysuria remain static.

Post Mortem examination

Post mortem examinations were performed in 12 cats and two dogs. Feline dysautonomia was definitively diagnosed at *post mortem* in 10 cases and canine dysautonomia in two cases. In two cats, the *post mortem* findings were inconclusive; in one case insufficient nervous tissue was provided for examination and in the second there were some features consistent with dysautonomia, such as a diffuse reduction in the number of neurones, but this was deemed insufficient for a definitive diagnosis. The findings were consistent with the previous reports[14 15], including neurone depletion within the autonomic ganglia, affected cells showed chromatolysis, vacuolated cytoplasm, cell shrinkage and pyknotic nuclei. No infectious organisms were identified.

Post mortem examinations were not performed in the remaining 22 cats and 17 dogs, however, the disease was strongly suspected based on clinical signs and results of pharmacological testing.

Clinical Significance

This is the first large scale multicentre study of canine and feline dysautonomia from the UK in over 30 years. Dysautonomia remains a rare diagnosis in general and referral practice. However, given the challenges associated with a definitive diagnosis and spontaneous regression in some animals, it is possible that mildly affected individuals are treated symptomatically without dysautonomia being considered. This paper may therefore be a poor representation of all dysautonomia cases, having been biased towards more severely affected animals. Nevertheless, it is important to raise awareness of dysautonomia as a differential diagnosis in animals with gastrointestinal signs, in order to prevent unnecessary diagnostic tests and associated morbidity.

Achieving a definitive *ante mortem* diagnosis of dysautonomia relies on histopathological examination of full thickness intestinal biopsies, including assessment of the mesenteric plexus. Otherwise, diagnosis is reliant on histological identification of pathognomonic lesions in the spinal cord, autonomic ganglia and/ or the brainstem nuclei, none of which can be performed *ante mortem*. Intestinal biopsies were not performed in any of the cases included in this study, therefore diagnosis was based on the attending clinician's ability to ruling out other differential diagnoses (unless a *post mortem* examination was available to confirm the diagnosis).

This study does have some inherent weaknesses; it is retrospective and multicentre resulting in incomplete data in some instances, and a lack of standardisation of investigations and treatments. There is a paucity of definitively agreed diagnostic criteria or testing for the *ante mortem* diagnosis of dysautonomia. Therefore, misdiagnosis in some of the cases included in this study is possible. It is probable that only the most severely affected individuals were referred on to specialist intuitions, introducing bias into the patient population. It is therefore feasible that the prognosis of dysautonomia is better than is reported in the veterinary literature. Further studies including data from general practitioners are required.

The signalment in this paper is similar to previously reported[13 15 16 21]. Domestic shorthair cats were the most commonly represented breed, which probably reflects their higher prevalence. In contrast with the population presented by Nash (1987)[22] where 75% of feline cases were less than three years of age, our median age at presentation was greater than three years, however, the vast majority of cats (79%) were less than seven years of age.

In dogs, the Labrador retriever and cross breed dogs were the most commonly represented. The Labrador retriever has been identified in two previous studies as possibly being over represented[13 23]; however, it is also a very popular breed of dog in the UK. As with feline dysautonomia, younger dogs are reportedly over represented[4 11 12 13 14 21 23 24 25]. This was loosely supported in the current study, given that 79% of cases were less than seven years of age.

Cases were fairly evenly distributed between rural and urban environments. It is possible that dogs who lived in an urban environment were exposed to rural environments during exercise. A previous paper reported that dogs with dysautonomia were more likely to come from rural areas[23].

There were four instances where two animals of the same species within a single household were affected. Dysautonomia outbreaks have been reported in both cats[10] and dogs[11 12]. The mechanism that results in multiple animals becoming affected remains unknown[10 11 12]. Where dysautonomia affects an individual in a multi-animal household, the owner should be advised to be extra vigilant for developing clinical signs in any in-contact animals.

As previously reported, the duration of clinical signs prior to referral was quite variable, perhaps indicating acute and chronic presentations of the condition[16 19]. This also appeared to be longer in dogs which perhaps indicates that dysautonomia can have a more insidious onset in this species.

The patients in this study had the same common presenting and physical examination findings as previously reported[4 16]. There were differences, as would be expected, in the incidence of some signs between the species, for example, constipation was relatively common in cats (n=17), but reported in only one dog, while diarrhoea was infrequently reported in cats. Signs consistent with urinary retention, such as dysuria and pollakiuria, were reported in 12 cats and 14 dogs. It is possible that in cats this clinical sign is more common than described as urination in this species is often unobserved by the owner.

The exact prevalence of some clinical signs is hard to ascertain in a retrospective study because subtler clinical signs, such as dry mucosae and third eyelid protrusion, might not be recorded in the clinical notes, thus underestimating their true prevalence.

Reduced or absent tear production is a recognised feature of dysautonomia in both cats and dogs[4 16]. A STT was used to document reduced tear production in this paper as in previous publications[4 11]. This is an economical and simple test to build evidence for an *ante mortem* diagnosis of dysautonomia. It is important to note that low STT values have been reported in normal cats; while Crispin (2007)[26] advised that values of approximately 12mm (+/-5) over 60 seconds are normal, Sebbag *et al.* (2015)[27] concluded that an abnormal

tear film should be suspected in this species when STT readings are less than 9mm over 60 seconds. Because of this, the STT as a diagnostic aid in this species is questionable. However, it has been included in previous studies on feline dysautonomia[10 15], hence the inclusion of the data in this study.

Pharmacological testing was used frequently in this study to provide additional evidence to support the suspected diagnosis. Pilocarpine is a direct-acting parasympathomimetic agent, that stimulates the cholinergic receptors in the iris causing miosis when applied topically. In dysautonomia, there is degeneration of the postganglionic neurones which results in enhanced sensitivity of the denervated muscle to cholinergic drugs[19]. This hypersensitivity enables dysautonomic animals to respond to a diluted solution of pilocarpine. O'Brien and Johnson (2002)[19] used a 0.05% solution of pilocarpine and considered the "rapid" development of miosis consistent with dysautonomia. They also note that it is possible for normal dogs to respond to this concentration, but that it would take 45 to 60 minutes for this to happen[19]. Harkin and others (2002)[4] used a 0.1% solution and considered a positive result as miosis within 30 minutes[4]. The retrospective nature of the current study prevented the utilisation of a standardised protocol for this pharmacological test, this was a limitation of this study. This test aided diagnosis in 19 cats and eight dogs where the patient demonstrated miosis within a time frame (miosis/ resolution of third eyelid protrusion within 45 minutes) and in response to a suitable concentration of pilocarpine, to be considered appropriate by the attending clinician for dysautonomia.

Bogucki and Noszczyk-Nowak (2017)[28] explain that the heart is principally regulated by the parasympathetic nervous system under physiological conditions. Atropine, a direct acting parasympatholytic agent, blocks the action of acetylcholine at the muscarinic receptors in the parasympathetic nervous system. Under normal circumstances, when given by intravenous or intramuscular injection, it causes an increase in heart rate as the sympathetic nervous system becomes dominant. Dysautonomia can cause a loss of sympathetic nervous system innervation to the heart; consequently, no change in heart rate is seen in response to the administration of atropine[4]. Atropine was utilised in only three cases in this study and in all cases, there was no increase in heart rate, supporting the diagnosis of dysautonomia.

All three of the canine long-term survivors presented with both gastrointestinal and urinary signs. However, in this species, the clinical signs associated with either the urinary tract or gastrointestinal tract, persisted and required further management. For example, the first canine case, an eight month old, female entire Labrador, presented with vomiting and dysuria but only received specific treatment for the latter. Only one of the feline long-term survivors had involvement of both the urinary and gastrointestinal tracts; a four year old, male neutered domestic shorthaired cat who presented with vomiting, anorexia, pollakiuria and dysuria in addition to third eyelid prolapse and bilateral mydriasis. In this case the gastrointestinal signs self-resolved and specific treatment was only given to manage the urinary tract signs. All the other long-term feline survivors had clinical

signs limited to a single body system alone. This might indicate that the prognosis is improved when persistent clinical signs are limited to one body system.

Treatments prescribed to patients in this study are comparable to those that have been reported previously[4] [12 13 14 15 29]. As the aetiology of dysautonomia is yet to be fully established, treatment is exclusively supportive and symptomatic.

The mortality rate in this study was high, agreeing with previous reports[15 16], and demonstrating that dysautonomia remains a highly challenging condition to treat. However, some cases were euthanised once the diagnosis was obtained due to the previously reported high mortality rate, this could result in an artificially poorer prognosis. This observation is supported by the fact that cases who survived were hospitalised for a longer median period and that 84% of the cases that died were hospitalised for less than seven days compared to 50% of the cases that survived. In this study 29% of cats and 47% of dogs survived to discharge. Our survival rate in dogs is much higher than previously reported, and may represent improvements in case management or changing attitudes toward disease.

There were nine long-term survivors (six cats and three dogs). All the long-term survivors had a combination of consistent clinical signs which would be hard to attribute to any other single disease process, and had a clinical diagnosis made by exclusion of other causes.

This is a large, multi-centre study that provides up dated information regarding this often devastating condition. Patients frequently display a range of clinical signs, none of which are pathognomonic, making an *ante mortem* diagnosis challenging. However, the presence of ocular signs (i.e. inappropriate mydriasis, third eyelid prolapse) in combination with lower urinary tract signs or megaoesophagus/ regurgitation does seem to be highly supportive of dysautonomia. This disease remains a relatively uncommonly diagnosed condition with a high mortality rate. The presentation of this disease in more than one animal in a single household could possibly indicate a degree of contagion or exposure to a common toxin or environmental contaminant. Prospective long-term studies are required to gain more information about the best way to treat this disease in domestic species, however the rarity of this disease will make this challenging.

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527