



Concurrent diseases in hyperthyroid cats undergoing assessment prior to radioiodine treatment

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Abstract

Hyperthyroidism is a common endocrinopathy of geriatric cats, which are also prone to various other diseases. This retrospective study examined the prevalence and type of non-renal concurrent diseases present in cats referred for radioiodine assessment that were believed to have no other comorbidities at the time of referral. Ninety-four cats were included and analysed. Seventeen cases (18%) were identified as having concurrent disorders, with alimentary lymphoma ($n = 5$) and chronic enteropathy ($n = 4$) as the two most common comorbid diseases. The eosinophil count, total bilirubin and total calcium were significantly higher in the concurrent disease group, although the differences are unlikely to be clinically useful. The results support the utility of careful and individual assessment for all hyperthyroid cats prior to receiving radioiodine.

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Introduction

Hyperthyroidism is the most common endocrinopathy in cats, with a reported median age of 12–13 years at the time of diagnosis.^{1,2} Treatment options include the use of antithyroid drugs, thyroidectomy, radioiodine administration and dietary iodine restriction. Although radioiodine therapy is limited to relatively few institutions in the UK, it is considered the treatment of choice owing to its curative outcome, high success rate, non-invasiveness, low prevalence of complications and longer survival time.^{3,4} In addition, long-term medical management may be detrimental as hyperfunctional thyroid tissue continues to grow with possible transformation to thyroid carcinoma over time.⁵ The disadvantages include the reluctance of some owners to isolate their cats for a long period of time and the risk of radiation to humans and the environment.^{6,7} In addition, the treatment of hyperthyroidism with radioiodine leads to an irreversible decline in the levels of thyroid hormones with possible iatrogenic hypothyroidism, a decrease of glomerular filtration rate and the emergence of azotaemia.^{8,9}

Life expectancy in cats has increased considerably over recent years, hence the emerging necessity to provide guidelines and protocols throughout different life stages, especially in senior and geriatric cats.^{10,11} A recent study has demonstrated the importance of routine health screening, providing further justification for health

assessment and the discovery of occult diseases in apparently healthy old cats.¹² Several publications have investigated the presence of chronic kidney disease (CKD) and hypertension with hyperthyroidism; however, other concurrent diseases should be also considered and not overlooked in the hyperthyroid population. A study presented in abstract form addressed this question and suggested that subclinical comorbid diseases are very common in hyperthyroid cats referred for radioiodine treatment.¹³

All the above factors emphasise the importance of an individual assessment for candidates for radioiodine treatment. The aims of this study were to identify unrecognised and serious non-renal comorbidities present in cats referred for radioiodine assessment, with the hypothesis that some cases who appeared to be clinically good candidates for radioiodine administration may have a concurrent disease making them unsuitable for

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treatment and isolation. In addition, we aimed to identify the presence of any predictors for the presence of a comorbid disease.

Materials and methods

The study population was selected from the records of hyperthyroid cats evaluated for radioiodine treatment at the Centre for Small Animal Studies (Animal Health Trust, Newmarket, UK) between January 2010 and April 2013. The inclusion criteria comprised cats diagnosed with hyperthyroidism without any overt concurrent disease. Diagnosis of hyperthyroidism was based on increased total thyroxine (tT4) above the reference level for the laboratory used. Lack of overt concurrent disease was defined as absence of kidney disease (defined as a urine specific gravity [USG] >1.035 and non-azotaemia) and no clinical signs, other than those ascribable to hyperthyroidism, reported by the referring veterinarian and owners prior to the referral. No medication other than antithyroid medication was allowed. Patients with clinical signs consistent with thyrotoxicosis (eg, weight loss, polyphagia, hyperactivity) and elevated tT4 were included. Patients defined as controlled were on treatment for hyperthyroidism, had a tT4 below the upper reference interval and lacked clinical signs compatible with hyperthyroidism.

The following data (when available) were collected for each case: age, sex, breed, date of diagnosis, length of medical treatment, tT4 at time of diagnosis and referral, medical treatment, standard physical examination findings, systolic blood pressure, full haematology and biochemistry values, retrovirus testing, urinalysis, echocardiography and abdominal ultrasound. All the above-mentioned data were obtained at the authors' clinic as part of the protocol for radioiodine assessment with the exception that haematology, biochemistry or urinalysis could be performed at the referring veterinarian's practice within the month prior to assessment at our clinic. In some cases, further tests (radiographs, biopsies) were performed for further evaluation of any abnormalities identified in the initial screening.

Blood samples were collected and placed in EDTA and serum tubes. Full haematology and biochemistry were performed using an AcT Diff analyser (Beckman Coulter) and a Konelab 20i analyser (Konelab), respectively. tT4 was submitted to an external laboratory (Cambridge Specialist Laboratory Services, UK) and measured by radioimmunoassay. When possible, urine was obtained by cystocentesis to perform USG by refractometry, dipstick (Combur9Test; Roche), sediment analysis, urine protein:creatinine ratio (UPC) and culture. Proteinuria was defined as a UPC >0.4.¹⁴ Feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV) were tested using an in-house enzyme-linked immunosorbent assay (SNAP Combo Plus; IDEXX).

Blood pressure measurement (Doppler) was performed following the protocol set out in the American College of Veterinary Internal Medicine consensus statement,¹⁵ and hypertension was defined as a mean systolic pressure >160 mmHg. During the study period, cats that underwent radioiodine treatment were injected with a fixed dose of 4 mCi I¹³¹ subcutaneously under sedation and kept in isolation for 3 weeks following local radiation safety regulations.

SPSS Statistics for Macintosh version 22.0 (IBM) was used for statistical analysis. Visual histogram evaluation confirmed the majority of the data to be non-normally distributed and so analysis was performed using non-parametric testing. Continuous data were expressed as a median and range. The Mann-Whitney U-test was used to make comparisons between groups (concurrent disease vs non-concurrent disease and controlled vs non-controlled) to identify significant differences. *P* values <0.05 were considered to be significant.

Results

One hundred and thirteen cases were referred to the Centre for Small Animal Studies during the study period for radioiodine assessment. Of these, 19 were excluded owing to overt concurrent diseases and clinical signs prior to presentation, with chronic gastrointestinal and liver disease being the most common disorders. Ninety-four cats were included and their data analysed. There were 42 (45%) male neutered cats and 50 female spayed plus two female entire cats (55%). The majority of the population were non-pedigree domestic shorthair cats (*n* = 75). Other breeds represented were domestic longhair cats (*n* = 13), Persians (*n* = 2), British Shorthairs (*n* = 2), Bengal (*n* = 1) and Ragdoll (*n* = 1). The median age of cats included in the study was 12 years (range 5.0–16.9 years). All of these cats were previously diagnosed with hyperthyroidism by their referring veterinarian within a median of 4.5 months (range 1.0–6.0 months) prior to the referral. The median age at diagnosis was 11.5 years (range 5.0–16.7 years). Sixty-two (66%) cats were well controlled at the time of evaluation by previous treatment for hyperthyroidism; 32 (34%) were non-controlled or poorly controlled despite previous treatment. Previous treatments included antithyroid medication (*n* = 86), low iodine diet (*n* = 3) and no treatment (*n* = 5).

Physical examination abnormalities recorded included gingivitis (*n* = 6), poor coat quality (*n* = 3) and small kidneys on palpation (*n* = 3). An enlarged goitre was palpated in 77 (82%) cats and a heart murmur was audible in 32 (36%) cats. The presence of a heart murmur was statistically non-significant between the controlled (31%) and non-controlled (38%) cats. Respiratory rate and heart rate were significantly higher in the non-controlled group compared with the controlled group. The non-concurrent disease group had a higher heart

rate. Median tT4 at the time of initial diagnosis was 113 nmol/l (range 53–304 nmol/l) and 36 nmol/l (range 4–300 nmol/l) at the time of assessment.

Blood pressure was assessed in 88 cats; hypertension was recorded in 16 (18%) animals. Although full urinalysis was performed in all cats, UPC was obtained only in 68 cats and urine culture in 70. Urine infection was detected in seven (10%) cases, although only two cats had active sediment. *Enterococcus* species was the most common isolate ($n = 4$). Female cats were over-represented ($n = 6$), and only one male cat had a urinary tract infection. No clinical signs associated with the urinary tract infection were observed in any of the seven cases. All cats with urinary infection were treated and subsequently received radioiodine therapy. The UPC median was 0.32 (range 0.1–3.0) and 27 (39%) cats had values >0.4 . Of those with proteinuria, eight cats were hypertensive and four had concurrent urinary tract infection. Ten of the 27 (37%) cats with proteinuria were uncontrolled. None of the cats tested for FeLV and FIV were positive. Haematology and biochemistry were performed in all 94 cats. When comparing the controlled and non-controlled groups, the alkaline phosphatase, alanine transaminase, UPC, phosphorus and tT4 levels were significantly higher, and cholesterol, creatinine and USG lower in the non-controlled group. The eosinophil count, total bilirubin and total calcium were significantly higher in the concurrent disease group. However, all the above significant median values were within normal limits. In addition, when a case with suspected paraneoplastic hypercalcaemia was excluded, total calcium was not significantly different between groups.

Seventeen (18%) cases were identified as having concurrent disorders during the assessment (concurrent disease group). Final diagnosis was achieved in 9/17 (52%) cases. None of these cases were treated with radioactive iodine. The most common diseases were alimentary lymphoma ($n = 5$) and chronic enteropathy ($n = 4$) followed by myocardial hypertrophy ($n = 2$), liver mass ($n = 2$), renal carcinoma ($n = 1$), cystic enlarged abdominal lymph nodes ($n = 1$), diabetes mellitus ($n = 1$) and liver disease ($n = 1$).

Abdominal ultrasound was performed in all 94 cats included in the study and 14/17 (82%) cases of the concurrent disease group had abnormal ultrasound findings compatible with disease. A mass was detected on ultrasound in 3/5 cases with alimentary lymphoma and a diagnosis of large-cell lymphoma was subsequently given in these three cases. Two remaining alimentary lymphomas were classified as low grade, and the ultrasonographic findings in these two cases showed diffuse thickening of the muscularis propria, enlargement of the mesenteric lymph nodes and diffuse hypoechoic appearance of the spleen. Fine-needle aspiration cytology of the mesenteric lymph nodes and small intestines was

diagnostic in 4/5 cases and full-thickness biopsy was performed in one case (low-grade lymphoma). Four cats were classified as chronic enteropathy based on the presence of diffuse or multiple changes in the intestines described as irregular and asymmetrical in appearance. All these cats lived both indoors and outdoors, and no information regarding vomiting or diarrhoea could be obtained. Two of these cases had cobalamin levels below the reference interval (250 pg/ml). Cobalamin was not measured in other cases in this study. No further investigations (cytology or biopsies) were performed. No significant differences were observed in recorded parameters when the gastrointestinal disease group (alimentary lymphoma plus chronic enteropathy cases) was compared with the remainder of the concurrent disease group.

The case classified as liver disease was defined by the presence of diffuse hepatic hypoechoic irregular nodules. Two cases showed the presence of large liver masses and one cat had cystic enlarged abdominal lymph nodes. No cytology or biopsies were taken for these four cases. Fourteen of 17 (82%) cases of the concurrent disease group had abnormal ultrasound findings compatible with disease.

Echocardiography was performed in 75 cats. Two myocardial hypertrophy cases (one with uncontrolled hyperthyroidism) were diagnosed based on the echocardiography findings, with end diastolic wall thicknesses of 7 and 7.8 mm and left atria diameters of 22 and 26 mm, respectively. No thoracic radiographs were obtained; thus, congestive heart failure could not be excluded, although it was not suspected.

Seventy-one (76%) cats received an injection of radioiodine following assessment and 23 (25%) were not injected. None of the cats with non-renal concurrent disease ($n = 17$) were injected, and neither were six cases that did not have any concurrent disease. The reasons for not injecting these patients included concerns about possible progression of the comorbid disease during hospitalisation or after treatment, a change in the owner's decision to treat and loss to follow-up.

Discussion

This study showed a relatively high prevalence of concurrent non-renal diseases in hyperthyroid cats at the time of radioiodine assessment, with 18% of cats suffering from a variety of clinical diseases and alimentary lymphoma being the most common comorbid disorder.

The entire population analysed did not differ from previous studies, with a similar median age at time of diagnosis and no major differences in breed or sex distribution. Physical examination findings were similar, including the presence of palpable goitre. We observed a lower prevalence of heart murmurs than previous studies. Although this could be attributable to 66% of the cats

being euthyroid and studies have shown the resolution of heart changes following treatment,¹⁶ the prevalence of heart murmurs between controlled and non-controlled cats was similar and statistically non-significant. The significant differences in the non-controlled cats were expected as the increased heart rate, respiratory rate, proteinuria, elevated liver enzymes and phosphorus, and decreased creatinine and cholesterol levels are usually observed in untreated hyperthyroid cats.¹⁷ In addition, the prevalence of urinary tract infection in the tested population was 10%, similar to that which has been previously reported (12%).¹⁸

Eighteen percent of cats in the present study suffered from a variety of clinical diseases. A retrospective study examined the incidence of systemic non-thyroidal illness in hyperthyroid cats and its influence on the tT4 concentrations with an overall disease prevalence of 35% (39/110).¹⁹ This study included cats with CKD; each cat was evaluated for systemic non-thyroidal illness 6 months prior and after the diagnosis of hyperthyroidism, and overt clinical signs were present in most of the cases. CKD, congestive heart failure and systemic neoplasia were the most common non-thyroidal illnesses present. Another retrospective study assessing the comorbid diseases in cats referred for radioiodine treatment showed that subclinical comorbid disease is very common. In that study, 30% of the cats were classified as having major comorbid diseases. Six of these 36 cats with major comorbid diseases had gastrointestinal neoplasia. In addition, major comorbid diseases had been only identified prior to the referral in 10/36 cases.¹³ Finally, a more recent paper based on a survey of owners with cats with hyperthyroidism, showed that additional health problems were reported in 47% of the cases.⁶ Therefore, and in agreement with previous studies, the data presented confirm a relative high prevalence of subclinical concurrent non-renal diseases in senior and geriatric cats with hyperthyroidism.

Among the diseases, alimentary lymphoma was the most common comorbid illness. Hyperthyroidism is not recognised as a risk factor for alimentary lymphoma and the most likely explanation is that both diseases affect primarily old cats and are common in the feline population.^{20,21} The presumptive diagnosis of chronic enteropathy in four cases was limited by the lack of clinical history and cytology or histopathology. However, the ultrasonographic changes were highly suggestive of disease rather than incidental findings. Two of these cases had low levels of cobalamin. Although this is a specific marker for pancreatic and intestinal disease in cats, a recent study has shown high prevalence of hypcobalaminaemia in hyperthyroid cats.²² Given the high prevalence of unrecognised chronic gastrointestinal disease identified in this study, it remains unclear whether hypcobalaminaemia is associated with

hyperthyroidism or whether it is an indicator of comorbid chronic gastrointestinal disease.

Two cases presented with findings compatible with myocardial hypertrophy. Neither of these cases had thoracic radiographs and heart failure could not be excluded, although this was not suspected based on history and physical examination. In addition, as one cat was not controlled, it was not possible to determine if the echocardiographic changes were due to the hyperthyroidism.^{16,23} Only one case had a concurrent endocrine disorder (diabetes mellitus). Owing to the lack of clinical signs reported by the owner it is possible that the cat, which was considered to be well controlled, was at an early stage of the disease. In a recent paper assessing the presence of multiple endocrine disorders in cats, the most common combination of multiple endocrine disorders was hyperthyroidism and diabetes mellitus in 73% of the cases.²⁴

When comparing the data from concurrent and non-concurrent disease groups, several blood parameters were significantly higher in the concurrent disease group. Although an increased eosinophil count and total bilirubin could be explained by the presence of gastrointestinal disease, no significant differences were observed when the gastrointestinal disease group (alimentary lymphoma and chronic gastroenteropathy) and the non-gastrointestinal disease group (rest of concurrent diseases) were compared. Despite total calcium being significantly higher in the concurrent disease group, only one case had a calcium level above the reference interval (1.9–2.9 mmol/l). This case was diagnosed with alimentary lymphoma and the most likely explanation would be a paraneoplastic mechanism. When this case was excluded from the analysis, total calcium was not significantly higher. In addition, the marginal differences seen between groups and the lack of clear explanation for these findings, it is likely that these differences were caused by type I error and may limit its value in clinical practice.

In a recent study, proteinuria was correlated with mortality in hyperthyroid cats.²⁵ The study did not identify the causes of death but a possible explanation was given to the multiple problems usually affecting old cats. Our study failed to demonstrate a relationship between any comorbid disease and proteinuria. Further studies are needed to clarify the role of proteinuria in these cases.

In our study, none of the cats with comorbid disease received radioiodine therapy. The main reasons for not injecting these patients included owners' concerns about the development of the clinical signs during or after hospitalisation, and loss to follow-up. However, not all the concurrent diseases reported were a contraindication for receiving radioiodine. We believe that concurrent subclinical disorders like chronic enteropathy, low-grade

lymphoma in remission or a stable liver disease can be safely treated. For this reason, the fact that radioiodine treatment was not administered in these cases should be taken cautiously and with retrospective criticism. Many of the concerns regarding the treatment of cats with comorbidities relates to the need to isolate cats after injecting radioiodine and the potential for the development of complications during this isolation period. In the UK this isolation is relatively long, with a minimum of 2 weeks' isolation and 3 weeks being commonly employed at our institute. In countries with shorter isolation requirements (eg, USA, Australia), such concerns may not be as great.

The results from this study identify the potential merit of routine screening tests (haematology, biochemistry, blood pressure and urinalysis) and abdominal ultrasound in cases undergoing a radioiodine assessment. Major abnormal ultrasound findings compatible with disease were found in 14/94 (15%) of all cats included in the study and in 14/17 (82%) of cats with comorbid disease. Although urinalysis (particularly UPC and urine culture) does not have a significant impact on treatment recommendations, this study confirms the findings of previous studies, namely that proteinuria and urinary tract infections do occur in a proportion of hyperthyroid cats and it is useful to identify such comorbidities with respect to long-term patient management. Further tests (retroviral testing, echocardiography) are less likely to have a significant impact on treatment advice in all cases but do contribute to higher costs. However, these tests should be considered on an individual patient basis.

Limitations in our study include the retrospective nature of it leading to incomplete medical records, and the different primary clinicians involved. However, during the study period most of the described tests (including abdominal ultrasound) were part of the radioiodine assessment protocol at the Animal Health Trust. Thoracic radiographs were not taken in most of the cases; therefore, the elevated predominance of abdominal disease identified in this study may be owing, in part, to the lack of respiratory investigations. In addition, ultimate diagnosis was only achieved in 9/17 (52%) cases and the clinical significance of some findings remains unclear. Euthyroid azotaemic cats were not included in the study as during the study period our institution was only accepting non-azotaemic cats for radioiodine assessment and treatment. The main purpose of this study was to identify unrecognised and serious comorbidities that may impact on the survival of hyperthyroid cats. Several studies have characterised the relationship between kidney disease and hyperthyroidism, and it has been established that the presence of elevated creatinine is not correlated with the survival of euthyroid cats; hence, azotaemia was not included in our analyses.²⁶ Finally, no

data regarding outcomes were obtained or analysed. Although this would add useful information to evaluate the decision to treat or not to treat cats with subclinical comorbid disease, this objective was not part of our study. We believe that further studies are needed to answer this interesting question.

Conclusions

Cats presented for radioiodine assessment with lack of clinical signs reported by the referring veterinarian and owners prior to the referral may suffer from a variety of concurrent clinical diseases. Among the diseases, alimentary lymphoma and chronic enteropathy were the most common comorbid illness identified in this population of cats, highlighting the importance of considering concurrent gastrointestinal disease in hyperthyroid cats. This study supports the value of abdominal ultrasound in cases undergoing radioiodine assessment in addition to the routine screening tests (haematology, biochemistry, blood pressure and urinalysis), as abnormal ultrasound findings compatible with disease were found in 14/94 (15%) of the cats in this study.

Conflict of interest The authors do not have any potential conflicts of interest to declare.

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