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Retrospective Case Control Study of Pet Ferrets with Cystine Urolithiasis in Quebec, Canada: Epidemiological and Clinical Features

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Abstract

Objective: To describe epidemiological and clinical features of cystine urolithiasis in pet ferrets.

Methods: Retrospective case control study on medical records from four private clinics and one teaching hospital for pet ferrets diagnosed with cystine urolithiasis confirmed by spectrophotometry presented between July 2014 and July 2019 in Quebec, Canada; these cases were then compared to a reference population of 210 ferrets (controls) presented at the same facilities over the same timeframe.

Results: Among the 36 identified cases, most affected ferrets were neutered males (32/36, 89%) and the mean age at presentation was 1.8 (± 1.0 standard deviation) year. Grain-free diets of six different brands were offered for at least three weeks prior to the presentation to 34/36 (94%) of the included cases. The ferrets that developed cystine urolithiasis were 57.9 times (Odds ratio [OR], 95% Confidence interval [95% CI]: 11.0, 304.8) more likely to receive a grain-free diet compared to the reference population. No significant difference in the values for the energy, protein, cysteine, and methionine contents were detected between the grain-free and the cereal-based diets offered to these pet ferrets- according to manufacturer provided information. Ferrets with uroliths, those with urethral calculi were 4.7 times (OR, 95% CI: 2.1, 10.4) more likely to develop an acute urinary tract obstruction.

Conclusion: Although a definitive causation could not be drawn solely from these clinical cases, this case control study highlights a possible nutritional aetiology in the complex pathogenesis of cystine urolithiasis in ferrets.

Keywords: Cystine; Diet; Ferret, Grain-free; Hematuria; Mustela putorius furo; Urinary retention; Urolithiasis

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Introduction

Cystinuria in humans and dogs is typically characterized by impaired renal tubular reabsorption of cysteine [1]. Although a genetic transmission is suggested in studies in humans and dogs, the aetiology of cystine urolithiasis in ferrets remains unknown [2,3]. In a retrospective study of cystine urolithiasis, the mean age at the time of diagnosis in ferrets was approximately four years [4]. The same authors postulated that an earlier onset of clinical manifestations would have been expected if a genetic disorder was the only aetiology. Nevertheless, the prevalence of cystine uroliths varies depending on the ferret population considered. Although no cystine urolithiasis was reported in ferrets in the United Kingdom, 15% of uroliths were composed of cystine in a large epidemiological study on North American ferrets from 1981 to 2007 [5,6]. A recent large-scale retrospective study reported a higher prevalence of cystine urolithiasis in North American ferrets, which accounted for 93% of the 1014 uroliths submitted between 2010 and 2018, while this prevalence was 27% among the uroliths submitted from European ferrets [7]. The aims of the present case-control study were to describe the epidemiology and some clinical features of clinical cystine urolithiasis in North American pet ferrets.

Materials and Methods

Case selection

Medical records of domestic ferrets diagnosed with cystine urolithiasis presented between July 2014 and July 2019 from four private clinics and one teaching hospital were retrospectively reviewed. For inclusion, the type of uroliths had to be confirmed by spectrophotometry. Case files were found through a keyword search within the species "ferret," using the keywords "cystine" or "urolith". The following data were deemed critical for inclusion and recorded: age at diagnosis, sex, clinical history, diet, clinical signs at presentation, abdominal radiography, location of the urolithiasis, therapeutic management and outcome; when available in the medical files, the following data were also recorded: origin, duration of exposure to the diet, and other diagnostic tests (ultrasonography, urinalysis, urine culture) and their results. Cases with missing inclusion criteria were excluded from the study.

Comparison to the control ferret population

The epidemiological characteristics of the reference ferret population were approximated by randomly selecting ferrets ('controls') admitted in the same veterinary facilities over the same time period with any reason for presentation, excluding confirmed cystine urolithiasis. To be included as controls, the following data had to be available in their medical files: date of consultation, age, sex, and diet. These controls were randomly selected using a random number generator until a control population of 210 ferrets (five controls per case) was reached. When available in the medical files, the following data were also recorded: origin, and duration of exposure to the diet.

Data collected on diets

The guaranteed analysis related to metabolized energy and the approximate nutrient composition of the six main diets fed to affected ferrets and the two main diets fed to ferrets of the reference population were obtained from the manufacturers. These eight diets represented 94% and 76% of the diets distributed to cases and controls, respectively. Grain-free diets were defined as diets containing no grain products in the ingredients listed in contrast to cereal-based diets which contained cereals (mostly wheat and corn). The data collected were: metabolizable energy, crude protein, cystine, and methionine concentrations, and the list of ingredients.

Statistics

To compare the epidemiological characteristics of the included ferrets with cystine urolithiasis and the control population, a t-test for unequal variances (age; normality checked with Anderson-Darling test) and chi-square tests (year of consultation, sex, diet) were used. Multivariable logistic regressions were performed to establish the odd ratios of having uroliths according to different independent variables (age, year of consultation, sex, diet), and to establish the odd ratios of having certain clinical signs (acute urinary retention, hematuria) as a function of the location of the uroliths (bladder, urethra). A non-parametric Wilcoxon test was used to compare the data obtained from the average analysis of each diet according to its type (cereal-based versus grain-free). All the descriptive analysis and statistical tests were performed with SAS software (SAS Institute, Cary, North Carolina, USA), and differences were considered significant at $p \leq 0.05$.

Results

Epidemiological overview of the control ferrets

Neutered males represented 112/210 (53.3%) of this population (**Table 1**). The mean age of admitted ferrets was 3.4 (± 2.1 Standard deviation [SD]) years. The origin was recorded for 151 controls (72%) and dominated by Marshall Ferrets (149/151, 99%), the remaining ferrets being of Canadian origin. The proportion of ferrets fed a grain-free diet was 28% (58/210, 95% Confidence interval [95% CI]: 21.7, 34.2). Among these grain-free diets, 35/58 (60%) ferrets were fed diets marketed for ferrets, 22/58 (38%) were fed diets marketed for cats. The duration of exposure to the current diet was recorded for 49 ferrets (23%), and ranged from one to 102 months prior to the presentation (median: 57 months, IQR: 20, 86).

Variables	Cases	Controls	p value
Age at presentation (years)[1]	1.8 ± 1.0 [0.4; 4.3]	3.4 ± 2.1 [0.2; 10.0]	<0.0001
Male:female ratio	1:0.12 (32 males, 4 females)	1:0.86 (113 males, 97 females)	<0.0001
Neutered animals	36/36 (100%)	207/210 (99%)	1
Marshall origin	29/29 (100%)	149/151 (99%)	1
Grain-free diet	34/36 (94%)	58/210 (28%)	<0.0001
Ferret grain-free diet	17/36 (47%)	35/210 (17%)	0.001
Cat grain-free diet	17/36 (47%)	22/210 (11%)	<0.0001
Cereal-based diet	2/36 (6%)	152/210 (73%)	<0.0001
Ferret cereal-based diet	2/36 (6%)	130/210 (62%)	<0.0001
Cat cereal-based diet	0/36 (0%)	21/210 (10%)	<0.0001
[1]Presented as mean ± standard deviation [minimum; maximum].			

Table 1: Demographics of and diets fed to ferrets with cystine urolithiasis (cases) compared with ferrets from the reference population (controls).

Epidemiological overview of the ferrets with cystine urolithiasis ('cases') and comparison to the control population

A total of 36 cases of confirmed cystine urolithiasis met the inclusion criteria. Thirty-two (89%) were neutered males and this prevalence was significantly higher compared to the controls (p<0.0001). The odds of developing cystine urolithiasis increased by a factor of 8.9 (Odds ratio [OR], 95% CI: 2.5, 31.5) among neutered males compared to neutered females (p=0.0007) (**Table 2**). The mean age at diagnosis was 1.8 (± 1.0 SD) year, and ranged from 5 months to 4.3 years; this was significantly lower than the age at presentation for the controls (p<0.0001). A grain-free diet was offered to 34/36 (94%) of the ferrets with cystine urolithiasis for at least three weeks prior to the presentation. This prevalence was significantly higher compared to the controls (p<0.0001). The ferrets that developed cystine urolithiasis were 57.9 (OR, 95% CI: 11.0, 304.8) times more likely to receive a grain-free diet compared to the controls (p<0.0001). Half of the grain-free diets fed to affected ferrets were marketed for ferrets, the other half was marketed for cats. The time to the transition to a grain-free diet was recorded for seven cases (19%), and ranged from one to

six months prior to the presentation (median: 8 weeks, IQR: 5, 14). Two ferrets in the same environment presented with cystine urolithiasis-related urinary signs a few days apart. The odds of having cystine urolithiasis did not vary significantly by year of consultation (p=0.290). The origin was recorded for 29 ferrets (80%) with all cases being of Marshall origin; the proportion of Marshall ferrets in the case and control populations was not significant different (p=0.335).

Variables	Odd ratio (95% confidence interval)	p value
Age at presentation	0.7 (0.5; 1.0)	0.0537
Diet	57.9 (11.0; 304.8)	<0.0001
Sex[1]	8.9 (2.5; 31.5)	0.0007
Urolith location	4.7 (2.1; 10.4)	0.0002
[1]Conducted only on neutered ferrets (100% of cases, 98.6% of controls).		

Table 2: Results of the logistic regression analyses evaluating the age at presentation, type of diet (grain-free vs. cereal-based), and sex on the odds ratio of developing clinical cystine urolithiasis in pet ferrets, and the location of urolithiasis (urethra vs. bladder only) on the odds ratio of presenting a urinary obstruction.

Analysis of the diets

Different commercial extruded grain-free diets were offered to the ferrets included in the study (**Table 3**). The six most commonly fed grain-free diets contained either peas and other legumes (5/6 diets) and potatoes (5/6 diets); these ingredients were not listed in the two most commonly fed cereal-based diets. The protein and amino-acid contents of these diets are presented (**Table 4**) there was no significant difference in the values for the energy, protein, cysteine, and methionine contents, nor for the ratio of cysteine and methionine on sulfur amino-acids between the grain-free and the cereal-based diets (p>0.11).

Diet	Ferrets with cystine urolithiasis	Reference ferret population
Grain-free diet #1[1]	7/36 (19%)	8/210 (3.8%)
Grain-free diet #2[2]	3/36 (8%)	12/210 (5.7%)
Grain-free diet #3[3]	10/36 (28%)	7/210 (3.3%)
Grain-free diet #4[4]	6/36 (17%)	6/210 (2.9%)
Grain-free diet #5[5]	3/36 (8%)	3/210 (1.4%)
Grain-free diet #6[6]	4/36 (11%)	21/210 (10.0%)
Cereal-based diet #1[7]	0/36 (0%)	51/210 (24.3%)
Cereal-based diet #2[8]	1/36 (3%)	51/210 (24.3%)
[1]ZuPreem Grain-free Ferret diet (ZuPreem, Shawnee, Kansas, USA).		
[2]Orijen Cat and Kitten (Champion Petfoods LP, Edmonton, Alberta, Canada)		
[3]Nutrience Grain-free dry food (Rolf C. Hagen Inc., Baie d'Urfé, Quebec, Canada)		
[4]True North Grain-free diet for ferrets (Rolf C. Hagen Inc., Baie d'Urfé, Quebec, Canada)		
[5]Oven-Baked Tradition Grain-free Chicken cat food (Bio Biscuit Inc., Saint-Hyacinthe, Quebec, Canada)		
[6]Versele-Laga Complete Ferret (Versele-Laga, Deinze, Belgium)		
[7]Totally Ferret Active Show & Pet Formula (Performance Foods Inc., Broomfield, Colorado, USA)		
[8]Marshall Premium Ferret (Marshall Pet Products, North Rose, New York, USA)		

Table 3: Distribution of the main diets fed to ferrets with cystine urolithiasis (cases) compared with ferrets from the reference population

Diet	Protein (g/1000 kcal)	Cysteine (g/1000 kcal)	Methionine (g/1000 kcal)	Ratio cysteine/sulfur amino-acids (%)	Ratio methionine/sulfur amino-acid (%)
Grain-free diet #1	88.1	0.95	1.81	34.4	65.6
Grain-free diet #2	106.2	1.04	2.26	31.5	68.5
Grain-free diet #3	95.2	1.14	2	36.4	63.6
Grain-free diet #4	97.7	NA*	NA*	NA*	NA*
Grain-free diet #5	96	1.09	2	35.3	64.7
Grain-free diet #6	92.2	1.22	2.3	34.6	65.4
Cereal-based diet #1	81.1	0.99	2.36	29.5	70.5
Cereal-based diet #2	96.7	1.14	3	27.6	72.4
*NA not available. The names of the diets are the same as in **Table 3**.					

Table 4: Energy, total protein and sulfur amino acid (cystine, methionine) contents and their proportions of the main grain-free diets fed to domestic ferrets diagnosed with cystine urolithiasis and cereal-based diets fed to the ferret reference population.

(controls).

Clinical presentation, diagnostic tests and management

Two main clinical presentations were reported in ferrets with urolithiasis: intermittent hematuria over a few days without urinary retention (15/36, 42%), or acute urinary retention often preceded by episodes of dysuria or stranguria (21/36, 58%). In ferrets with the first clinical presentation, uroliths were only detected in the urinary bladder, whereas uroliths were visualized in the urethra of 20/21 (95%) of the ferrets with the latter clinical presentation. When in the urethra, calculi were always in both penile and pelvic portions. The odds of developing an acute urinary retention increased by a factor of 4.7 (95% CI: 2.1, 10.4) when calculi were present in the urethra compared to in the bladder only (p=0.0002). The location of the uroliths as reported in the radiographic reports are summarized (**Table 5**). When only present in the bladder, uroliths were single large stones whereas multiple small uroliths were visible when the urethra and the ureters were involved. Urine pH measured by dipstick at presentation (without treatment received) was recorded in 12 cases, and ranged from 5.0 to 7.0 (median of 6.0, Interquartile Range [IQR]: 6.0, 6.6).

Location of uroliths	Proportion
Bladder only	16/36 (44%)
Bladder and urethra*	15/36 (42%)
Urethra* only	3/36 (8%)
Bladder, urethra*, and ureter	2/36 (6%)
*When in the urethra, calculi were always in both penile and pelvic portions.	

Table 5: Location of the cystine uroliths diagnosed in domestic ferrets as reported in the radiography reports.

Most of the recorded cases (28/36, 78%) were managed surgically by cystotomy (26/36, 72%) or by percutaneous cystolithotomy (PCCL; 3/36, 8%), a minimally invasive calculus retrieval technique described in pet animals [8]. Post-operative complications led to the euthanasia of three of the operated individuals. Overall, euthanasia (at presentation or following surgery) accounted for the outcome in 10/36 (28%) of the cases. Of note, all the cases euthanized presented with urethral urolithiasis. Overall, 10/21 (48%) ferrets presented with urethral cystine uroliths were euthanized. One case was managed medically after urethral catheterization and supportive care with meloxicam (Metacam; Boehringer-Ingelheim, Burlington, Ontario); this ferret was also transitioned to a cereal-based diet and survived for three years after the initial presentation with the stone still present.

A recurrence of cystine urolithiasis was identified in three cases; one case, offered a cereal-based diet, developed another episode nine months after its initial cystotomy. Two other cases, initially fed a grain-free diet at the time of the first presentation also presented with a recurrence of cystine urolithiasis respectively two and seven months after their initial presentation; no diet transition was performed after their first episodes. No recurrence was reported in the other ferrets of the case series. Seven ferrets were radiographed five to eleven months following their initial presentation; none of them showed recurrence of urolithiasis. All these seven cases were transitioned to a cereal-based diet after their initial presentation.

Discussion

Owing to its reduced solubility in acidic urine, urinary cystine in high concentrations in affected individuals precipitates to form crystals and uroliths leading to urinary obstruction [1,2]. Neutered males were overrepresented in the present case series, accounting for the majority of cases. The same trends have been reported in a previous study in which male ferrets accounted for 77% of the affected individuals and appeared to be 2.5 times more likely to develop cystine uroliths as females [4,8,9]. As no difference in urine pH was found between males and females, this sex difference may likely be related to the anatomy of the urethra of male ferrets that could predispose to partial or total urethral obstruction [4,9,10]. Male ferrets have a longer lower urinary tract combined with a tightly angled pelvic urethral flexure, rigid os penis, and narrow urethral diameter that may predispose them to urinary blockage [11]. The more straightforward urethra of female ferrets may allow the passage of small stones. Hence, some females may remain asymptomatic while having cystine uroliths in their urinary tract. The mean age at diagnosis in the present study was 1.8 year with most cases between one and three years of age. This is younger than the mean age of 4.1 years reported in the case series of Nwaokorie and others (2013), however, in the same study, 51% of the cases occurred between two and four years old. Our data were also in agreement with a recent study that demonstrated a strong association between cystine urolithiasis and younger age of the ferret [7]. In this large-scale retrospective study from 2010 to 2018, two other features were strongly associated with cystine urolithiasis: North American origin, and later year of submission. The marked difference in prevalence between populations of different origins and the increase in prevalence in the last few years may highlight other contributors to the aetiopathogeny of this affection, particularly environmental or genetic factors.

The most striking finding of the present case-control study was a history of consuming a grain-free diet in most affected cases (94%) whereas only 27.6% of the ferrets in the reference population were fed grain-free diets. The ferrets that developed cystine urolithiasis were also 57.9 times more likely to receive a grain-free diet compared to the reference population. The popularity of grain-free diets in the pet food industry has increased in the recent years; the percentage of grain-free cat food purchases has increased from 4% of total cat food purchases in 2012 to 9% in 2014, and represented 47% of cat foods in all channels in 2017 in the USA [12,13]. Similar trends may apply to ferret food although no published data were available; since many ferrets are fed cat food (20.5% in the present control population), they may be more likely to be exposed to grain-free diets. Some anecdotal correlations between an increased incidence of cystine urolithiasis in ferret and the introduction in North America of ferret diets containing legumes, peas and lentils as alternative carbohydrate sources have been suggested before [11,14]; this article represents more tangible evidence of an association between grain-free diets and the development of cystine urolithiasis in ferrets.

The statistical comparison of the nutrient content of the main grain-free diets fed to affected ferrets of the present study and the main cereal-based diets distributed in the reference population did not demonstrate significant differences in the protein and sulfur amino-acid contents. However, legumes and peas are high in plant protein that may alter the urinary environment such as pH or urine concentration. The solubility of cystine in urine is pH-dependent; it is relatively insoluble at the usual urine pH range of 5.5 to 7.5 in dogs [1]. The urine pH can vary according to the diet, and the normal pH in ferrets was reported to be 5.0 to 7.5, which is consistent with the results of the ferrets in the present study; however, the pH was only available for few affected cases [10,15]. Future studies should investigate whether the protein source may induce changes in the assimilation of these amino-acids, or other factors such as urine pH.

Two individuals that did continue to be fed grain-free diets experienced recurrence of cystine urolithiasis two and seven months after the initial presentation. In contrast, six of the affected ferrets that underwent cystotomy and were then offered cereal-based diets did not show evidence of urolithiasis recurrence on radiographs taken five to 11 months after the surgery. However, not all ferrets fed a grain-free diet develop a cystine urolithiasis and two affected ferrets in the present study were fed cereal-based diets. Moreover, only some individuals were reported to develop cystine urolithiasis in several multi-ferret households that fed all ferrets exclusively grain-free diets [11].

A possible nutritional origin does not rule out a genetic basis that may predispose some lineages to produce this type of urolith; evidence of little genetic variability among most pet ferrets in North America may support a familial predisposition for this disease [16]. In humans, dogs and cats, cystinuria is an inherited metabolic defect of amino-acid transport causing a failure in reabsorption of filtered cystine in the proximal tubule [1,2], and has been documented to be caused by mutations in either the SLC3A1 or SLC7A9 genes [3,17-19]. Excessive inbreeding of domesticated ferrets in North America could have contributed to an increase in the prevalence of one or more mutations contributing to faulty amino acid reabsorption in the proximal tubules. This genetic predisposition may also be supported by the two ferrets of the present series that developed cystine urolithiasis but were never fed grain-free diets. A complex aetiopathogenesis involving genetic and environmental components in the development of cystine urolithiasis in pet ferrets may also be emphasised by the low prevalence of this condition in the United Kingdom, where ferrets more commonly are fed whole-prey or legume-free diets [5,11]. The impact of the origin of the ferrets included in the present study could not be evaluated as all animals were of North American origin, and most of them of Marshall origin.

The present study highlights two main clinical presentations linked to the location of the calculi: most cases with identified calculi in the urethra presented with urinary retention, often preceded by hematuria. On the other hand, cases with uroliths in the bladder mostly presented with intermittent hematuria. Overall, uroliths were identified in the bladder of 92% cases and in the urethra of 56% cases. This is in agreement with the description of the lower urinary tract as the main source of submissions of cystine uroliths in ferrets [4]. Abdominal radiography was useful in the detection of ferrets with suspected urolithiasis in the present retrospective study; cystine calculi were identified in all the ferrets with confirmed cystine urolithiasis. Double contrast cystography may even be more sensitive in detecting small cystine uroliths than survey radiography [20].

The outcome of the surgical managements (cystotomy or PCCL) in the present study was fair as survival was recorded in most cases (89%). Overall, euthanasia (at initial presentation or following surgery) accounted for 28% of all cases which emphasises the need for implementation of preventative measures to reduce its incidence. Of importance, intermittent hematuria in ferrets should be addressed early before the condition may evolve into urinary retention, of most guarded prognosis.

Euthanasia of ferrets presenting with cystine urolithiasis may even be more prevalent as this study included only ferrets with confirmed cystine urolithiasis by spectrophotometry; some animals presented with similar clinical signs during the same time period and euthanized because of poor prognosis or financial restrictions were not included because the presence and composition of uroliths were not confirmed (at least 25 euthanized ferrets fed grain-free diets were excluded as the type of uroliths was not confirmed).

As a retrospective case-control study, this paper presents some limitations and biases that may influence its conclusions or reduce its relevance. Firstly, some data recorded in the medical files were missing, which led to the exclusion of some records; the medical files analysed were also from different veterinary clinics with differences in medical data recording. This study highlights a possible association between grain-free diets and the development of cystine urolithiasis in ferrets; nevertheless, the duration of exposure to a grain-free diet was occasionally recorded in the medical files, and further work will be needed to assess this association.

Conclusion

This case series allowed to evaluate new elements in the epidemiology of cystine urolithiasis that showed a marked increase in incidence in pet ferrets in the last decade. As already mentioned in several studies, male ferrets and young individuals were overrepresented; a strong association with grain-free diets was shown, without causation being established. This study therefore reinforced the possibility of a complex aetiopathogenesis of cystine urolithiasis in ferrets for which genetic and environmental factors (including diet) are probably involved. Future studies are needed to assess possible genetic mutations, as in humans or other domestic carnivores, or changes in urinary environment and amino-aciduria in affected ferrets.

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