Case Series

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Recurrent episodes of feline lower urinary tract disease with different causes: possible clinical implications

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Abstract

Case series summary While descriptions of cats with recurrent episodes of feline idiopathic cystitis (FIC) exist, little is published on cats with recurrent episodes of feline lower urinary tract disease (FLUTD) where the cat is diagnosed with different causes of FLUTD at separate episodes. In the present paper, six cats, originally part of larger studies of FLUTD among Norwegian cats, are described. In the project period (2003–2009), these cats had several episodes of FLUTD. At each episode, the cats had a complete physical examination, abdominal imaging, blood work, urinalysis and urine culture performed. Two of the cats initially presented with urolithiasis and subsequently with episodes of non-obstructed FIC. Four of the cats presented with non-obstructed FIC at one or more episodes, but were later diagnosed with urolithiasis or bacterial cystitis without prior catheterisation or other known predisposing factors.

Relevance and novel information Cats with recurrent episodes of FLUTD may present with different causes at different times. The need to thoroughly work-up cats with recurrent episodes of FLUTD at each presentation is emphasised. FIC may be considered as a predisposing factor in cats developing urolithiasis or bacterial cystitis; alternatively, interrelated FLUTD disease mechanisms exists. Thus, applying multimodal environmental enrichment and modification (MEMO) to cats with signs of FLUTD independent of diagnosis should be considered.

Keywords: Lower urinary tract; feline idiopathic cystitis; stress; aetiology; recurrence

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Introduction

The term 'feline lower urinary tract disease' (FLUTD) describes a collection of conditions affecting the urinary bladder and urethra of cats, characterised by clinical signs such as periuria, haematuria, stranguria, dysuria and/or pollakiuria, with or without obstruction.[1–3] Possible causes are reported to be infections, urolithiasis, urethral plugs, neoplasia, anatomical defects or iatrogenic causes.[1–5] However, in a large proportion of cats with signs of FLUTD, thorough diagnostic investigation does not reveal a specific cause; these patients are classified as having feline idiopathic cystitis (FIC).[5–8]

FIC has many similarities to interstitial cystitis/bladder pain syndrome (IC/BPS) in humans, including the clinical signs, a tendency of reoccurrence, comorbid conditions and a relation to stress.[9–11] Despite years of research, these are still diseases of incompletely understood aetiology.[7,9–11]

Recurrent episodes of FIC are commonly described, affecting 39–65% of the cats within 1–2 years after the initial episode.[9,10] There are, however, few descriptions of cats with recurrent episodes of FLUTD, where different causes were identified at the separate episodes.

The aim of the present paper is to present six cats with recurrent episodes of FLUTD, including the causes identified for each episode, and discuss the possible implications.

Case series description

A PhD study of a total of 246 cats with FLUTD presented at the clinics of the Small Animal Section, Department of

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Companion Animal Clinical Sciences, Faculty of Veterinary Medicine, Norwegian University of Life Sciences, was conducted from 2003–2009.[12–16] Some of the cats included had several episodes of FLUTD during the period of data collection. Long-term follow-up was not part of the project plan and recurrent episodes after inclusion were therefore not routinely registered. However, when reoccurrence of FLUTD was noted by the authors, a full diagnostic investigation in accordance with the study protocol was, nevertheless, performed during each episode of FLUTD for some of the cats. A separate episode was defined as signs of FLUTD occurring after a minimum of 2 months without clinical signs of FLUTD. The six cats presented in the present paper were chosen as examples as the cause of FLUTD was investigated thoroughly for at least four consequent episodes.

All cats included in the PhD study were primary accession cases. In addition to the owners' informed consent, the inclusion criteria were clinical signs (eg, dysuria, stranguria, haematuria, pollakiuria and/or periuria) and a diagnosis consistent with FLUTD. Exclusion criteria were treatment that could interfere with the diagnostics (antimicrobial medication, hormones or medication altering blood pressure, urine production and/or urine composition) and concurrent diseases likely to be of influence on the urinary findings, such as chronic kidney disease, diabetes mellitus or hyperthyroidism. Only cats 6 months or older were included; no sex or breed restrictions were made.

A standardised questionnaire was used to register age, breed, sex, reproductive status, body weight, prior health history and information concerning housing conditions and feeding regime for each cat. A veterinarian performed a physical examination, and blood samples for routine haematology and biochemistry were collected. Abdominal imaging was included as part of the diagnostic investigation, predominantly in the form of ultrasound examinations; radiographs were included in some cases of obstruction. All urine samples were obtained by cystocentesis if not otherwise stated. Standard urinalysis was performed, including commercial urine dipstick analysis (Krulab; Kruuse), urine specific gravity measured with a refractometer (URC-Ne; Atago) and microscopic examination of the urine sediment (native wet samples and wet samples stained with Sternheimer-Malbins).

Urine samples were obtained in the acute phase when the cat was admitted to the clinic and all samples were cultured on the day of collection. Quantitative bacteriology was performed by streaking 1 µl urine onto blood agar (Blood Agar Base II; Difco) and qualitative bacteriology by cultivation on blood agar and selective bromothymol agar (Difco) from sediments after centrifugation, incubated at 37°C in a 5% CO_2-enriched atmosphere and aerobically.

Of the cats with significant bacterial growth on culture from cystocentesis ($\geqslant 10^3$ colony forming units of $\leqslant 2$ types of bacteria per ml urine), only those that did not have concurrent findings such as urolithiasis or urethral plugs were given a diagnosis of bacterial cystitis.

Information concerning signalment, home environment and the causes determined for the separate episodes of FLUTD for each of the six cats is presented in Table 1. No consistent patterns with regard to interval between episodes or seasonality were detected, with the exception of cat number 5 in Table 1. This cat had yearly episodes of FLUTD in the autumn. The six cats are representative of the study sample of cats included in larger studies of FLUTD among Norwegian cats with regard to age, breed, sex and reproductive status, and do not represent a subset of cats in any aspect noted by the authors.

Discussion

The recurring episodes of FLUTD with both similar and different diagnoses in this small group of six cats support the need to thoroughly investigate each and every episode of FLUTD in a cat. As argued by Kruger et al,[9] recurrent episodes of FLUTD may be a result of delayed manifestation of the original disease. Spontaneous or iatrogenic urethral strictures could occur as a result of prior episodes of obstructive FLUTD or catheterisation, respectively. Such scenarios may explain the development observed in cats 2 and 4 in Table 1. However, 4/6 cats presented in the present paper (cats 1, 3, 5 and 6 in Table 1) were diagnosed as having non-obstructive FIC at first onset, prior to developing uroliths or bacterial cystitis during later episodes of FLUTD. These cats were not catheterised as part of the initial diagnostic work-up or treatment. Although iatrogenic intervention in the form of cystocentesis may have been of some influence, the idea of FIC as an underlying disorder or predisposing factor, with urolithiasis, urethral plugs or bacterial cystitis as possible complications, may be considered. Another possibility is a more complex interrelated aetiology across the different acknowledged causes of FLUTD. In addition, there is a possibility of partial obstructions in some cases being missed by the owners or attending clinicians at the first episodes of FLUTD.

Chew and Buffington describes four different urinary presentations of FIC: a single acute seemingly self-limiting episode, frequently recurring episodes, persistent forms and FIC with urethral obstruction in male cats.[17] They suggest that these presentations may represent a spectrum of signs from the same disease process. Neuroendocrine abnormalities in combination with stress are suggested as a primary causal factor in the development of FIC.[18] In a comprehensive review by Buffington, a summary of current available evidence is presented, indicating the possibility of an even more complex aetiology of FIC and other possibly stress-related disease processes, extending outside the urinary system – the Pandora syndrome.[10] While relatively recent case-control studies have confirmed stress and a nervous

Table 1 Signalment, housing conditions and cause for each episode of recurrent feline lower urinary tract disease (FLUTD)

Case	1	2	3	4	5	6
Sex/reproductive status	MN	FN	MN	MN	FN	MN
Age at first episode (years)	2	2	2	2	2–3	2
Breed	DSH	DSH	DSH	DSH	DSH	DSH
Body condition score	4/5	4/5	3/5	3/5	3–4/5	3/5
Nervous disposition	Yes	Yes	No	No	Yes	No
Indoor/outdoor	Outdoor access	Indoor only	Indoor only	Indoor only	Indoor only	Outdoor access
Additional cats in the household	3	0	0	1	1	0
First episode FLUTD	FIC	Uroliths struvite	FIC	Uroliths struvite, obstructed	FIC	FIC
Second episode FLUTD	Plug/small urolith, *E coli*, partly obstructed	FIC	Uroliths struvite	FIC	FIC	FIC
Third episode FLUTD	BC, *Corynebacterium* species,* obstructed	FIC	FIC, crystalluria struvite, obstructed	FIC	FIC	Uroliths struvite
Fourth episode FLUTD	FIC, crystalluria struvite, obstructed	FIC	FIC	FIC	BC, *E coli*	FIC, obstructed
Fifth episode FLUTD	FIC					

*Urine sample obtained as voided urine from sedated cat – collected into sterile container. Remaining urine samples obtained by cystocentesis
MN = male neutered; FN = female neutered; DSH = domestic shorthair; FIC = feline idiopathic cystitis; E coli = *Escherichia coli*; BC = bacterial cystitis

predisposition as risk factors for FIC,[8,19,20] studies of FLUTD among Norwegian cats have shown that there was no significant difference between cats diagnosed with FIC, bacterial cystitis, urolithiasis or urethral plugs with regard to the cats being defined as nervous or not by their owners.[16]

Stress may induce changes in a cat's drinking and/or eating pattern, affecting water intake, which has been found to be of importance in the prevention of additional episodes of FIC, as well as urolith formation.[18,21] In addition, stress-related changes in urine pH have been previously suggested.[22] Hyperventilation and/or an influence of the sympathetic nervous system on the renal tubular acid–base dynamics was hypothesised to cause the presence of alkaline urine and struvite crystalluria in a cat fed an acidifying diet.[22] Three of the cats in the present study (cats 1, 3 and 6 in Table 1) had episodes of FIC before developing uroliths at later episodes of signs of FLUTD, which may support an interrelated aetiology of these conditions.

One of the cats developed signs of FLUTD each autumn (cat 5 in Table 1) and was diagnosed with bacterial cystitis on its fourth episode of FLUTD after negative cultures at previous episodes. This cat was kept indoors only, and had not been catheterised prior to developing bacterial cystitis. The urine sample was, as with the previous ones, obtained by cystocentesis. Whether the presence of bacteria was of clinical importance is open to discussion. Clinically, it may be challenging to differentiate between a cat with FIC and asymptomatic bacteriuria and a cat with a primary bacterial cystitis. While various prevalences of asymptomatic bacterial cystitis are described in cats,[23–25] viable, but unculturable, bacteria are found in the urine of humans and mice, and bacterial DNA has been detected in culture-negative urine from humans and cats.[26–30] In 2015, a study of bacterial DNA in culture-negative urine from cats with and without signs of FLUTD in Norway did not demonstrate the presence of unculturable bacteria as a common finding in either group of cats.[31] However, the sensitivity of the assays used may have precluded detection of very low levels of unculturable bacteria.[31]

In both human and veterinary medicine, infectious agents are generally not considered to be the cause of the clinical signs present in patients with idiopathic cystitis, interstitial cystitis or related pain syndromes, but some evidence indicates an increased risk of developing infections among these patients.[10,32] Further, the presence of various components in urine from patients with FIC or IC/BPS not found in urine from control cases hints at the possibility of intracellular microorganism as part of the aetiology.[33] While previous studies primarily based on referral cases have shown relatively low prevalences of bacterial cystitis in young-to-middle-aged cats without concurrent diseases,[34,35] recent European studies based on first-opinion cases have demonstrated that this may be more common in at least some populations of cats.[2,15,36]

A clinically reliable diagnostic biomarker of FIC would make it possible to determine the aetiological relationships between the different causes of FLUTD. This is, unfortunately, not available at present. In a previous study evaluating differences in results from standard urinalysis from cats with different causes of FLUTD, few differences of diagnostic value were found.[15] However, recent studies have demonstrated differences between cats with FIC and healthy control cats, for instance with regard to levels of Trefoil factor 2 in the urine and tryptophan levels in serum.[37,38] Lemberger et al also found differences in fibrinogen content in the urine of cats with FIC vs cats with bacterial infection or urolithiasis, which may speak against a theory of FIC as an underlying disorder or predisposing factor in all cats exhibiting clinical signs of FLUTD.[7] The ongoing research by Chew and Buffington,[17] which aims to determine whether FIC can be distinguished from other causes of FLUTD based on examination of dried blood spots, may also help determine or exclude similarities in aetiology between the various causes.

Conclusions

Cats with recurrent episodes of FLUTD may be diagnosed with different causes of FLUTD during separate episodes, and the possibility of FIC as an underlying disorder or predisposing factor in cats developing urolithiasis or bacterial cystitis may be considered. These results emphasise the need to investigate these cats thoroughly at each episode of FLUTD. However, the present paper is based on only six cases and, although indications of interrelated disease mechanisms between the different acknowledged causes of FLUTD were found, firm hypotheses are precluded. Nevertheless, besides the time invested in these patients, no adverse side effects are associated with reducing potential stressful factors in any cat's life. Thus, applying multimodal environmental enrichment and modification (MEMO) to cats with signs of FLUTD independent of diagnosis should be considered.[16,39,40]

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