FELINE PANDORA'S SYNDROME: A BIBLIOGRAPHIC REVIEW

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ABSTRACT

Pandora's syndrome is a multifactorial disorder in which other systemic aetiologies may influence clinical signs in a target organ. In cats with chronic and idiopathic lower urinary tract disease, diagnosis requires a criteria of exclusion and must fulfil at least four other criteria as a confirmation of the diagnostic. Fundamental treatment of the syndrome is based on the elimination of stress factors as well as environmental enrichment.

Keywords: urology, cats, urinary bladder, urination.

SÍNDROME DE PANDORA EM FELINOS: REVISÃO DE LITERATURA

RESUMO

A síndrome de Pandora é uma doença de caráter multifatorial onde outras etiologias sistêmicas podem influenciar sinais clínicos em um órgão alvo. Em gatos com doença do trato urinário inferior crônicas e idiopáticas, o diagnóstico além de ser por exclusão, deve preencher no mínimo três outros critérios para que a síndrome seja ocorrente. Seu tratamento fundamental baseia-se na eliminação de fatores estressantes bem como o enriquecimento ambiental.

Palavras-chave: urologia, gatos, bexiga urinária, micção.

SÍNDROME DE PANDORA EN FELINOS: REVISIÓN DE LITERATURA

RESUMEN

El síndrome de Pandora es un disturbio multifatorial, en el cual otras etiologías pueden influenciar en signos clínicos en un órgano diana. En los gatos con enfermedad del tracto urinario inferior crónica e idiopática, el diagnostico requiere criterios de exclusión y debe completar al menos otros cuatro criterios para su confirmación. El tratamiento fundamental de esta síndrome es basado en la eliminación de los factores de estrés, además de enriquecimiento ambiental.

Palabras clave: urología, gatos, vejiga urinaria, micción.

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INTRODUCTION

Feline Lower Urinary Tract Disease (FLUTD) has been studied and evaluated in the last forty years. Nevertheless, it is possible to find variations in its nomenclature such as "Feline Urological Syndrome" (FUS), "Feline Lower Urinary Tract Disease" (FLUTD), and "Feline Idiopathic Cystitis" (FIC) (1).

Due to the increased incidence of FLUTD in recent years, it has been noted that, along with an acute or chronic nature (obstructive or non-obstructive), it can also result from various combinations of abnormalities within the lumen of the lower urinary tract (LUT) (local external abnormalities), in the LUT itself (intrinsic abnormalities), or abnormalities of other systems that cause LUT dysfunction (systemic or internal abnormalities) (2).

The terminology "Pandora's Syndrome" appears more appropriate than FLUTD or FIC for two reasons: first, its aetiology does not apply to a specific organ; and second, there are conflicts between medical specialties in the determination of the external aggravants and adjuvants of the organ in question (2).

The clinical signs of patients are the combination of signs related to diseases of the LUT (periuria, pollakiuria, stranguria and hematuria) and/or urinary obstruction in acute cases (3). Although most of these signs occur in acute non-obstructive self-limiting episodes from between five and seven days without previous clinical treatment (80-90%) (4), these animals can also present recurring episodes (2-15%), chronic, persistent episodes (2-15%), and total urethral obstruction (15-20%) (1).

Being multifactorial, Pandora's Syndrome occurs in cats of all ages, sexes and breeds (in accordance with its geographic distribution), with a greater prevalence in males between four and seven years of age (4). Felines with a history of obesity, neutered, under confinement or in agglomerated conditions, principally fed with a poor dry diet and exposed to daily stress factors also present a greater predisposition (1).

With the lack of clinical and epidemiological studies in our country, brasilian veterinarians depend completely on foreign literature for diagnostic and clinical treatment (3), and it becomes the total responsibility of the professional to choose therapies based on the quality of evidence, with preference for those based on results of randomized and controlled scientific studies.

TERMINOLOGY

The term Feline Urological Syndrome (FUS) was created by Osbaldiston and Taussig in 1970 to describe 46 cases of cats that presented a history of periuria, stranguria, urethral obstruction, hematuria and urolithiasis (5). The authors also reported that, of the 19 animals that died, four showed a non-urological cause, which indicated that the condition is more complex than previously thought, and thus required future research for a better terminological determination of that disease.

The concept of the syndrome was altered again by Osborne and colleagues in 1984 after finding that the sites (ureter, bladder, urethra, etc.), the causes (neoplasia, metabolic disturbances, infections, uroliths, idiopathic manifestations, etc.) and the pathophysiological mechanisms (bladder sphincter dissynergia, obstructive uropathies, etc.) manifest in a broader and heterogeneous manner. In this way, the term FUS was substituted by FLUTD (6).

Afterward, Buffington and colleagues exercised a new terminology for patients with a chronic and idiopathic profile of FLUTD, similar to the model studied in women in human medicine. The term "Feline Idiopathic Cystitis" (FIC) was proposed to characterize animals with chronic inflammatory urinary symptoms, and exhibiting negative urine culture and

cytology, absence of ultrasound findings, and the presence of petechiae in vesical epithelium when submitted to cystoscopy (7).

Due to the limitations employed by the conditions cited above, apart from the discovery of new clinical and pathophysiological evidence of the systemic comorbidities of extra-urinary origin, which implies the recurrence of chronic Buffington (2) describes a new syndrome based upon the models of nosology applied by Feinstein criteria, the Pandora's Syndrome (PS) (8).

Therefore, the syndrome affecting felines with chronic and recurring LUTD in the presence of other systemic comorbidities (dermatological, cardiovascular, behavioural, endocrine, gastrointestinal, neurological, etc.) is described as Pandora's Syndrome until a more appropriate nosological term can be identified and determined (2).

PATHOPHYSIOLOGY

The urinary bladder is a complex organ, its principal function being the storage of urine produced by both kidneys (9). It possesses an internal layer comprised of a specific layer of glycosaminoglycan (GAG) called GP-51, responsible for the inhibition of bacterial adhesion and the protection of the uroepithelium (the second internal layer) against the harmful components of the urine (9,10). A third layer consisting of smooth and striated muscle cells encases both with a rich neurovascular tissue of underlying support. These structures exercise a complex neuroendocrine communication with the rest of the body to determine the time and adequate conditions for emptying the bladder (2). Apart from this, the bladder is also influenced by adrenocortical and sexual hormones (1).

ALTERATIONS IN CELLULAR AETIOLOGY

The GAGs are long linear polymers composed of repeated units of disaccharides, omnipresent components in animal tissue. Studies have shown that animals and humans with suspected idiopathic cystitis (IC) or lower urinary tract disease (LUTD) exhibit a diminished urinary excretion of GAG and GP-51 (2). Another possibility is that these animals can also have a diminished concentration of GAG in the blood stream (11).

If the layer of GAG in the bladder is compromised, the urinary components (hydrogen, calcium and potassium) stimulate the sensory neurons and promote a greater susceptibility to vesical inflammation and the trigger of neurogenic inflammation is activated (1).

The concentration of urinary potassium performs an important role in the pathophysiology of IC; excess intravesical absorption of potassium by the urothelium results in a near complete inhibition of firing through the afferent path (2). Patients with IC tend to retain urine, worsening their condition (1).

The presence of mast cells in felines with CI caused principally by stress can also be found in bladder biopsies (2). The activation of mast cells promotes a release of countless activator molecules that are responsible for inflammation, vasodilation, pain, fibrosis and contraction of smooth muscle, which exacerbates the effects of C fibres (4).

For many authors, a better characterization of the structural or functional changes of the GAG layer is essential to determine if these abnormalities are the specific reason for the idiopathic cause of the disease or if there is another unspecific secondary effect arising from another etiologic presence (4).

NEUROENDOCRINE ALTERATIONS

Neurogenic inflammation is a process initiated by the stimulation of the C fibre sensory afferent neurons which, when activated, release neuropeptides (substance P, neurokinin and

calcitonin gene-related peptide) (10). Other signalling molecules arising from other systems (ATP, nitric oxide, acetylcholine, substance P and prostaglandins) also promote the activation of afferent sensory neurons and mast cells (4).

The expression of substance P receptors in the bladder is increased in felines with FIC (2). The interaction of these neuropeptides promotes vasodilation of intramural blood vessels, submucosal oedema, an increase in vascular permeability and of the vesical wall, intrapelvic pain, leukocyte migration and activation of mast cells, leading to an intensification of the disease resulting from the persistent recruitment of C fibres (12).

Elevated concentrations of catecholamines can also be observed in affected animals both in moments of rest and in crises of stress. The adrenoceptors α_2 are found in *locus cerulus* (LC), localized in the pons, in the spinal medulla, and peripherally in the mucosa of the urinary bladder, and are responsible for the inhibition of the release of catecholamines, signalization of pain in the cerebral level and regulation of the blood flow, respectively (10).

Apart from sensory, central and efferent neural abnormalities described above, hypothalamus - pituitary - adrenal axis activity is also found present in felines with IC associated in the presence of the sympathetic nervous system (SNS). The sympathetic neuron output is normally controlled by adrenocortical production; however, felines with FIC exhibit an increased output without the co-activation of the adrenal cortex (13). In addition, the adrenocortical response to stimulate the adrenocorticotropic hormone (ACTH) during stressful situations is reduced, and felines with FIC often exhibit small adrenal glands and fasciculata and reticularis zones are morphometrically reduced in histopathologic exams (4).

In summary, the relationship between stress, the hypothalamus - pituitary - adrenal axis and the SNS results in an intense release of the corticotropin-releasing hormone (CRH) from the hypothalamus which induces the release of ACTH from the anterior pituitary gland lobe and the activation of SNS from the brainstem, resulting in the production of catecholamines (adrenaline and noradrenaline) (1).

In healthy cats, cortisol has a negative feedback effect over the hypothalamus, the anterior pituitary gland and brain stem. In felines with FIC, the inhibition of this feedback at the levels of the anterior pituitary gland and the hypothalamus is reduced, causing a continuous production of CRH. It is presumed that the reinforced sympathetic activity increases the permeability of the tissue in the bladder, resulting in the increase of sensory afferent activity and the typical clinical signs of FIC (13).

When the increase in concentrations of CRH and ACTH in response to stress and the absence of an increased concentration of plasmatic cortisol are observed, it suggests either a primary insufficiency or a reduction in the reserve of adrenocortical hormones in felines with FIC (2).

DIAGNOSIS

For Buffington and colleagues, the development of a diagnosis for PS consists of four criteria: [1] the presence of clinical signs regarding other organic systems in conjunction with chronic idiopathic signs attributed prominently to a particular organ for which the patient is evaluated: for example, combinations of clinical signs regarding other systems (gastrointestinal, skin, respiratory, cardiovascular, neurological, endocrine and immune system) in felines with chronic and idiopathic LUTD; [2] the severity of clinical signs correlated with the events that, presumably, activate the central stress response system (SRS); [3] evidence of early adverse experience (abandonment, orphaning); and [4] the resolution of clinical signs associated with an effective environmental enrichment (14).

The diagnosis of PS also results from the elimination of other differential diagnoses of the LUT. Patient history and detailed physical exam, urinalysis, urine culture, radiographic

exams, contrast urography, ultrasound and/or uroendoscopy and biopsy are necessary so that the Pandora's Syndrome criteria can be assessed (14).

Buffington also details a questionnaire formulated for the owners of house cats with LUTS with the purpose of determining whether their animals are candidates for adjunctive therapy, with prospective controlled clinical trials as a follow up (15). Another article completes with a questionnaire and a checklist of accessible household resources is available online to aid veterinary doctors in a better evaluation of felines with FLUTD (14).

TREATMENT (BASED ON SCIENTIFIC EVIDENCE)

When the diagnosis is suggestive of PS, the efficacy of treatment is strongly correlated to the efficacy of environmental enrichment, suggesting that pharmacological therapy and other complementary therapies are important factors in better clinical treatment of the animals suffering from this syndrome (14,15).

Another important factor is the pharmacological approach that requires restraint and "force"; for example, the administration of capsules and pills that can also release the activation of SRS. However, due to a lack of evidence of the efficacy of pharmacological treatments currently available for felines with signs of chronic and idiopathic FLUTD, such approaches should be realized with caution (2).

ENVIRONMENTAL FACTORS AND STRESS MANAGEMENT

In clinical studies, the period between the introduction of the animal to a stress factor and the appearance of clinical signs is around 48 hours. In such cases, the early identification of these stress factors can prevent the animal from exhibiting adverse clinical signs, and can be sufficient to keep the disease from intensifying or turning recurrent (16).

Stressors include the presence of other contactants (exterior or cohabiting), abrupt changes in diet, climatic or environmental changes, overpopulation, stress caused by the owner, and the inclusion of new people or animals within the same environment (12).

Environmental management does not only include the physical space (interior or exterior) of the feline, but also its social interaction including responses to contact with humans. Felines are not accustomed to expressing signs of stress and anxiety; however, studies suggest that even exotic felines can exhibit elevated levels of catecholamines and other stress hormones while they are not showing signs of stress (17).

Cats require free and prompt access to water, food, sanitation, rest areas and access points (entrance and exit) to their territory. Of great importance is not just the number of access points but their distribution. Felines need to be able to select locations that offer privacy while they feed, drink water and rest; preferably without visual contact with other animals or humans while they realize these activities (18).

Regarding the physical space, the goal is to establish three-dimensional environments favouring an increase in range and extent of territory, apart from the ground territory, for new exploration. Elevations and hiding places are behavioural strategies in the regulation of stress for cats (18). Stress can also be controlled with the usage of toys and entertainment tools for felines, apart from positive daily interaction with their owners (17).

For felines that already exhibit a history of chronic LUTD, it is necessary that each cat in the household have its own litter box plus an additional one. External sanitary spaces (backyards and gardens) are also principally suggested for the practice of territorial behavior (18). The usage of a cat litter with similar texture to regular granulous sand is recommended; litters with a fine or powdered texture, as well as large crystals can increase stress in the animal when covering its excretions (10).

Felines that use backyards or external spaces, which can be exposed to other animals or stressors, need safety zones, hiding places or priority access inside and out of the home. The combination of vases and plants, bushes, trellises and boxes or crates allow the blockade of external agents. Another alternative is the use of spiky plastic door mats to maintain any aggressor far from the internal/external access. Small electronic doors that only open with a signal from the animal's microchip are already being used abroad (18).

In severe cases, it is recommended to consult animal behaviour veterinarians with the intention of a comprehensive behavioural adjustment; desensitization and counterconditioning can be instituted by the professional (1).

USE OF PHEROMONES

Pheromones are bioactive compounds emitted and detected by animals of the same species, and are responsible for influencing their social behaviour and reproductive status. They are described as non-volatile molecules that regulate innate social behaviour and the activation of sensory neurons of the vomeronasal organ (1).

A recent systematic revision in the work of the use of pheromones in felines with FIC affirms that there is not sufficient evidence that their use improves the control of felines with FIC, decreases stress in hospitalized patients or calms felines in unknown environments (19).

Forrester and Roudebush also recommend considering the use of pheromones in felines with signs of stress when the clinical signs persist after the implementation of environmental enrichment and as an alternative method to stimulate the ingestion of water (20).

USE OF NUTRITIONAL SUPPLEMENTS AND THERAPIES FOR STRESS

For centuries, practitioners of traditional Chinese medicine have recommended the use of nutritional supplements as a therapy for disorders of a behavioural nature, such as stress or anxiety. Natural treatments including amino acids, minerals and fatty acids have demonstrated beneficial effects in altering concentrations of neurotransmitters and improving the signs of anxiety in animals and humans (21).

In one study, L-tryptophan, a precursor of serotonin synthesis, was evaluated in the behavioural control of felines diagnosed with stress. In two months of study, the authors observed a significant change in the behaviour of these animals, and concluded that a daily supplement of 12.5mg/kg of L-tryptophan reduced the signs of anxiety in stressed cats (22).

Another study evaluated the beneficial and anxiolytic effects of α-casozepine/α-casein (another amino acid isolated from milk, dose of 15mg/kg) administered to 17 cats with a diagnosis of chronic stress. Although the study was of a short duration, 71.4% of the treated animals exhibited remission of the clinical signs (23).

Although both of these treatments suggest beneficial effects in the control of stress, the veterinary professional should question whether the patient in question can tolerate oral administration; if not, stress may be redoubled. However, even for felines with a history of chronic LUTD that can tolerate oral treatment, environmental enrichment should not be ignored (1).

HYDRATION AND NUTRITIONAL MANAGEMENT

Nutritional management in cats with chronic LUTD is recommended with the objective of making the urine less concentrated also lowering the amount of substances that irritate the mucosa of the urinary bladder, meaning methods to increase the ingestion and excretion of water (20).

The attempt to increase the ingestion of water by the introduction of wet diets, water fountains, high sodium diets, the introduction of cat broth or other methods may be beneficial in felines with LUTD or FIC. Among these methods, only wet diets have been evaluated in felines with this comorbidity (1).

Two studies detailed the benefit of wet diets in felines with FIC. In both, the increase in consumption of the wet diet was associated with less concentrated urine and an urine specific gravity (SG) less than 1.040, which resulted in an improvement of clinical signs. However, it is unclear whether the properties of wet food (texture, taste, owner-animal-food relationship) could have served as an indirect manner of environmental enrichment, creating a doubly positive impact (24,25).

High sodium diets are another therapeutic proposal for urinary dilution; however, studies do not exist in animals with chronic LUTD. In healthy cats, the increase in sodium ingestion may result in the reduction of SG and/or the increase in the volume of urine. In a continuing study, SG diminished significantly in the third month, however, there was no difference in comparison to the sixth, twelfth, or twenty-fourth month (26).

However, an immediate introduction to a wet diet is recommended if it is not a stressor for the patient. If it is, a gradual transition from a dry diet to a wet diet is recommended so that there is no complementary stress. There are no contraindications with respect to high sodium diets in healthy cats; however, different opinions exist in regards to the safety of an excess of sodium intake in cats with undetectable kidney disease (1).

Despite a lack of therapeutic diets for patients with FIC, some elements of therapeutic urinary diets like omegas (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), including tocopherol as an antioxidant, are powerful anti-inflammatory agents in the control of vesical inflammation (27,28). The prescription of these therapeutic diets is valid for patients with LUTD that is recurrent, of an acute nature, or that does not exclude the possibility of urolithiasis caused by struvite stones (20).

GLYCOSAMINOGLYCANS

Oral or intravesical supplementation of GAGs has the objective of absorption by the injured uroepithelium, decreasing its permeability and improving its internal coating, and resulting in control of inflammation of the neurogenic bladder (10).

Gunn-Moore and Shenoy in 2004 performed a study with the prescription of the oral administration of GAGs (Cystease 125mg/day) in felines with FIC; even though there was a discrete improvement in the patients at the end of the study, no statistically significant improvement was reported (25).

Another study done with 107 cats with a history of FIC demonstrated that, independent of the dose of pentosan polysulfate (2 mg/Kg, 8 mg/Kg and 16 mg/Kg), all the animals exhibited clinical improvement (29).

However, the recommendations for the use of GAGs are for those that exhibit persistent clinical signs, even after implementation of environmental enrichment and an increase in the ingestion of water. The recommended dosage of pentosan polysulfate is 8 mg/Kg/twice a day combined with glucosamine/chondroitin (125 mg/100 mg/4,5 Kg (cat)/day) (20).

AMITRIPTYLINE

Amitriptyline is a tricyclic antidepressant that has beneficial effects in felines with FIC due to its antidepressant, analgesic (reduction in nervous sensory transmission by C fibres), anti-inflammatory (control of the release of mast cells), anti-α-adrenergic and anticholinérgic (inhibition of the recapture of serotonina) properties (10).

In one study, the medication was administered in felines with recurrent FIC and a history of failed response to other treatments over 12 months. In the sixth month, a clinical improvement was observed in 60% of these patients (30).

Due to its hepatotoxicity, its initial dosage is 2.5 mg/cat/once a day, which can be adjusted up to 12.5 mg/cat until there is a clinical improvement. The principal side effects are sleepiness, urinary retention and an increase in hepatic enzymes. Periodic returns to the veterinarian are recommended from one month after beginning treatment, and afterward between 6 and 12 months (12).

Even with a lack of evidence, amitriptyline is highly recommended for chronic cases in felines with FIC in which clinical signs persist even after environmental management and an increase in consumption of water (1).

ANTI-INFLAMMATORIES AND ANALGESICS

The application of anti-inflammatories and analgesics are generally recommended in felines with LUTD that principally manifest in acute phase due to intense discomfort. No studies exist for opioids (butorphanol) or non-steroidal anti-inflammatories drugs (NSAIDs) (meloxicam, piroxicam) in felines with LUTD (20). However, even though there is no evidence that supports the usage of analgesics and anti-inflammatories for pain control, the use of both may reduce the severity of the clinical signs, although rarely sufficient to eliminate them (12).

The use of prednisone (1 mg/Kg/every 12 hours) did not present a clinical improvement when compared to the placebo in 10 days of treatment in felines with FIC (31).

Caution should be exercised when using NSAIDs due to the function of the renal profile of the patients. The tolerated duration of these medications is at a maximum three to four days. The dosage of butorphanol for oral intake is (0.2-0.4 mg/Kg/every 8 hours), meloxicam (0.1 mg/Kg/every 24 hours) or minimum dosage (0.025 mg/kg/every 24 hours) during 7 to 10 days, dipyrone (25 mg/kg/every 24 hours) and hydrochloride of tramadol (2-4 mg/Kg/every 12 hours) (3).

FINAL CONSIDERATIONS

Due to Pandora's Syndrome being the result of different comorbidities reflected in a specific region, such as the lower urinary tract, its diagnosis should be detailed and should fulfil all criteria reviewed by the authors. The efficacy of pharmacological treatment and complementary therapies for this syndrome is principally correlated with an effective environmental enrichment and to the suppression of stress factors. It is still unclear if the lack of success in therapeutic studies is correlated with a poor environmental enrichment or if there is a lack of criteria to be applied based on scientific evidence. The prognosis for felines with this syndrome depends on the commitment of their owners to a rigorous modification of environment and control of the animal's stress. Additionally, cats tend to maintain an underlying vulnerability, even after long periods without incidence of clinical signs, and can also be predisposed to recurrent conditions.

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