What's new in Treating Hyperthyroidism in Cats

David Bruyette, DVM, DACVIM
VCA West Los Angeles Animal Hospital
Los Angeles, CA

A. The most common endocrine disorder in the cat.
B. First cases of functional thyroid tumors reported in 1978.

Etiology

A. Thyroid adenoma or adenomatous hyperplasia.
B. 80 % are bilateral on presentation.
C. 1-2% due to thyroid carcinoma.
D. Etiology unknown:
   1. Two recent large studies have looked at possible environmental or dietary factors involved in the pathogenesis of hyperthyroidism. One of the studies with a case controlled design looked at 100 cats with hyperthyroidism and 163 control cats. The cats medical records were reviewed and the owners were asked to complete a mailed questionnaire. Data included demographic variables, environmental exposures and diet to include the preferred flavors of canned cat food. In this study, housing, exposure to fertilizers, herbicides, regular use of flea products, and the presence of a smoker in the house were not associated with an increased risk but cats that preferred fish or liver and giblets flavors of canned cat food had an increased risk. The results suggested that cats that prefer to eat certain flavors of canned cat food may have a significantly increased risk of hyperthyroidism.
   2. In the second case controlled study owners of 379 hyperthyroid and 351 control cats were questioned about their cats' exposure to potential risk factors including breed, demographic factors, medical history, indoor environment, chemicals applied to the cat and environment, and diet. The association between these hypothesized risk factors and outcome of disease was evaluated. Two genetically related cat breeds (Siamese and Himalayan) were found to have diminished risk of developing hyperthyroidism. Cats that used litter had higher risk of developing hyperthyroidism than those that did not. Use of topical ectoparasite preparations was associated with increased risk of developing hyperthyroidism. Compared with cats that did not eat canned food, those that ate commercially prepared canned food had an approximate 2-fold increase in risk of disease. When these 4 variables (breed, use of cat litter, consumption of canned cat food, and use of topical ectoparasite preparations) from the univariate analysis were selected for further, a persistent protective effect of breed (Siamese or Himalayan) was found. In addition, results suggested a 2- to 3-fold increase in risk of developing hyperthyroidism among cats eating a diet composed mostly of canned cat food and a 3-fold increase in risk among those using cat litter. In contrast, the use of commercial flea products did not retain a strong association. The results of this study indicate that further research into dietary and other potentially important environmental factors (cat litter) is warranted.
   3. Altered G protein expression was found in thyroid gland tissue from hyperthyroid cats compared to normal control cats. Adenomatous thyroid glands obtained from 8 hyperthyroid cats and thyroid glands obtained from 4 age-matched euthyroid cats were examined for expression of G inhibitory protein (Gi) and G stimulatory protein (Gs). Expression of G(i) was significantly reduced in thyroid gland adenomas from hyperthyroid cats, compared with normal thyroid gland tissue from euthyroid cats. Expression of G(s) was similar between the 2 groups. A decrease in expression of G(i) in adenomatous thyroid glands of cats may reduce the negative inhibition of the cAMP cascade in thyroid cells, leading to autonomous growth and hypersecretion of thyroxine. What we don't know is why or what causes the reduction in G(i) in hyperthyroid cats. The factors mentioned above in the studies of environmental and dietary risk factors may play in role in altering the G protein expression found in this study.
   4. Oncogenes and the tumor suppressor gene p53 were examined in cats with hyperthyroidism. Formalin-fixed, paraffin-embedded thyroid glands from 18 cats diagnosed with hyperthyroidism were evaluated immunohistochemically for overexpression of the products of oncogenes c-ras (a mitogenic oncogene) and bcl2 (an apoptosis inhibitor) and the tumor suppressor gene p53. Fourteen thyroid glands from euthyroid cats without histologically detectable thyroid lesions were examined similarly as controls. Results from these investigations showed that all cases of nodular follicular hyperplasia/adenomas stained positively for overexpression of c-Ras protein using a mouse monoclonal anti-human pan-Ras antibody. The most intensely positively staining regions were in luminal cells surrounding abortive follicles. Subjacent thyroid and parathyroid glands from euthyroid cats did not stain immunohistochemically for pan-Ras. There was no detectable staining for either Bc12 or p53 in any of the cats. These results indicated that overexpression of c-ras was highly associated with areas of nodular follicular hyperplasia/adenomas of feline thyroid glands, and mutations in this oncogene may play a role in the etiopathogenesis of hyperthyroidism in cats. As with the study on G protein abnormalities, C-Ras mutations could either be an initiating cause of hyperthyroidism or simply mediate the effects of a yet unidentified dietary or environmental initiator.

5. Alterations in the thyrotropin (TSH) receptor were also examined in cats with hyperthyroidism. The authors used the polymerase chain reaction (PCR) to amplify codons 480-640 of the previously uncharacterized feline thyrotropin receptor (TSHR) gene, and determined the DNA sequence in this transmembrane domain region. They then analyzed single stranded conformational polymorphisms in thyroid DNA from 11 sporadic cases of feline thyrotoxicosis and leukocyte DNA from two cases of familial feline thyrotoxicosis. They also determined the DNA sequence of this region of the TSHR in five of the cases of sporadic feline thyrotoxicosis and the two familial thyrotoxic cats. The normal feline TSHR sequence between codons 480-640 is highly homologous to that of other mammalian TSHRs, with 95%, 92%, and 90% amino acid identity between the feline receptor and canine, human, and bovine TSHRs, respectively. Thyroid gland DNA from 11 cats with sporadic thyrotoxicosis did not have mutations in this region of the TSHR gene. Leukocyte DNA from two littermates with familial feline thyrotoxicosis did not harbor mutations of this region of the TSHR gene. These studies suggested that TSHR gene mutations are likely not involved in feline hyperthyroiodism.

Signalment

A. No sex or breed predilection.
B. Average age 13 years.
C. Age range 4-24 years.

Clinical signs

A. Weight loss
B. Polyphagia
C. Polydipsia
D. Diarrhea
E. Hyperactive
F. Vomiting
G. Bulky, foul smelling stool.
H. In about 10% of cats, apathetic hyperthyroidism is seen with clinical signs dominated by extreme lethargy and weakness, weight loss with anorexia, and cardiac abnormalities.
    1. Many cats are now asymptomatic at the time of diagnosis due to the increased screening of senior cats with TT4 levels.
    2. With time we have seen both an increase in the diagnosis of hyperthyroidism as well as a decrease in the severity of the clinical signs associated with thyrotoxicosis. This is most likely due to an increased awareness on the part of the pet owner and the veterinarian as well as the increased use of T4 concentrations as an integral part of routine feline health screening. We have also seen additional work on some of the less obvious manifestations of hyperthyroidism such as hypertension which may be clinically silent and/or present initially with ocular signs, as well as the effects of hyperthyroidism on the cardiovascular and renal system (to be discussed later).
    3. As stated earlier, the clinical signs associated with hyperthyroidism have been deceasing in severity over the years. A paper examined the electrocardiographic and radiographic changes seen in hyperthyroid cats today versus those seen 10-12 years ago. Two populations (1992 to 1993 and 1979 to 1982) of confirmed hyperthyroid cats were compared to determine whether the incidence of certain cardiovascular specific manifestations of feline thyrotoxicosis had experienced similar changes. Sinus tachycardia, which is the most commonly recognized cardiac manifestation of feline thyrotoxicosis, was not as prevalent in the 1993 group when compared to the 1982 group. This was also true for the finding of an increased R-wave amplitude on lead II electrocardiography. Both groups had a similar low incidence of atrial and ventricular dysrythmias; however, the 1993 group had a significantly higher occurrence of right bundle branch block. Thoracic radiographs were deemed necessary in a larger proportion of the 1982 group when compared to the 1993 group. Although there were no significant differences in radiographically defined cardiac size between the two groups, a larger number of cats in the 1982 group had evidence of congestive heart failure. These findings suggest that feline hyperthyroidism is being diagnosed earlier and with less severe clinical signs than when studied a decade ago.

Physical examination

A. Palpable thyroid gland(s). Normal thyroids can not be felt.
B. An enlarged gland may be found at the thoracic inlet
C. Cardiac examination:
    1. Tachycardia > 220 BPM.
    2. Murmurs. Be sure to listen over the sternum.
    3. Gallop rhythms.
D. Dehydration/emaciation

E. Small kidneys
    1. Common in older cats.
    2. Renal disease and hyperthyroidism both cause PU / PD.
    3. Will need to monitor renal function to differentiate the two.

Over the last ten years with increased awareness of the disease and the ease of diagnosis the clinical signs have become less dramatic as more cats are diagnosed and treated earlier.

Differential diagnosis

A. Diabetes mellitus
B. Renal disease
C. Liver disease
D. Heart disease
E. Gastrointestinal disease
    1. Pancreatic exocrine insufficiency.
    2. Inflammatory bowel disease.
    3. GI lymphosarcoma. .

Laboratory abnormalities

A. PCV and RBC may be increased due to dehydration.
B. Urinalysis
    1. Decreased concentrating ability.
    2. Presence of concurrent renal disease.
C. Serum biochemistry profile
    1. Elevated SAP, SGPT (50-75%)
        a. Liver function is normal.
        b. Will decrease following treatment.
    2. Elevated BUN and creatinine (30-40%)
        a. Most are increased secondary to dehydration.
        b. Will need to be re-evaluated post-treatment as up to 5% of cats treated for hyperthyroidism (any form of therapy) will develop progressive renal insufficiency.
    3. Hyperphosphatemia (20%)
        a. Felt to be due to increased bone turnover.
            1) Fructosamine

Serum fructosamine concentrations in cats are thought to reflect the mean blood glucose concentration of the preceding one to two weeks. However, fructosamine concentrations are affected by the concentration and metabolism of serum proteins. Hyperthyroidism can have a profound effect on protein metabolism and therefore, possibly on serum fructosamine concentrations. In one study, 22 cats, ranging in age from 8 to 20 years, were diagnosed with hyperthyroidism, based on clinical signs of hyperthyroidism, detection of a palpable thyroid gland, and a serum thyroxine (T4) concentration >45 nmol/L. Blood glucose, total protein (TP), and albumin concentrations were within their respective reference ranges. Results for the 22 hyperthyroid cats were compared with those of 42 healthy control cats, 10 newly diagnosed diabetic cats, and nine cats with hypoproteinemia. Serum T4 concentrations ranged from 46-475 nmol/L (median, 86 nmol/L). Serum fructosamine concentrations of hyperthyroid cats were between 154-267 umol/L (median, 198 umol/L), significantly less than those of healthy cats. Serum fructosamine concentrations in cats with hypoproteinemia ranged from 124-254 umol/L (median, 174 umol/L) and were significantly less than those of healthy cats. Serum fructosamine concentrations did not differ between hypoproteinemia and hyperthyroid cats. In hypoproteinemic cats, concentrations of serum TP and albumin were significantly lower than those in hyperthyroid cats, while blood glucose concentrations did not differ between the two groups of cats. Serum fructosamine concentrations of diabetic cats were significantly increased, compared with those of healthy cats, hypoproteinemic cats, and cats with hyperthyroidism. After two weeks of carbimazole treatment in six of the hyperthyroid cats, serum fructosamine concentrations were not significantly different from the initial concentrations. After six weeks of carbimazole treatment, serum fructosamine concentrations were significantly higher than the initial concentrations. Serum T4 concentrations were significantly decreased at both two and six weeks after initiating treatment. The authors concluded that concentrations of serum fructosamine are lower in cats with hyperthyroidism independent of blood glucose concentrations. In the clinical setting this means that serum fructosamine concentration should not be used to initially diagnose or assess the adequacy of diabetic control in cats with concurrent hyperthyroidism in which the hyperthyroidism has not been controlled for at least six weeks.

In another paper fructosamine levels were evaluated in 30 non-diabetic hyperthyroid cats pre and 30 days post treatment with radioiodine and compared to normal control cats. Fructosamine levels were significantly lower in the hyperthyroid cats both pre and post treatment with radiodine. However, treatment was associated with a statistically significant increase in the fructosamine concentration. This paper, like the paper above in cats with diabetes, shows that fructosamine concentrations in hyperthyroid cats will be lower than non-hyperthyroid cats (normal or diabetic) and that this effect is likely due to the effects of hyperthyroidism on protein turnover.

Cardiac evaluation

Important to assess in animals with clinical signs or abnormalities on physical examination prior to deciding on optimal therapy and to differentiate thyrotoxic heart disease from the two primary feline myocardial diseases, hypertrophic and dilated cardiomyopathy.

A. Radiographs
   1. 20 – 30 % have cardiomegaly.
   2. < 5 % show signs of failure (pleural effusion, edema).

B. EKG
   1. Tachycardia and increased R wave amplitude the most common abnormalities.

C. Ultrasound
   1. The best way to differentiate between primary and secondary cardiac disease.

Diagnosis

A. Elevated T4 concentration. Measurement of T3 of little help.

B. May be able to palpate a thyroid nodule before the T4 is elevated. Recheck T4 3 every 3 – 6 months or when signs occur.

C. Occasionally cats with hyperthyroidism may have a T4 in the normal range at the time of sampling. This is especially true in cats with mild hyperthyroidism. A second sample may be needed in those cats with strong clinical evidence of thyrotoxicosis. The second sample should be taken a few days to weeks later, as more pronounced fluctuations in thyroid hormone levels occur over days rather than hours. Non-thyroidal illness may also result in high-normal serum T4 concentrations even in the face of hyperthyroidism. Following correction of the underlying illness or discontinuation of medications, T4 levels will increase into the hyperthyroid range.

In animals in which hyperthyroidism is suspected, but the basal T4 levels are consistently normal, four additional tests can be considered.

1. T3 Suppression Test:
   a. Basis of the Test: The normal pituitary-thyroid axis will be suppressed following supplementation with T3. A decrease in TSH concentration will lead to a decrease in T4 levels.
   b. Performing the Test
      1) Determine basal T4 level.
      2) Administer T3 (25 ug) every 8 hours for two days, giving the last dose on the morning of day 3.
      3) Determine T3 and T4 concentrations 4 hours following the last dose of T3.
      4) Normal cats:
         a) T4 levels suppress greater than 50% from pretreatment value.
2. TRH Stimulation Test:
   a. Basis of the Test: TRH is the hypothalamic peptide that regulates TSH release from the pituitary. TSH response to TRH is blunted in patients with hyperthyroidism.
   b. Performing the Test:
      1) Obtain basal T4 level.
      2) Administer 0.1 mg/kg TRH IV.
      3) Obtain 4 hour post TRH T4.
      4) Normal cats:
         a) Two-fold rise in T4 post TRH
         b) Hyperthyroid cats have minimal to no increase in T4.
3. Free T4
   a. In cats where the TT4 is in the upper 50% of the basal resting range, an elevated fT4ED in the face of clinical signs is highly predictive of hyperthyroidism. Use of fT4ED should not be used as the initial screening test as some euthyroid senior cats have have elevated fT4ED. Due to the simplicity of the test, fT4ED should be the first line test in diagnosing cats with hormonally occult (normal TT4) hyperthyroidism.
4. Imaging
   a. Technetium scans may be helpful in hormonally borderline cases where bilateral uptake is clearly increased or unilateral disease is present.

Summary

In the last few years it is still apparent that the best test to use in the initial approach to the patient with hyperthyroidism is measurement of total T4 (TT4) concentrations. TT4 testing is simple and inexpensive and will provide the correct diagnosis in the majority of feline patients presented for evaluation. However, we are now faced with attempting to diagnose or confirm hyperthyroidism in cats that are asymptomatic, have only mild clinical signs, and/or have concurrent illness that may affect accurate laboratory assessment of thyroid function. These cases can be very challenging though recent work seems to indicate that measurement of free T4 by equilibrium dialysis (fT4ED) represents the logical next step (though it should be emphasized, not the first step) in the approach to these patients. This approach will likely eliminate the need for additional expensive or

problematic tests such as TRH stimulation and T3 suppression testing. We also have seen recent work on the effects of thyrotoxicosis on bone and calcium metabolism and how hyperthyroidism can affect our laboratory assessment of concurrent diseases such as diabetes.

Two excellent papers have assessed the value of fT4ED in the diagnosis of hyperthyroidism in cats and/or the effects of non-thyroidal illness on thyroid function. As is the case in dogs, euthyroid cats with non-thyroidal illness may have a decrease in TT4 levels that is most likely the result of protein binding abnormalities. In a study looking at 98 cats with non-thyroidal illness and 50 normal control pet cats thyroid function was assesses by measurement of TT4 and fT4ED. T4 concentrations were measured by radioimmunoassay, and serum free T4 concentrations were measured by direct equilibrium dialysis. Serum total T4 concentrations were significantly ($P < 0.001$) lower in sick cats (mean +/- SD, 17.18 +/- 8.14 nmol/L), compared with healthy cats (mean +/- SD, 26.00 +/- 7.62 nmol/L). Serum total T4 concentrations were inversely correlated with mortality. Differences in serum free T4 concentrations in sick cats (mean +/- SD, 27.70 +/- 13.53 pmol/L), compared with healthy cats (mean +/- SD, 24.79 +/- 8.33 pmol/L), were not significant. A few sick cats had serum free T4 concentrations greater than the reference range. This study showed that as is the case in dogs and man, euthyroidism is maintained in sick cats, despite low serum total T4 concentrations. In addition, measurement of serum total T4 concentrations was a valuable prognostic indicator as it appeared to be an excellent predictor of mortality. Lastly and perhaps more importantly with respect to diagnosing hyperthyroidism, some euthyroid older cats have elevated fT4ED concentrations. This would indicate that initial use of fT4ED as a screening test for hyperthyroidism in older cats can lead to false positive results.

One of the challenges in diagnosing hyperthyroidism is the effect of non-thyroidal illness on thyroid function tests in cats with concurrent hyperthyroidism. In a recent very large study TT4, ft4ED and T3 concentrations were measured in 917 cats with hyperthyroidism, 221 cats with non-thyroidal illness, and 172 clinically normal cats. Ft4ED was significantly more sensitive (0.985) then TT4 (0.913) as a diagnostic test for hyperthyroidism, however of the 221 cats with non-thyroidal illness, 12 cats had a high fT4ED (false postive). Therefore the calculated specificity of fT4ED as a diagnostic test for hyperthyroidism was significantly lower (0.937) than the specificity of TT4 (1.0). This study indicates that measurement of fT4ED is only indicated in those cats with clinical signs and a TT4 in the upper 50% of the normal resting range. It appears that concurrent non-thyroidal illness in some cats with hyperthyroidism may be sufficient to drop TT4 values into the upper half of the normal resting range. In these animals the fT4ED will be elevated. In our experience we see this most commonly in cats with moderate to severe GI disease (IBD, lymphoma) or in cats on concurrent glucocorticoids. The biggest challenge to the clinician is on deciding on how to treat such cats appropriately. In general, one must decide what role both diseases are playing with respect to the clinical signs and address each disease separately.