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Dysautonomia in two littermate kittens

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Abstract

Case summary Two 6-month-old littermate Russian Blue cross kittens presented for megaesophagus, intermittent vomiting and regurgitation. The male kitten was diagnosed with aspiration pneumonia and was suspected to have a hiatal hernia on thoracic radiographs. It presented 1 month later in acute respiratory distress and was euthanized. Post-mortem examination revealed a severe gastroesophageal intussusception with approximately 90% of the stomach inverted into the distal esophagus. Histologic examination confirmed dysautonomia with marked neuronal dropout and degeneration with necrosis, satellitosis of the celiac ganglion and the myenteric and submucosal plexuses throughout the gastrointestinal tract. The less-affected littermate showed improvement on cisapride and was doing well at home at the time of writing.

Relevance and novel information Dysautonomia is rare in cats, with only a few reports of affected littermates. Both kittens are significantly younger than the median age previously reported. Detailed descriptions of diagnostic and histopathology findings are included. Gastroesophageal intussusception is a novel complication to consider when managing feline dysautonomia.

Keywords: Megaesophagus; mydriasis; aspiration; pilocarpine; gastroesophageal intussusception

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Case description

Two 6-month-old littermate Russian Blue cross kittens (male and female) from Colorado presented for mega esophagus, intermittent vomiting and regurgitation. One week prior to referral, the male kitten was lethargic, had decreased appetite, was diagnosed with aspiration pneumonia and was started on antibiotics (cefovecin 8 mg/kg SC once [Convenia; Zoetis]). Both kittens were started on sildenafil (0.5 mg/kg PO q12h; compounded) to decrease the tone of lower esophageal sphincter, without clinical improvement. Both kittens were fed a liquid diet and held in an upright position for 20 mins post-feeding. The kittens were originally adopted at 3 months of age and were not fully vaccinated. According to the owner, there was a third kitten in the litter that died prior to adoption.

Upon referral, on physical examination, the male kitten was quieter, smaller and had a lower body condition score (3/9) than the female kitten (4/9). It was also tachypneic and had increased respiratory effort. The female kitten had a dry and crusted nose. Both kittens were normothermic and had a normal heart rate (200–240 beats/min [bpm]). Bilaterally, both kittens had severe mydriasis, moderate-to-severe blepharospasm with photophobia, and absent direct and indirect pupillary light reflexes (PLRs). The male kitten had a plantigrade stance and normal proprioception. The female kitten had normal mentation, gait and proprioception. Both kittens tested negative for feline immunodeficiency virus (FIV)/feline leukemia virus

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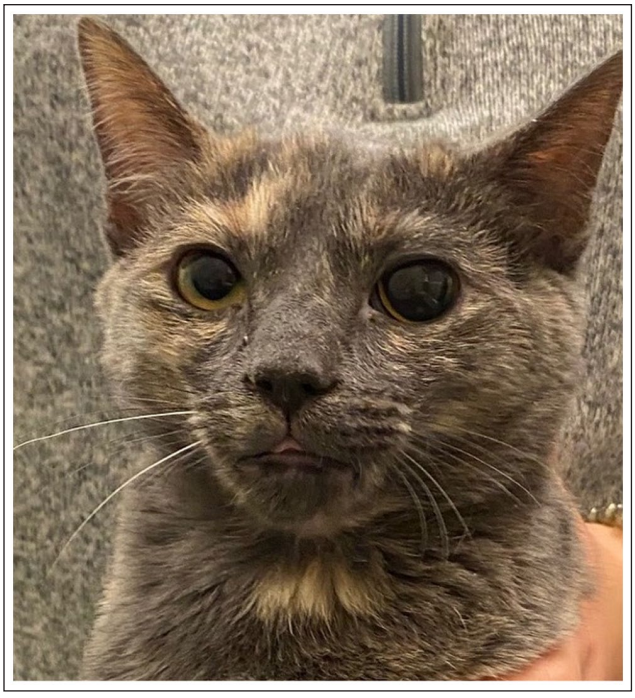

Figure 1 Pupil constriction 60 mins in the right eye post-0.05% pilocarpine, suggestive of dysautonomia. Pilocarpine was not applied to the left eye as a control

(FeLV), as well as parvovirus infections, by SNAP Combo FeLV antigen/FIVantibodies and Snap Parvo test (IDEXX Laboratories). Previous in-house hematology by the primary care veterinarian was unremarkable and in the male kitten, serum chemistry showed increased symmetric dimethylarginine (15 µg/dl; reference interval [RI] 0–14) and potassium (7.1 mmol/l; RI 3.7–5.9); serum potassium had decreased (6.2 mEq/l) at another recheck.

Non-sedated thoracic radiographs of the female kitten showed megaesophagus with gastric distension. The male kitten's thoracic radiographs showed marked diffuse esophageal dilation and a convex soft tissue opacity in the caudal dorsal thorax, suspicious for hiatal hernia. Schirmer tear test was low in both kittens (0 mm/min in both eyes [OU]). A pilocarpine (0.05%) response test showed pupil constriction at 60 mins (Figure 1) and histamine intradermal testing performed by intradermal 0.05 ml injections of histamine (1:10,000) and 0.9% saline and showed no response to histamine. An atropine response test was not performed as neither of the kittens were bradycardic. A presumptive diagnosis of dysautonomia was made and both kittens were started on cisapride (1 mg/cat PO q8h; compounded) and artificial tears; all other medications were discontinued, but elevated feeding was continued at home.

One month later, the male kitten presented for acute respiratory distress and was euthanized. Post-mortem examination revealed a markedly dilated and thinned esophagus with approximately 90% of the stomach and

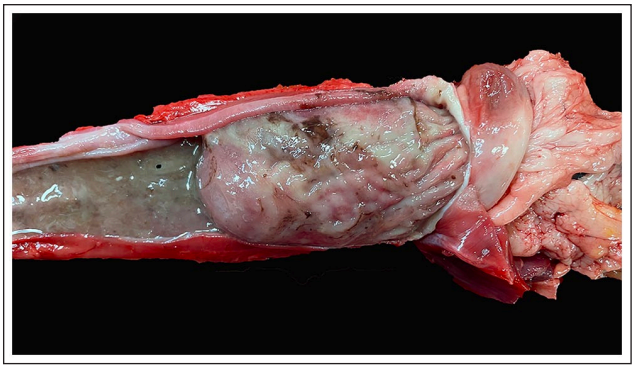

Figure 2 Esophagus and stomach in a 7-month-old male Russian Blue cross kitten. The esophagus (which is on the left) is markedly dilated and thinned, with inversion of the stomach into the distal aspect. The gastric rugae are visible with scant tan mucus adhered to the mucosa. On cut section the gastric submucosa is expanded by 4 mm of diffuse edema. A significant portion of the greater omentum is also present within the esophagus

greater omentum inverted into the distal esophagus; however, no evidence of hiatal hernia was present on necropsy (Figure 2). The gastric submucosa was diffusely expanded by edema. The lungs were atelectatic, and the left cranial lung lobe sank in 10% neutral-buffered formalin, which correlated to regional aspiration pneumonia microscopically. Histologic examination of the celiac ganglion, and the myenteric and submucosal plexuses throughout the gastrointestinal tract, revealed marked neuronal dropout and degeneration with necrosis and satellitosis. Special stains including glial fibrillary acidic protein, and neurofilament protein highlighted neuronal dropout and were compared with a 1-year-old healthy cat as a non-age-matched control (Figures 3 and 4).

Three months later, the female kitten presented for re-evaluation. According to the owner, the kitten had been doing much better since starting cisapride and only regurgitated once or twice per month. On physical examination, the mydriasis OU, and dry and crusty nose were mildly improved but still lacked direct or indirect PLR; body condition score remained at 4/9. No further diagnostics were performed. The owner reported that the patient was doing well at the time of writing (5 months since diagnosis) and continued to receive cisapride and artificial tear medications.

Discussion

Dysautonomia in cats was first reported in 1982 in five cats in the UK.[1] Since then, multiple cases of feline dysautonomia have been reported in Europe, New Zealand, the United Arab Emirates and the USA.[2–4] Dysautonomia is the result of autonomic denervation leading to failure of both the sympathetic and parasympathetic functions of multiple organ systems and has

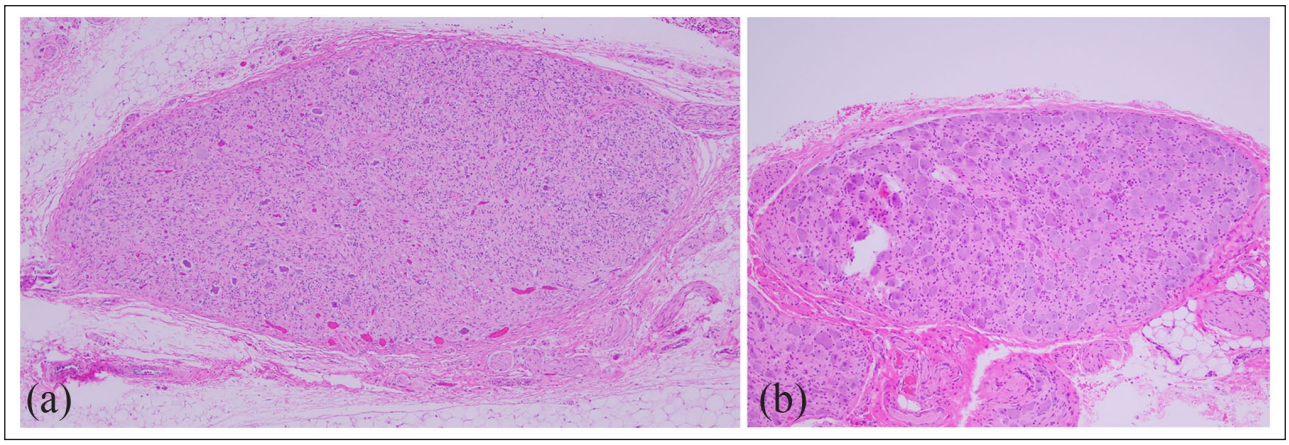

Figure 3 (a) Celiac ganglion (hematoxylin and eosin) staining in a 7-month-old male kitten with dysautonomia. There is marked neuronal dropout and remaining ganglion are frequently necrotic, characterized by shrunken borders, cytoplasmic hypereosinophilia and pyknotic nuclei, or degenerate, characterized by cytoplasmic vacuolation and central chromatolysis. Ganglion are also frequently flanked by glial cells (satellitosis). (b) Celiac ganglion (hematoxylin and eosin) in a 1-year-old cat (non-age-matched) with normal neuronal density and no microscopic abnormalities

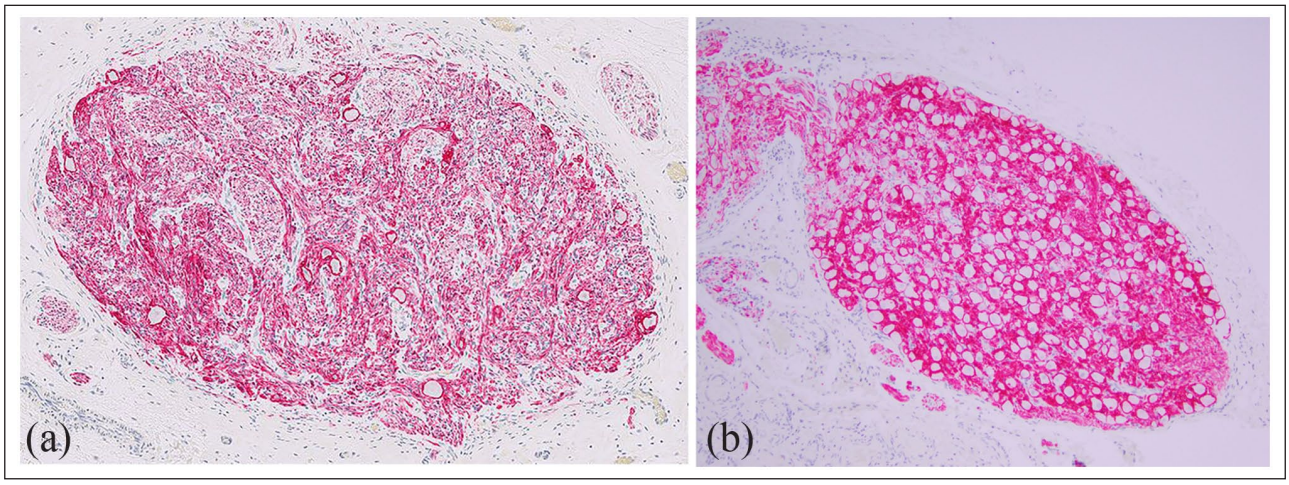

Figure 4 (a) Celiac ganglion (glial fibrillary acidic protein [GFAP]) staining in a 7-month-old male Russian Blue cross kitten with dysautonomia. There is a marked decrease in immunoreactivity highlighting neuronal dropout. (b) Celiac ganglion (GFAP) in 1-year-old cat (not age-matched) with normal neuronal density and no microscopic abnormalities

been reported in multiple species, including cats and dogs,[4] with similar histologic lesions described across all species. Histologic lesions in the acute phase are characterized by extensive chromatolysis and necrosis of ganglion cells throughout the peripheral autonomic ganglia with axonal degeneration in autonomic nerve fibers. Other areas of neuronal degeneration can include nuclei of cranial nerves (III, V, VII and XII, the dorsal motor nucleus of the vagus and nucleus ambiguus), dorsal root ganglia and ventral horn of intermediolateral areas of the spinal gray matter.[5] In chronic cases, depletion of neurons is evident in the previously mentioned sites. On electron microscopy, affected neurons have autophagocytic vacuoles, dilated cisternae and complex intracytoplasmic stacks of smooth endoplasmic membranes.[6]

The etiology of dysautonomia is unknown, but several suggestions of toxic damage such as from *Clostridium botulinum* (type C/D) neurotoxin involvement have been made,[7–9] as well as possible amino acid alterations.[10] The necropsy of the male kitten was not suggestive of an infectious or toxic etiology; however, next-generation sequencing and infectious and toxicological testing were not performed on post-mortem tissues, which is a limitation of this case report.

Cats with feline dysautonomia may present with clinical signs such as anorexia or hyporexia (92%), vomiting or regurgitation (85%), constipation (55%), nasal discharge or crusting (46%), lower urinary tract signs (43%), respiratory signs (37%), bradycardia (30%), altered anal tone (20%) and diarrhea (16%).[11] Specific

ocular signs also occur in cats with dysautonomia, including reduced lacrimation (90%), absent or delayed PLR (88%), mydriasis (81%) and third eyelid protrusion (77%).[11] Both kittens in this case presented with signs of vomiting and regurgitation. The female kitten had crusting of the nasal planum, while the male kitten had decreased appetite and increased respiratory rate and effort secondary to aspiration pneumonia. Aspiration pneumonia was also diagnosed in 13% of cats with dysautonomia in a recent study.[11] Both kittens were also diagnosed with megaesophagus on thoracic radiographs, and megaesophagus was identified in 65% of cats with dysautonomia in a previous study.[11] One study summarizing diagnostic imaging findings in cats with dysautonomia reported that the most common findings were megaesophagus, esophageal dysfunction, gastric distension and intestinal ileus; aspiration pneumonia and megacolon appeared less commonly.[12]

Dysautonomia affects cats with a wide range of ages and lifestyle factors. While dysautonomia has been reported in cats from 2 months of age to 11 years, it is more common in younger cats (median age 3.9 years);[11,13] however, these two littermates were considerably younger. Dysautonomia has been reported to occur in cats with outdoor access[13] and those kept indoors only.[4] The kittens in this case report were indoor-only cats; however, outdoor access prior to adoption is possible. In multi-cat households, feline dysautonomia usually affects only one cat,[4,11] although there have been several reports of multiple cases in the same household.[11,14,15] In dogs, dysautonomia has been reported in multiple litters of puppies; four 10-week-old Havanese puppies from a litter of five developed clinical signs of canine dysautonomia in one study; another study reported dysautonomia in four 5-week-old German Shorthair Pointers from a litter of five puppies, with the dam of the puppies also being affected.[16,17] One study previously reported feline dysautonomia in related kittens from multiple litters in a closed colony of pet cats; however, no further reports of multiple cases feline dysautonomia in siblings have been described.[14] Reports on clusters of affected animals are especially valuable to better understand genetic or environmental etiologies and other epidemiologic factors.

Ante mortem diagnosis of dysautonomia can be challenging in cats, and presumptive diagnosis is usually made based on clinical signs, physical examination findings and pharmacologic tests of autonomic function, and by excluding other differential diagnoses such as congenital or acquired megaesophagus, myasthenia gravis and polymyositis. No mediastinal mass was seen on chest radiographs and the client declined testing for hypothyroidism, as well as a serum acetylcholine receptor autoantibody titer for myasthenia gravis, due to financial limitations.

In these kittens, a pilocarpine response test was positive in both kittens; however, a negative response to pilocarpine does not rule out dysautonomia in cats, as only 86% of cats were reported to have a positive response to a pilocarpine response test in a recent study.[11] An intradermal injection of histamine has been used for diagnosis of dysautonomia in animals and humans, and the typical response in healthy cats is a formation of a visible wheal and flare in response to histamine; this response is lacking in cats with dysautonomia and was also absent in both kittens.[18–20] Another test used for diagnosis of dysautonomia is the atropine response test, which leads to an increase in heart rate >20 bpm with subcutaneous injection of atropine (0.04 mg/kg). Cats with dysautonomia will not have an increase in heart rate secondary to parasympatholytic drugs such as atropine. Neither of the kittens were bradycardic at presentation, and the atropine response test was therefore not performed. A normal heart rate has been shown to be more common in dysautonomia survivors vs non-survivors with bradycardia, which in our case report was only true for the female kitten as the male kitten was euthanized due to the severity of the disease and complication of the aspiration pneumonia and gastro esophageal intussusception.[14] Gastroesophageal intussusception is rare in both domestic and large felids. It has been reported in felids with laryngeal paralysis and idiopathic megaesophagus;[21–23] however, no reports of gastroesophageal intussusception secondary to dysautonomia in cats have been reported.

Feline dysautonomia generally carries a poor prognosis in cats and reported survival rates vary between 29% and 50%.[6,11] Complete and long-term resolution of clinical signs of dysautonomia has also been reported; generally, cats with milder clinical signs have a better prognosis.[6,11] This is consistent with the outcome for the two kittens in this case report, as the female kitten presented with milder clinical signs and the more severely affected male kitten was euthanized. The reason why some cats are more affected than others is currently unknown. The prevalence and outcome of cats with dysautonomia that present with complications such as hiatal hernia and/or gastroesophageal intussusception are also unknown, as this is the first reported case of gastroesophageal intussusception in a kitten diagnosed with dysautonomia.

Conclusions

Dysautonomia is rare in cats. This is the second report of two kittens from the same litter being affected and the first reported case of gastroesophageal intussusception in a kitten diagnosed with dysautonomia. The less affected kitten in this case report showed improvement on cisapride and is doing well at home. Cats showing milder

clinical signs have a better chance at long-term survival; however, the reason why some cats are more affected than others is currently unknown.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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