UPDATE ON THE PATHOGENESIS, DIAGNOSIS AND TREATMENT OF FELINE HYPERTHYROIDISM

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INTRODUCTION
Hyperthyroidism is a syndrome caused by the excessive production and secretion of the thyroid hormones T₃ and T₄ by an autonomous thyroid gland. Feline hyperthyroidism was first reported in 1979 and since then it has become a common disease in cats. Histopathology of affected thyroids usually reveals thyroid hyperplasia or benign thyroid adenoma, however in a small percentage of cases thyroid adenocarcinomas are diagnosed. Pathologic changes may affect one or both lobes of the thyroid gland. In addition ectopic thyroid tissue may be present within the neck or thorax. Ectopic tissue may sometimes be difficult to distinguish clinically from metastasis of thyroid adenocarcinoma.

PATHOGENESIS OF FELINE HYPERTHYROIDISM
There are two recent case control studies that have evaluated the role of environmental or nutritional factors in the pathogenesis of feline hyperthyroidism. In one study of 100 hyperthyroid cats and 163 controls, cats that preferred certain flavors of canned cat food were at increased risk of hyperthyroidism, but housing, exposure to fertilizers or herbicides, use of flea control products and presence of a smoker in the house were not associated with increased risk. In a second study of 379 hyperthyroid cats and 351 control cats, risk factors identified as significantly associated with an increased risk of hyperthyroidism were breed, a diet composed of predominantly canned cat food, and use of cat litter. Both these studies support many of the findings of an earlier case control study. We have recently completed another case control study of 109 cases and 173 controls focusing on collection of more detailed dietary histories. In our study, consumption of canned food especially canned food fed from pop-top cans was associated with increased risk of hyperthyroidism. Consumption of cat food without overt iodine supplementation was also associated with an increased risk of hyperthyroidism. Early studies of hyperthyroid cats in which abnormal thyroid tissue was transplanted to nude mice confirmed that hyperthyroidism is due to autonomous function of the thyroid gland itself, rather than an effect of a circulating antibody or excessive secretion of TSH or TRH. Altered G protein expression and overexpression of the protein product of the c-Ras oncogene have also been detected in thyroid tissue collected from hyperthyroid cats. It is likely, although not proven, that such mutations mediate the effect of a nutritional or environmental factor.

APPROACH TO DIAGNOSIS AND TREATMENT OF FELINE HYPERTHYROIDISM
Feline hyperthyroidism is the most common endocrine disease of cats older than 8 years (mean age 12.8 +/- 0.2 years). Since it is an almost exclusively geriatric problem, it is important to actively investigate for the presence of concurrent disease and to take into account the special needs of geriatric patients when planning therapy. The minimum data base necessary for evaluation of a cat with hyperthyroidism includes a detailed history and physical examination, serum thyroxine (T₄) concentration, complete blood count, serum chemistry panel, urinalysis,
thoracic radiographs, and arterial blood pressure. Other diagnostic tests that may be indicated in some patients include cardiac ultrasound, abdominal radiographs, ophthalmologic examination, and an ECG. A technetium scan is strongly recommended in all hyperthyroid cats prior to surgical thyroidectomy.

**HISTORY/PHYSICAL EXAMINATION**

The mean age of onset of feline hyperthyroidism is 13 years but the condition has (rarely) been identified in cats as young as four years of age. Most studies have shown no sex or breed predisposition, although Siamese and Himalayan cats are underrepresented. In the Purdue case control study female cats were found to be at increased risk. Clinical signs that are suggestive of hyperthyroidism include weight loss, diarrhea, vomition, polyphagia, polyuria, polydipsia, muscle weakness, poor hair coat, and hyperactivity. Anorexia, and lethargy are also seen in a smaller subset of patients. Findings on physical examination in addition to the clinical signs noted above may include tachycardia, heart murmur, signs of cardiac failure, cardiac arrhythmias, dehydration, and a palpable thyroid nodule. Ventroflexion of the neck is seen in a small percentage of patients. A combination of the above findings is highly suggestive of hyperthyroidism, however other disorders common in older cats such as renal failure, congestive heart failure, gastrointestinal disease and diabetes mellitus may mimic some or all of this constellation of the clinical signs.

**LABORATORY AND RADIOGRAPHIC FINDINGS**

The complete blood count is usually normal, although polycythemia (47% cases), or a stress leukogram may be present. A biochemical panel usually reveals mild to moderate increases in ALT (SGPT) and alkaline phosphatase. At least a proportion of the increased alkaline phosphatase is the bone isozenzyme, suggesting that bone turnover is increased in hyperthyroid cats. Other abnormalities that support these findings include increased osteocalcin, increased serum phosphorus, increased parathyroid hormone, and reduced ionized calcium in many hyperthyroid cats. Hyperglycemia (stress induced) and azotemia (concurrent renal disease or prerenal azotemia) are also common findings in hyperthyroid cats. Thoracic radiographs may reveal cardiomegaly (due to hypertrophic cardiomyopathy), pleural effusion, pulmonary edema, or pericardial effusion. Thoracic radiographs may also identify evidence of concurrent disease such primary or metastatic neoplasia. Hyperthyroid cats with cardiomegaly alone usually do not require additional treatment other than control of the hyperthyroid state, however cats that have evidence of congestive heart failure need specific therapy for hypertrophic cardiomyopathy. An electrocardiographic evaluation is important if cardiac arrhythmias are detected on physical examination. The most common abnormalities are sinus tachycardia and increased amplitude of the R wave (lead II). Premature atrial contractions, atrial fibrillation and premature ventricular contractions may also be seen in cats with cardiomyopathy and may require treatment with antiarrhythmic drugs (propanolol, atenolol, or diltiazem). Echocardiography is indicated in hyperthyroid cats with evidence of more severe cardiac disease as demonstrated by significant cardiomegaly, pulmonary edema, pleural effusion, or cardiac arrhythmias. Echocardiography will often show evidence of mild hypertrophic cardiomyopathy in cats with no other signs of heart failure, however in this circumstance the only treatment that is usually required is control of the
hyperthyroid state. Most cardiac changes resolve after treatment of the underlying disorder, however some severe cardiomyopathies do not resolve after treatment and require continued treatment. Occasionally dilated cardiomyopathy occurs in cats with hyperthyroidism.
DIAGNOSIS

A diagnosis of hyperthyroidism can usually be confirmed by measurement of a single serum T4 concentration. In some cats with early hyperthyroidism or which have concurrent nonthyroidal disease, the T4 concentration may intermittently fluctuate into the normal range. If the T4 is high normal or borderline, diagnostic options include repeating the measurement at a later date after concurrent diseases have been treated and/or the hyperthyroid state has become more severe, or measurement of a free T4 concentration (by equilibrium dialysis or equivalent assay). Other diagnostic options include a T3 suppression test, TRH stimulation test, or occasionally a technetium scan.

A study of 917 hyperthyroid cats, 221 cats with non-thyroidal illness, and 172 clinically normal cats evaluated the usefulness of measurement of free T4 (measured by direct equilibrium dialysis) as a diagnostic test for hyperthyroidism. The sensitivity of the free T4 concentration (98.5%) as a diagnostic test for hyperthyroidism was significantly higher than the sensitivity of the T4 concentration (91.3%), however the specificity was lower with 14 of the sick euthyroid cats having false positive results by free T4. The free T4 concentration is a sensitive test for use in cats with suspected hyperthyroidism with a normal T4 concentration, however the test should only be used in conjunction with the total T4 concentration. Some cats with a low T4 concentration and a high free T4 concentration are euthyroid. In this situation (low to low normal T4 and high free T4), other factors such as presence of a palpable thyroid mass, clinical signs, other concurrent illness, need to be taken into account and further diagnostic testing such as a TRH stimulation test or technetium scan should be considered.

In cats in which the total T4 and free T4 are normal, but hyperthyroidism is still suspected, a T3 suppression test or a TRH stimulation test should be considered. To perform a T3 suppression test, baseline T3 and T4 concentrations are measured and then T3 is administered at a dose of 25 µg/cat orally q 8 hours for 7 treatments. A second T3 and T4 concentration are then measured 4-6 hours after the last treatment. In euthyroid cats, a suppression of greater than 50% of baseline or less than 2 µg/dl for the post value should occur. Failure to suppress is consistent with a diagnosis of hyperthyroidism. T3 concentrations are measured pre and post T3 administration to confirm client compliance and adequate absorption of the drug. To perform a TRH stimulation test, a baseline T4 is measured, then TRH is administered at a dose of 0.1mg/kg. Adverse effects (salivation, vomiting, tachypnea, defecation) are common after TRH administration. A second T4 concentration is measured 4 hours later. In euthyroid cats there is an increase of greater than 60% of the baseline T4 value, whereas in hyperthyroid cats there is less than a 50% increase in T4. The TRH stimulation test is most useful in those cats with low normal T4 concentrations, in which hyperthyroidism is suspected, but in which the T4 is too low to be able to interpret a T3 suppression test. Recent studies suggest however that the TRH test is unable to differentiate hyperthyroid cats from euthyroid cats in the presence of severe concurrent disease. In our practice the TRH stimulation test is rarely performed. A technetium scan may be more useful in diagnosis of hyperthyroidism in cats with severe concurrent illness.

In most cats, if the T4 concentration is in the low or low normal range, a diagnosis of hyperthyroidism is unlikely and other diagnoses should be pursued, however recent studies suggest that some hyperthyroid cats with concurrent illness can have very low T4 concentrations. Whether a diagnosis of hyperthyroidism should be pursued in an individual cat
with a low or low normal T₄, depends upon the clinical signs and physical examination. Spontaneous acquired hypothyroidism is extremely rare in the cat, so in most cases the finding of a low T₄ concentration should prompt investigation for nonthyroidal disease rather than further evaluation of the thyroid axis.

It is not uncommon to palpate a cervical nodule in a cat with no clinical or laboratory signs of hyperthyroidism. Possible differential diagnoses include early hyperthyroidism in which a goiter is present but the thyroid gland is not fully autonomous, thyroid cyst, or non-functional thyroid adenoma or carcinoma. Non-functional thyroid carcinoma does occur but is rare in the cat. If an obvious cervical nodule is palpated in a cat with a normal T₄ concentration, a fine needle aspirate should be considered to determine the tissue of origin. Unfortunately the accuracy of cytology to differentiate benign from malignant thyroid disease is poor.

**TREATMENT**

A number of options are available for the treatment of feline hyperthyroidism. These include oral anti-thyroid therapy, surgical thyroidectomy, and radioactive iodine therapy. The choice of treatment depends on the presence of other disease states, the age of the cat, the cat’s tolerance for hospitalization, tolerance of anti-thyroid medications, owner preference, and the results of other diagnostic tests (cardiac evaluation, technetium scan).

**Anti Thyroid Drugs**

Oral anti thyroid drugs are indicated in most hyperthyroid cats prior to definitive therapy, and in some cases may be the treatment of choice for long-term therapy. Anti-thyroid drugs are especially useful in extremely old patients, in patients with serious concurrent medical problems, as test therapy in patients with renal failure, and in cases where the cost of definitive therapy is not acceptable to the owner. The anti-thyroid drug of choice is methimazole, which should be initiated at a starting dose of 2.5-5 mg q 8-12 hours and then titrated to effect. Most cats (90 %) become euthyroid within 2-3 weeks of starting therapy. The dose required to maintain euthyroidism is quite variable from cat to cat (2.5-20 mg/day). A small percentage of hyperthyroid cats may be resistant to the effects of methimazole. Adverse clinical reactions occur in 10-15% of cases and include anorexia, vomition, lethargy, excoriation of the head and neck, icterus, and bleeding diatheses. Mild hematological abnormalities develop in 16% of cats and include leucopenia, lymphocytosis, and eosinophilia. More severe hematologic abnormalities develop in 4 % of cats and include agranulocytosis, and thrombocytopenia. Cats on anti-thyroid drugs should have a CBC, platelet count, and T₄ concentration performed every 2 weeks for the first 3 months of therapy. A recent study of forty four hyperthyroid cats compared response to treatment with oral methimazole compared with topical methimazole for treatment of hyperthyroidism. Cats were treated with methimazole at a dose of 2.5 mg q 12 hours. Seventeen cats received oral methimazole, whereas 27 cats received methimazole in a pleuronic lecithin organogel (concentration 5mg/0.1 ml) which was applied to the non-hairied portion of the pinna. After 4 weeks of treatment 9/11 cats treated with oral methimazole were euthyroid, compared with 14/21 cats treated with topical methimazole. This difference was not statistically significant. Cats treated with oral methimazole had a higher incidence of gastrointestinal side effects (4/17 cats) than those treated topically (1/27), but there was no difference in the incidence of other side effects.
Propylthiouracil (PTU) is also an effective anti thyroid drug in cats, but the risk of adverse reactions is significantly higher. For this reason it is no longer recommended for use in cats. In cats which do not tolerate methimazole and in which the owners are unwilling to consider other options, PTU could be considered, if the risks are fully understood by the owner. Carbimazole is an anti thyroid drug, which is available in Europe. This drug is closely related to methimazole and is converted to methimazole in vivo. Adverse effects are similar to those associated with methimazole but may be less frequent. Ipodate is an organic radiocontrast agent which blocks the peripheral conversion of $T_4$ to $T_3$. The drug has been evaluated in a small number of hyperthyroid cats and appears to be effective in improving clinical signs and decreasing $T_3$ concentration for up to 6 months. Disadvantages include the lack of long-term efficacy and the fact the drug is not currently available in US. It is possible that other iodine containing drugs may replace this drug in the future.

The advantages of oral anti-thyroid drug therapy include the low cost, avoidance of anesthesia, and avoidance of a surgical procedure. The disadvantages include the risk of side effects, failure to respond in some patients, problems with owner compliance, and control rather than cure of disease. I only recommend long-term anti-thyroid drug therapy in cats with other severe concurrent disease, in very old patients, and in those cases where the owner cannot afford definitive treatment. Methimazole is often used in patients with renal failure to evaluate the effect of euthyroidism on renal function. It is difficult to predict which hyperthyroid cats are at risk for worsening of renal function, but in my experience clinically significant renal failure is rare in a hyperthyroid cat with a BUN and creatinine within the normal range even if the specific gravity is low. I do however recommend a 4-week trial with methimazole in hyperthyroid cats that have elevated renal parameters. If BUN and creatinine remain stable or increase only slightly after euthyroidism is achieved, it is likely definitive therapy will be well tolerated. If there is a significant increase in BUN or clinical signs of renal failure, consideration should be given to titration of the methimazole dose with the aim of controlling clinical signs of hyperthyroidism with smallest possible dose of methimazole. Definitive therapy with $^{131}$iodine or thyroidectomy should be avoided in these cats.

**THYROIDECTOMY**

The advantages of surgical thyroidectomy include rapid response to treatment, short hospital stay, convenience in the private practice setting, and opportunity to evaluate the removed thyroid tissue histopathologically. Disadvantages include the need for general anesthesia, the risk of inducing iatrogenic hypoparathyroidism, morbidity associated with the surgical procedure, and the higher cost when compared to anti-thyroid medication. Whether cats treated with surgery have a higher risk of recurrent disease than those treated with $^{131}$iodine has not been proven. If surgical thyroidectomy is the treatment chosen, careful attention should be paid to the pre surgical cardiac evaluation, choice of anesthetic protocol, and use of fluid therapy. If there is evidence of significant cardiac disease, medical therapy should be used to stabilize the patient prior to surgery. Methimazole, together with atenolol or diltiazem, is usually effective in controlling the hyperthyroid state and improving cardiac function. In some cases diuretic therapy may also be necessary. Surgery is most appropriate in those patients in which there is unilateral thyroid involvement based on the results of a technetium scan. In cases of bilateral...
thyroid disease, the owners need to fully understand the potential risk of hypoparathyroidism. The surgical techniques of choice are either a modified extracapsular or a modified intracapsular technique. These techniques minimize the chance of hypocalcemia while at the same time decreasing the chance of recurrence. It is almost impossible to predict at the time of surgery whether or not clinical hypocalcemia is likely to occur, so in all cases of bilateral thyroidectomy, cats should be carefully monitored for signs of hypocalcemia for 3-5 days after surgery. In my opinion, 24-hour monitoring is necessary in those cats that undergo bilateral thyroidectomy. If it is not possible to perform a technetium scan prior to surgery, the whole cervical region should be explored at the time of surgery. Ectopic thyroid tissue is found in as many as 12% of hyperthyroid cats. Normal thyroid tissue should be atrophic, so thyroid tissue that appears grossly active is abnormal. Rate of recurrence after surgical thyroidectomy is 5-12%.

**RADIOACTIVE IODINE**

The thyroid gland concentrates iodine within the colloid of the gland. Radioactive iodine emits _β_ particles which destroys functional thyroid tissue without causing damage to normal tissues such as the parathyroid glands. Normal thyroid tissue is spared because it is atrophic due to lack of TSH, and does not concentrate much iodine. \(^{131}\)Iodine is the radionuclide of choice for the treatment of hyperthyroidism. It has a half-life of 8 days and is a beta and gamma emitter. The beta particles travel a maximum of 2 mm in tissue so they cause only local destruction within the thyroid gland. The advantages of this therapy are that it is safe, no anesthesia is required, and it is effective for the treatment of ectopic thyroid tissue or metastatic thyroid carcinoma. The disadvantages are the expense, limited availability, and requirement for isolation in an approved facility from several days to 2 weeks following treatment depending on local regulations. All anti thyroid drugs should be discontinued 7-14 days prior to treatment. \(^{131}\)Iodine is administered IV or SC at a dose which is either a fixed dose (4 - 6 millicuries), a calculated dose based on the weight of the cat, the size of the thyroid gland, and the T4 concentration, or calculated from \(^{131}\)I uptake trace studies. In animals known to have thyroid carcinoma, doses of 20 - 30 millicuries are used. T3 and T4 concentrations decline in 5 - 10 days and clinical improvement is usually observed within 2 weeks although in some cats the response may be delayed. Hypothyroidism may occur in cats secondary to bilateral thyroidectomy or radioactive iodine therapy. In many cases this is transient and unassociated with clinical signs. It is therefore recommended that thyroid supplementation is only initiated if cats demonstrate clinical signs of hypothyroidism. These include anorexia, lethargy, weight gain, poor hair coat and alopecia.

The advantages of \(^{131}\)iodine therapy are that all sites of thyroid tissue are destroyed, there is no risk of hypoparathyroidism, no anesthesia is required, and it is possible that the risk of recurrence may be lower. Disadvantages include the need for prolonged hospitalization in some facilities, lack of opportunity to evaluate thyroid tissue histopathologically, and limited availability of treatment facilities, although availability is improving rapidly. In the majority of hyperthyroid cats radioactive iodine is the treatment of choice, however it should be avoided in patients with other serious medical problems that require therapy during isolation, in cats with renal failure that worsens with the use of anti-thyroid drugs, and in those patients that do not tolerate hospitalization well.
REFERENCES