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

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

37

38 Abstract

39 Background

40 Dysautonomia is a disease characterised by degeneration of autonomic neurons.

41

42 Methods

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

45

46 Results

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

54

55 Conclusion

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

58

59 Introduction

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

62

63 Dysautonomia has been reported worldwide in a variety of species including horses¹, cats^{2,3}, dogs⁴, hares⁵ and
64 a llama⁶. The aetiology of dysautonomia in veterinary species remains uncertain, although a possible
65 association with *Clostridium botulinum* (type C/D) neurotoxin has been described in horses and cats^{1,7,8}.
66 McGorum *et al.* (2017)⁹ reported that dysautonomic cats were deficient in sulpha-containing amino acids
67 (methionine and cysteine/ cystine) despite an adequate dietary intake. They hypothesised this deficiency was
68 due to consumption of an unidentified dietary neurotoxic mycotoxin or xenobiotic that resulted in the signs of
69 dysautonomia as well as the deficiency in sulpha-containing amino acids⁹. Outbreaks have been reported in

70 both cats¹⁰ and dogs^{11,12} indicating possible contagion or interaction with/ ingestion of contaminated food, an
71 environmental toxin or infectious pathogen (e.g. *Clostridium botulinum* type C neurotoxin).

72

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

79

80 Definitive diagnosis can be confirmed by *post mortem* identification of pathognomonic lesions in the ventral
81 horns of the spinal cord, the autonomic ganglia and/or the brainstem nuclei^{4, 16}. A histopathological *ante*
82 *mortem* diagnosis can sometimes be made on full thickness intestinal biopsies. Findings in acute cases include
83 neuronal chromatolytic degeneration and nuclear pyknosis, while neuronal loss and proliferation of satellite
84 cells are seen in more chronic cases¹⁷.

85

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

92

93

94 **Methods and materials**

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

102

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

105 eyelids, mydriasis, absent or delayed pupillary light response (PLR), bradycardia (defined as a heart rate less
106 than 120 in cats and less than 70 in dogs¹⁸), altered anal tone, and excessively dry mucous membranes or nares.

107

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

110

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

114

115 Results

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

117 Cats

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

122

123 Dogs

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

129

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

131

132 Location

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

135

136 Multi-pet households

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

141

142 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. <i>Post mortem</i> 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 <i>post mortem</i> 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.

143

144

145 Duration of illness prior to referral

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

149

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

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

154

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

156

157

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

159

160

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

163

164

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

168

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

179

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

187

188 Treatment

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

192

193 Hospitalisation

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

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

199

200 Gastrointestinal dysmotility

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

206

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

209

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

212

213 Urinary retention

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

216

217 Other medications and management strategies

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

226

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

232

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

239

240 Survival

241 Cats

242 Of the 34 cats included in this study, 10 survived to discharge (29%). Three of these 10 cats were euthanised
243 within eight days of discharge due to progressive signs consistent with dysautonomia. One case was euthanised
244 186 days following discharge from hospital due to suspected triaditis, with the dysautonomia having resolved.
245 There was complete and long-term (greater than two years) resolution of dysautonomia in six cases, which are
246 discussed below.

247

248 Dogs

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

256

257 Long Term Survivors

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

261

262 Table 5: Long term survivors of canine and feline dysautonomia

263 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: megaesophagus. 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.

264

265 **Post Mortem examination**

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

274

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

277

278 Clinical Significance

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

287

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

295

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

303

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

309

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

315
316 Cases were fairly evenly distributed between rural and urban environments. It is possible that dogs who lived
317 in an urban environment were exposed to rural environments during exercise. A previous paper reported that
318 dogs with dysautonomia were more likely to come from rural areas²³.

319
320 There were four instances where two animals of the same species within a single household were affected.
321 Dysautonomia outbreaks have been reported in both cats¹⁰ and dogs^{11 12}. The mechanism that results in
322 multiple animals becoming affected remains unknown^{10 11 12}. Where dysautonomia affects an individual in a
323 multi-animal household, the owner should be advised to be extra vigilant for developing clinical signs in any
324 in-contact animals.

325
326 As previously reported, the duration of clinical signs prior to referral was quite variable, perhaps indicating
327 acute and chronic presentations of the condition^{16 19}. This also appeared to be longer in dogs which perhaps
328 indicates that dysautonomia can have a more insidious onset in this species.

329
330 The patients in this study had the same common presenting and physical examination findings as previously
331 reported^{4 16}. There were differences, as would be expected, in the incidence of some signs between the
332 species, for example, constipation was relatively common in cats (n=17), but reported in only one dog, while
333 diarrhoea was infrequently reported in cats. Signs consistent with urinary retention, such as dysuria and
334 pollakiuria, were reported in 12 cats and 14 dogs. It is possible that in cats this clinical sign is more common
335 than described as urination in this species is often unobserved by the owner.

336
337 The exact prevalence of some clinical signs is hard to ascertain in a retrospective study because subtler clinical
338 signs, such as dry mucosae and third eyelid protrusion, might not be recorded in the clinical notes, thus
339 underestimating their true prevalence.

340
341 Reduced or absent tear production is a recognised feature of dysautonomia in both cats and dogs^{4 16}. A STT
342 was used to document reduced tear production in this paper as in previous publications^{4 11}. This is an
343 economical and simple test to build evidence for an *ante mortem* diagnosis of dysautonomia. It is important
344 to note that low STT values have been reported in normal cats; while Crispin (2007)²⁶ advised that values of
345 approximately 12mm (+/-5) over 60 seconds are normal, Sebbag *et al.* (2015)²⁷ concluded that an abnormal

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

349

350 Pharmacological testing was used frequently in this study to provide additional evidence to support the
351 suspected diagnosis. Pilocarpine is a direct-acting parasympathomimetic agent, that stimulates the cholinergic
352 receptors in the iris causing miosis when applied topically. In dysautonomia, there is degeneration of the
353 postganglionic neurones which results in enhanced sensitivity of the denervated muscle to cholinergic drugs¹⁹.
354 This hypersensitivity enables dysautonomic animals to respond to a diluted solution of pilocarpine. O'Brien
355 and Johnson (2002)¹⁹ used a 0.05% solution of pilocarpine and considered the "rapid" development of miosis
356 consistent with dysautonomia. They also note that it is possible for normal dogs to respond to this
357 concentration, but that it would take 45 to 60 minutes for this to happen¹⁹. Harkin and others (2002)⁴ used a
358 0.1% solution and considered a positive result as miosis within 30 minutes⁴. The retrospective nature of the
359 current study prevented the utilisation of a standardised protocol for this pharmacological test, this was a
360 limitation of this study. This test aided diagnosis in 19 cats and eight dogs where the patient demonstrated
361 miosis within a time frame (miosis/ resolution of third eyelid protrusion within 45 minutes) and in response to
362 a suitable concentration of pilocarpine, to be considered appropriate by the attending clinician for
363 dysautonomia.

364

365 Bogucki and Noszczyk-Nowak (2017)²⁸ explain that the heart is principally regulated by the parasympathetic
366 nervous system under physiological conditions. Atropine, a direct acting parasympatholytic agent, blocks the
367 action of acetylcholine at the muscarinic receptors in the parasympathetic nervous system. Under normal
368 circumstances, when given by intravenous or intramuscular injection, it causes an increase in heart rate as the
369 sympathetic nervous system becomes dominant. Dysautonomia can cause a loss of sympathetic nervous
370 system innervation to the heart; consequently, no change in heart rate is seen in response to the
371 administration of atropine⁴. Atropine was utilised in only three cases in this study and in all cases, there was
372 no increase in heart rate, supporting the diagnosis of dysautonomia.

373

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

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

384

385 Treatments prescribed to patients in this study are comparable to those that have been reported previously⁴
386 ^{12 13 14 15 29}. As the aetiology of dysautonomia is yet to be fully established, treatment is exclusively supportive
387 and symptomatic.

388

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

397

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

401

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

411

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