



CASE REPORT

A case of recurrent feline idiopathic cystitis: The control of clinical signs with behavior therapy

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stress

Abstract Feline idiopathic cystitis (FIC), is the most common medical cause of elimination change in the cat, and hence is an important differential when working up cats presenting with inappropriate elimination. A recent case-control study found that case cats were more likely than the control population to be male, overweight, and pedigreed, but the study also found that several stress factors were “flare factors” associated with the onset of a bout of clinical signs. A 5-year-old male, neutered, domestic shorthaired cat presented with recurrent bouts of dysuria and hematuria. A full medical work up eliminated other causes, leading to the diagnosis of FIC. On behavioral assessment, the cat was found to be one of 6 within the household. He showed no signs of regarding any of the other cats as part of his social group. A program of behavior therapy was instituted, which involved ensuring the patient had a separate “core area” and easy access to important resources. In addition, visual access to cats from outside the household was restricted. The cat was followed up for a period of 7 months. There was no further recurrence of clinical signs for 6 months, after which clinical signs returned. Further investigation revealed that this outbreak occurred 2 days after the owner confined the cats in close proximity again. This case provides an interesting example of how bouts of clinical signs in FIC cats can often be linked to specific “stressful” events, and how such outbreaks can be reduced or prevented through the implementation of a specific program of behavior therapy.

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Case presentation

A 5-year-old male neutered domestic short-haired cat presented with recurrent bouts of dysuria and hematuria

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of 3 months duration. Other presenting signs were standing to eliminate and inappropriate locations of elimination around the house. Urination was often preceded by pacing and restlessness and was associated with vocalization, suggesting distress, either from pain or anxiety. The owner also observed excessive grooming of the perineal region, caudal ventral abdomen, and inner thigh regions.

Physical and laboratory evaluation

On clinical examination by the referring veterinarian, the cat was found to be subdued and slightly tense on abdominal palpation, with a moderately sized, hard bladder. Otherwise, physical examination was unremarkable. The cat was anesthetized, and a urinary catheter was easily passed prior to referral to the University of Bristol for further investigations.

On presentation at the university's small animal hospital, the urinary catheter was draining urine well, and the bladder was small. Physical examination at this stage was otherwise unremarkable.

Routine hematology and serum biochemistry were largely unremarkable. Urinalysis revealed mild hematuria, concentrated urine (specific gravity 1.047), and the presence of scant white blood cells and struvite crystals. Bacterial culture yielded no growth (Table 1).

A retrograde urethrogram and double contrast pneumocystogram were performed, revealing mild thickening of the bladder wall with no urethral abnormalities or uroliths.

Feline idiopathic cystitis (FIC) is often a diagnosis of exclusion. In this case, other differential diagnoses for dysuria such as urethral strictures, neoplasia, and urolithiasis were excluded following the investigations. The results of urinalysis and contrast radiographs are consistent with common findings in FIC.

Following investigations, medical treatment was started, the urinary catheter was removed, and the cat was hospitalized for a further 2 days to monitor urination. During this time, he was observed to urinate without straining or discomfort on several occasions and so was discharged. However, at home the dysuria returned, and 2 weeks later the cat was readmitted to the university's hospital. At this stage the cat underwent behavioral assessment.

Behavioral history

On behavioral assessment, the cat was found to be one of 6 within the household. The 6 cats formed 4 distinct social

groups, with the patient showing no signs of regarding any of the other cats as part of his social group. The patient typically avoided the other cats, with intermittent bouts of agonistic behavior. The patient had several bouts of urinating on carpet in the corners of both the lounge and the hall. Cats from neighboring households also entered the garden on a regular basis, and the patient had experienced several episodes of aggression from these cats and now was no longer confident to go into the back garden without his owners being present. Prior to the owners moving house 5 months previously, the patient had free access outside and had been able to maintain a small territory area by chasing off other cats. In the present house, the patient had very restricted access outside, and hence he was unable to prevent or discourage other cats from entering the garden and therefore was unable to maintain a territory area. The garden appeared to be part of the territory of cats from neighboring households, and as a result the patient was anxious when outside, showing signs of keeping to the covered areas at the edges of the territory and increased vigilance. The patient spent a lot of time sitting and watching other cats through the windows. In addition, he showed signs of fear when exposed to unfamiliar people and anxiety when exposed to stimuli that might predict a change in the environment, such as scents entering the household, and would run and hide. There were, therefore, a number of environmental factors that could be described as "chronic stressors" for this cat: other household cats that he did not see as part of his social group and neighborhood cats coming into the garden that he could not chase off. In addition, specific situations that caused additional ("acute") stress appeared to occur prior to bouts of FIC. For example, 2 days prior to the recent bout of FIC, all 6 cats from the household were shut into a room together because builders were in the house.

Diagnosis

The full medical investigation eliminated other causes of lower urinary tract disease, leading to the diagnosis of FIC.

The behavioral history suggested that stress may be a flare factor, and a number of factors that could be causing the patient stress were identified: other household cats that he did not see as part of his social group, cats coming into the garden that he could not chase off, unfamiliar people bringing unfamiliar scents into the house, and being kept in the same room with the 5 other cats that he did not see as part of the same social group. Significantly, since the change of circumstances associated with the owners moving house, the patient was not only exposed to more "stressful" situations, but he was also less able to show behaviors that had previously been successful in resolving or "coping with" these stressors. For example, he was not able to avoid the other cats in the household by going outside and was unable to chase off cats coming into the

Table 1 Urinalysis results

Urine	Day 1
pH	6.1
Blood	+++
Glucose	Negative
Ketones	Negative
Protein	76.9 mg/L
Specific gravity	1.047
Fat droplets	+
Red blood cells	++
White blood cells	+
Struvite crystals	Scant
Epithelia	Scant
Culture	No growth after 48 hours

garden, owing to his limited access to outside. The flare factor identified as likely to have precipitated the recent bout of FIC was close confinement with the other cats in the household because of the builders being present in other areas of the house.

Treatment

Treatment of this case had 3 main elements: initial medical management; management changes to increase fluid intake; and a program of behavior therapy to reduce the impact of environmental factors identified as potential “stressors.”

Initial medical management

Initial medical management aimed at reducing inflammation, pain, and any urethral spasm was instituted with meloxicam (Metacam), smooth and striated muscle antispasmodics (prazosin [Hypovase] and dantrolene [Dantrium]). As some cats suffering from FIC have a decrease in the protective glycosaminoglycans (GAG) layer in the bladder, GAG supplementation is often recommended; however, clinical trials have shown a variable response between individuals (Gunn-Moore and Shenoy, 2004). However, some individuals do seem to respond very well to replacement, and so this cat was started on GAG supplementation (Cystaid). The medical treatment was continued for 3 weeks after first presentation.

Management changes to increase fluid intake

Increasing fluid intake is important to encourage production of more dilute, and therefore less noxious, urine (Markwell et al., 1998). Therefore, the patient was changed onto a wet diet, with extra water mixed in, provided with water flavored with fish, and given a “water fountain,” as he preferred to drink fresh running water. In addition, these sources of water were provided in the patient’s separate core area within the household; previously the owner had observed his access to the water bowl being blocked by the other household cats, resulting in him drinking less frequently. As the patient was also overweight, a long-term (wet) weight-control diet was started.

Behavior therapy

A program of behavioral therapy was instituted to remove or reduce the effects of the identified environmental “stressors” likely to precipitate new bouts of disease. To reduce the stress caused by the household cats, the patient was given a separate “core area” with easy access to all of his resources: food, water, litter tray, and access to the owners during part of the day, without needing to come into

contact, and hence conflict, with the other cats. Hiding places were provided to increase security within the home (Kry and Casey, 2007), and all the cats were provided with 3-dimensional space, such as shelves, to allow them to pass each other on different levels to decrease conflict, particularly in narrow “passing places” in the house. The cat had been observed to both hide and climb to avoid social contact with other cats. Visual access to the garden was blocked by using opaque strips on the windows, so that the patient could not become aroused by the sight of intruding cats that he could not chase off. Additionally, when workmen were in the house, the patient was to be kept away from the work, but also separated from the other cats to minimize the effects on him. It was not felt that adjunctive psychopharmacological therapy was required in this case, as the circumstances of the owner and household meant that the potential “flare factors” for the disease could be controlled through behavior therapy alone.

Follow-up

The cat was followed up for a period of 15 months. The owner was very compliant in following the management and behavioral advice, and there was no further recurrence of clinical signs for 6 months. However, at this point clinical signs returned. Further investigation revealed that the owner had changed the area accessed by the other cats in the household at this time and had again left the house, confining all the cats in close proximity in error. This event occurred 2 days prior to the recurrence of signs of FIC. The importance of the behavioral program was emphasized to the patient’s owner again at this point, and the separate core areas were reinstated. The patient had no further recurrence of signs for a further 6 months, at which time signs again returned. Investigation of this bout revealed the cat had been chased by a dog in its garden 48 hours prior to the signs returning. Further advice on making the garden secure and providing elevated hiding places in the garden was given to the owners, and there has been no further recurrence of clinical signs.

Discussion

Feline idiopathic cystitis (FIC), also known as idiopathic feline lower urinary tract disease (iFLUTD), is the most common medical cause of abnormal urination in the cat, and hence it is an important differential diagnosis when investigating cats presenting with inappropriate elimination (Kruger et al., 1991; Buffington et al., 1997; Gerber et al., 2005) (Table 2).

Although the different causes of abnormal elimination often result in similar presenting signs, it is important to attempt to achieve a definitive diagnosis where possible, because the appropriate treatment may differ considerably depending on the cause. Feline idiopathic cystitis is

Table 2 Possible causes of FLUTD (Adapted from Kruger et al., 1991; Buffington et al., 1997; Gerber et al., 2005)

Cause	Approximate frequency
Idiopathic cystitis (FIC)	55%-69%
Urolithiasis	10%-25%
Anatomical/neoplasia/other	<10%
Bacterial Infection	<2%
Behavioral problems	5%-10%

diagnosed by excluding other causes of lower urinary tract signs (Kalkstein et al., 1999).

Many of the presenting signs shown by this patient are related to the pain associated with FIC. Cats with FIC appear to sometimes associate the pain of urination with the specific location in which they have urinated, leading to a series of repeated changes in the location of urination. Pain on urination can also cause the cat to appear distressed and vocalize during urination and pace before urination in anticipation of the pain. Male cats may also change their posture from a squat to standing up as squatting bends the urethra, which may cause further discomfort on urination (Seawright, 2007).

Recent research has focused on the effect of environmental stressors as an important “flare factor” in the multifactorial etiology of this condition (Cameron et al., 2004; Buffington et al., 2006). During periods of emotional arousal, there is increased activity in the neurons in the locus coeruleus, increasing the synthesis of catecholamines and therefore increasing activity in the sympathetic nervous system (Makino et al., 2002). Activation of the sympathetic nervous system, either by this central trigger or local bladder triggers (e.g., low urine pH), stimulates C fibers (pain fibers) in the bladder wall, causing release of substance P. Substance P can result in pain, vasodilation, increased bladder wall permeability, submucosal edema, smooth muscle contraction, and mast cell degranulation (Theoharides et al., 1995). Stimulation of the sympathetic nervous system may also directly increase bladder permeability, allowing noxious substances in the urine greater contact with sensory-afferent neurons, which adds to the inflammation (Figure 1). Histopathology of bladder biopsies from affected cats has shown that cats suffering from FIC have relatively normal epithelium and muscularis layers, but may show submucosal edema and an increase in bladder wall and vascular permeability (Chew et al., 1996; Lavelle et al., 2000). Mast cells are often present, although there tends to be minimal inflammatory infiltrate, and additionally, biopsies show an increase in C-fibers and substance P receptors (pain receptors). Some affected cats have also been shown to have a decreased urinary excretion of GAGs, and it is postulated that this decrease in the protective GAG layer of the bladder allows noxious urinary components to contact the bladder wall, predisposing to urothelial inflammation (Buffington et al., 1996b).

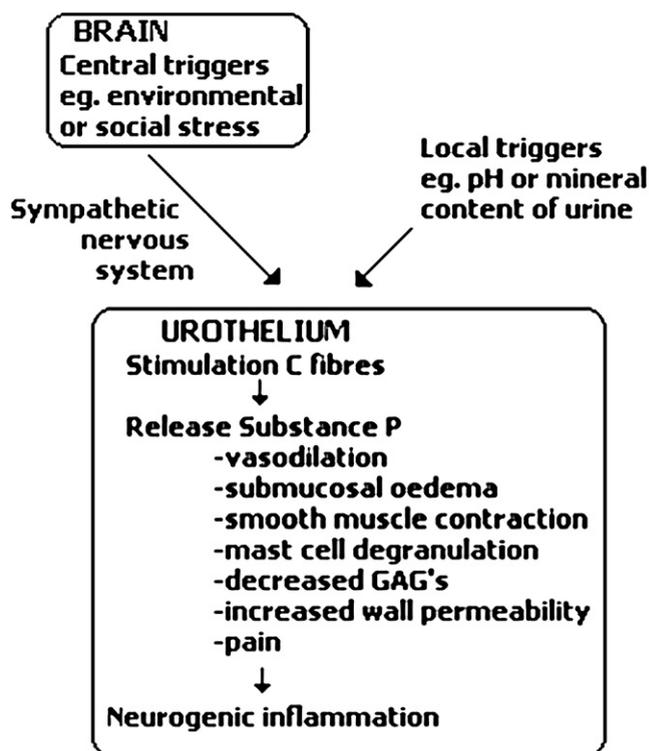


Figure 1 Hypothesis for neurogenic inflammation (Adapted from Buffington et al., 1996a).

As in this case, a functional urethral obstruction may result from urethral spasm owing to the inflammatory response associated with FIC, which can be confused with a physical obstruction caused by urethral blockage or scarring. An indwelling catheter may exacerbate the spasm, which may be an important cause of dysuria after the catheter is removed when an obstruction has been relieved.

Further evidence for the role of stress in this condition comes from evaluating the physiological stress response systems in these cats. Studies have suggested that cats with FIC have an increase in sympathetic activity, with significant increases in plasma norepinephrine and dihydroxyphenylacetic acid (a catecholamine metabolite), as well as a trend toward increased epinephrine levels (Buffington and Pacac, 2001; Westropp et al., 2006). Evaluation of the hypothalamic–pituitary–adrenal (HPA) axis by assessing the response of the adrenal glands to exogenous ACTH revealed a hypersecretion of cortisol followed by a blunting of the adrenal cortex response, and several case studies have revealed that cats with FIC have small adrenal glands (Westropp et al., 2003, 2006). Under normal circumstances, cortisol should inhibit sympathetic nervous system outflow and should act as a negative feedback on the hypothalamus and adrenal glands to inhibit its own release. However, in individuals suffering from extreme chronic stress, this system becomes disrupted (McEwen, 2000).

The production of stress hormones in response to an acute stressor is adaptive: they enhance the animal’s ability

to physically respond to the stressor, and they also facilitate the formation of memories of stimuli or contexts associated with strong emotions (McGaugh, 2000). However, when stress hormones are overproduced, or not “shut off” after response to a stressor, their effect can be maladaptive (McEwen, 2000). The causes of such changes are direct, when the corticosteroid acts directly on the hypothalamus to influence the pulses of activity in the HPA axis (Casey, 2002), and also genomic. Genomic changes involve the altering of relative proportions of different affinity glucocorticoid receptors, from those that aim to prevent homeostatic disturbance to those that facilitate adaptation in response to stressors (De Kloet and Derijk, 2004). There is, therefore, a progressively reduced negative feedback effect of cortisol on the hypothalamus, leading to a heightened HPA axis response to stressors (Figure 2).

The overall changes that occur in the brain in response to chronic exposure to stressors are complex and involve chemical and structural changes in multiple brain regions, as well as direct changes within the HPA axis. Repeated exposure to stressors initially appears to result in adaptive plasticity within the brain, a complex process of neuronal remodeling involving the action of several neurotransmitters on NMDA receptors, notably in the dentate gyrus and hippocampus, which is reversible once exposure to the stressor is removed, and provides a significant resilience to aversive situations (McEwen, 2000). However, prolonged, repeated exposure to stressors leads to atrophy of the prefrontal cortex and hippocampus and neuronal proliferation in the amygdala (McEwen, 2004), changes which are more difficult to reverse. Changes in the amygdala include increased excitability of neurons within the basolateral area, which results in a heightened emotional response to stressors (Shekhar et al., 2005). These changes result in an individual that responds immediately to a potentially stressful situation with a heightened emotional response, leading to excitation of the locus coeruleus, and therefore a rapid and heightened activation of the sympathetic nervous system (Figure 2). Atrophy of the prefrontal cortex is likely to lead to a reduction in the effect of inhibitory

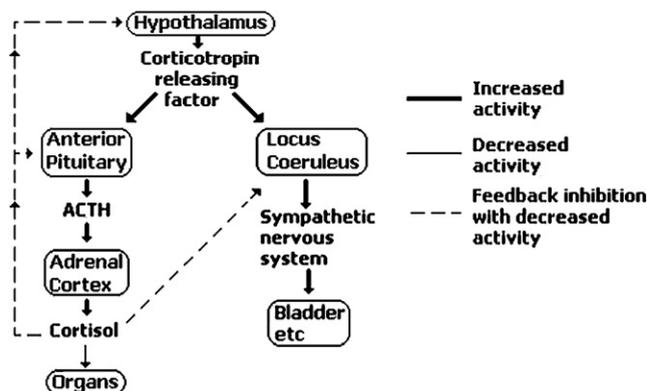


Figure 2 Schematic diagram of changes in the stress response system due to chronic stress (Adapted from Buffington, 2004).

pathways that would balance immediate responding to a stimulus in a normal individual (Correll et al., 2005).

Behaviorally, chronically stressed cats are often hyper-vigilant and appear to respond immediately to novel or mildly aversive stimuli (Casey, 2002). Heightened HPA and sympathetic nervous system responses to aversive events lead to the changes in bladder wall integrity, as described earlier. Clinical experience suggests that the period between exposure to a stressor and clinical signs is often approximately 48 hours. It is therefore important in such cases to identify which factors are causing the animal to suffer from the changes associated with chronic exposure to stressors, as well as those that are aversive enough to precipitate bouts of disease.

A recent case-control study found that case cats were more likely than the control population to be male, overweight, and pedigreed, but the study also found that several stress factors were “flare factors” associated with the onset of a bout of clinical signs (Cameron et al., 2004). In this study, the environmental factor that was the most influential on bouts of disease was living with another cat in a household in which there was conflict, as in the case described in this paper. Research in other species has suggested that psychosocial stress is one of the most potent influences on the stress response system, and it is a potent cause of changes associated with chronic stress (McEwen, 2000; Honess and Marin, 2006). Given the limitations on ability to display complex visual social signaling in the domestic cat because of their largely asocial ancestral history (Casey and Bradshaw, 2005), it seems logical that the stress associated with social interaction is particularly relevant in this species, as reflected in the cases of FIC seen in clinical practice; in over 70% of cases seen in a referral center over a 6-month period, the major “stressor” identified was conflict between cats either within the same household or between cats in different households (Figure 3). Other potential stressors found in this case series were: moving house in the previous 3 months; changes in owner routine or interaction with the cat; and various other factors, such as an increase in days with rainfall (Casey, unpublished data).

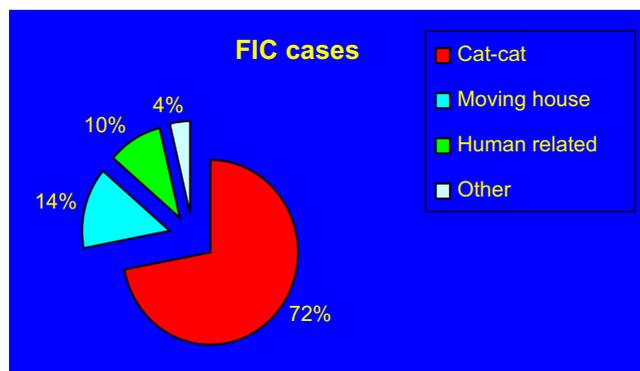


Figure 3 Primary environmental stressors in clinical cases of FIC seen in a behaviour referral centre (Casey, unpublished data).

Although epidemiological and clinical studies are important in identifying major environmental “risk factors” for FIC, it is important to remember that the specific events or contexts that an individual cat finds “stressful” will vary depending on a number of factors. These events or contexts include genetic factors (which influence “personality type” and individual differences in response to stress); experiences during the socialization period; the specific learning of that cat throughout its life; and the availability of a coping strategy (such as hiding or running away) (Casey and Bradshaw, 2005). In addition, the degree of an individual’s response depends on the nature of presentation of the “stressor” and the chronicity and perceived severity of the stimulus and whether its presentation is predictable to the individual (Weiss, 1972).

The aim of behavioral therapy in each case, therefore, is to identify the specific stressors involved and then to tailor an individual program to remove or reduce the effect of these stressors on the cat, or to change the cat’s perception of stressors through systematic desensitization and counterconditioning. Although adjunctive psychopharmacological therapy was not judged to be required in this case, it is often indicated in addition to behavior therapy. In particular, the tricyclic antidepressant amitriptyline can be beneficial in cases of FIC (Chew et al., 1998; Kruger et al., 2003), probably in part because it also has an analgesic and antihistaminic action (Chew et al., 1998; Hanno et al., 1989). Amitriptyline is often used in people as a treatment for various causes of chronic pain (its mechanism is through altered perception of pain [Rang et al., 1987]), and hence it can be beneficial in reducing the period in which the cat experiences discomfort during each bout of the disease. Clinical trials investigating the use of amitriptyline have shown variable results; they suggest that short-term use is not efficacious in reducing clinical signs (Kraijer et al., 2003), although a study looking at its long-term use did suggest a benefit in some individual cats (Chew et al., 1998). In general, the efficacy of anxiolytic therapy is greatest when used in conjunction with a suitable regime of behavior therapy, and as there are potential side effects that can include somnolence, urinary retention, and an increase in liver enzymes, drug use should be reserved for cases where the threshold at which the cat responds to stressors is particularly low, or where it is difficult to remove or reduce stressors from the environment.

The development of FIC in cats is clearly complex, and more research needs to be carried out. It is likely that there are genetic predisposing factors, which may be linked to individual differences in response to stress (Casey and Bradshaw, 2005). Some cats are active responders, who have an active coping strategy in response to a stimulus, such as running away, hiding, or fighting, whereas others are inactive responders, who lack a suitable coping response and consequently internalize their emotions, thus maintaining high cortisol levels. Clinical experience suggests that cats that are “inactive responders” to the stressors

in their environment appear to be overrepresented in the population of cats diagnosed with FIC, but it is not clear whether this behavioral “strategy” is genetically determined or a result of changes resulting from inability to display a normal behavioral response, that is, “learned helplessness” (Seligman and Maier, 1967), or both.

Conclusion

In this case report, the use of a program of behavior therapy to control the exposure of the affected cat to identified stressors was found to successfully control further clinical signs. This case provides an interesting example of how bouts of clinical signs in FIC cats can often be linked to specific “stressful” events, and how such outbreaks can be reduced or prevented through the implementation of a specific program of behavior therapy.

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ERRATUM

In the September/October issue of the *Journal of Veterinary Behavior: Clinical Applications and Research* (Volume 2, Issue 5), the following article's title was published incorrectly: Rosado, B., García-Belenguer, S., León, M., Palacio, J., 2007. Spanish dangerous animals act: Effect on the epidemiology of dog bites. *J. Vet. Behav.: Clin. Appl. Res.* 2, 166-174.

The correct title of this article should have been published as "Spanish dangerous animals act: Impact on the epidemiology of dog bites." The Journal regrets this error in the published title of this article.