

FELINE HYPERTHYROIDISM

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Feline hyperthyroidism is a relatively newly recognized clinical entity in cats with the first detailed clinical reports appearing in the literature in 1980. It may be the single most commonly diagnosed endocrinopathy in cats next to diabetes mellitus with an incidence of 1/300 cats reported at the Animal Medical Center in NYC. This is generally a disease of aged cats with a mean age of occurrence of 12 to 13 years and a range of 4 to 22 years old. No sex or breed predilection has been identified. The cause for the disease is the spontaneous development of adenomatous hyperplasia (thyroid adenoma) in 98-99% of all cases. In approximately 70% of cats the condition is bilateral. Only 1 to 2% of cats where histopathology of the thyroid has been performed had thyroid adenocarcinomas.

### Clinical Signs

All the signs seen in these cats can be traced back to the chronic hypermetabolic state they are in. This is due to excessive concentrations of thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) in the circulation. Clinical signs in individual cats are highly variable and relate to the polysystemic nature of the disease and the fact that cats in this age group often have more than one problem going on simultaneously. The longer the cat has the problem the more severe the signs and the more signs that become apparent. Weight loss is the most common complaint, present in 96% of cases. This is due to the chronic catabolism induced by excess circulating thyroxine. In addition, polyphagia (77%) and hyperactivity (68%) are commonly recognized. These cats are typically voracious eaters, constantly looking for food and act like "kittens". Polydipsia and polyuria are seen in 54% of cats secondary to an increased GFR, decreased medullary solute concentration (washout), and a psychogenic component. Vomiting is seen in 49% of cats, often soon after eating, and may be associated with gastric overload. These cats are often characterized as "gulpers" rather than "pickers" as is more common in normal cats. Fecal volumes and frequency of defecation are high and diarrhea may be seen in some cases (31%). The diarrhea probably reflects intestinal overload and relative maldigestion due to the high food intake of these cats. They have clinical signs typical of exocrine pancreatic insufficiency and may partially respond to pancreatic enzyme supplementation. Late stage signs typical of "apathetic hyperthyroidism" are those of anorexia (28%), muscle weakness (22%), and inactivity and are only seen in cats with severe, long standing disease. Polypnea and/or open mouth breathing is seen in 28% of cats and is a result of hypertrophic cardiomyopathy and/or fever. Signs compatible with congestive heart failure may be seen in up to 13% of cases. These cats are particularly intolerant of stress and the process of bringing the cat to the hospital and its examination may result in severe respiratory distress, tachycardia, arrhythmias and even cardiac arrest. Gentle handling is the watch word in cats with advanced hyperthyroidism.

### Physical Examination Findings

The classic presentation is an aged cat that is hyperactive, bright eyed, restless, inquisitive and acting like a kitten during exam. They are constantly pacing around the room. In advanced stages of the disease they more typically reflect any of a number of chronic severe diseases that geriatric cats are prone to. This subgroup of cats (apathetic hyperthyroidism) is lethargic, weak and very quiet. Anorexia may be present as well. Occasionally severe ventral neck flexion will be seen presumably related to muscle weakness. Both groups of cats are usually quite thin to emaciated or at least have a history of significant weight loss over several weeks to months. A low grade fever of 102.8 to 103°F is common. They have a rough dry hair coat and seborrhea may be severe. Other than generalized cachexia, the cardiovascular system may have the most significant abnormalities. Cats usually have a tachycardia (rate 180-260 bpm). Arrhythmias are common characterized by premature beats, and gallop rhythms. Systolic or holosystolic grade I-IV/VI murmurs are frequent. Dyspnea, moist rales and open mouth breathing may be noted as well. The one physical exam finding that is most useful in establishing a diagnosis of hyperthyroidism is the presence of a palpable thyroid enlargement in 85 to 90% of affected cats. These can be quite small and it helps to elevate the cats head and neck and gently palpate the neck from the larynx to the thoracic inlet. In cats with large thyroid nodules, the thyroid gland often migrates ventrally towards the thoracic inlet and is not in its usual anatomical location.

### Diagnostic Plans

Because of the multiplicity of systems involved in hyperthyroid cats, it is imperative that thyroid function be evaluated in any middle aged to older cat in which an obvious answer for its signs is not readily apparent. This is particularly important in any cat that is found to have hypertrophic cardiomyopathy, as the majority of cats with this form of cardiomyopathy are ultimately found to be hyperthyroid and can be cured by reversing the thyroid abnormality. A minimum data base for hyperthyroid cats should include a CBC, chemistry profile, urinalysis, and T<sub>4</sub>. If clinical signs of cardiomyopathy are present an ECG, thoracic radiograph, and echocardiogram may be warranted.

Multiple hematologic and biochemical abnormalities are present in hyperthyroid cats. The hemogram typically has a neutrophilia and eosinopenia. Erythrocytosis is present in 15% of cats characterized by an increase in PCV, RBC's and hemoglobin. Occasionally a mild anemia (nutritional?) will be seen.

Thyroid function tests provide a definitive diagnosis in nearly all cases. The T<sub>4</sub> concentration by definition should always be elevated in hyperthyroid cats. Normal values for the University of Minnesota are 0.6 to 3.6 micrograms/dl. Affected cats have values ranging from 4 to 65 micrograms/dl. Recently a

few hyperthyroid cats have been shown to occasionally have high normal values at some time during a 24 hour period. If a cat has all the clinical signs but has a high normal resting value, repeated samples over a period of weeks may be necessary to diagnose the problem. T<sub>3</sub> values are also usually elevated in hyperthyroid cats (90%) and range from 90 to 700 nanograms/ml with 60-200 nanograms/ml being normal. A T<sub>3</sub> suppression test may be used to identify borderline hyperthyroid cats. This test is performed by obtaining a basal T<sub>4</sub> level and administering exogenous T<sub>3</sub> at 25 micrograms/cat every 8 hours for 2 days and giving the last (7th) dosage on the morning of the third day. two to four hours after the last dose of T<sub>3</sub>, another serum T<sub>4</sub> value is obtained. In normal cats, suppression of thyroxine should occur to values approximately 50% or less of baseline, usually to a value of less than 1.5 micrograms/dl. In hyperthyroid cats, little or no decrease in resting T<sub>4</sub> concentrations will be seen since the exogenous T<sub>3</sub> will not suppress the autonomous hyperplastic tissue. An additional test to use to identify mild hyperthyroid cats is the thyrotropin-releasing hormone stimulation test (TRH-Stimulation). TRH is administered intravenously @ 0.1 mg/kg. A baseline T<sub>4</sub> and a second sample 4 hours after the TRH are obtained. Normal cats or those with other illnesses typically have a twofold or greater rise in the serum T<sub>4</sub> concentration. Cats with hyperthyroidism, however, typically have either no increase or a marginal increase in the T<sub>4</sub> concentration. The relative increase over baseline is most useful in differentiation of the mildly hyperthyroid cat from normal cats. Cats with mild hyperthyroidism should have less than a 50% increase in T<sub>4</sub> while normal cats and those with other illnesses resembling hyperthyroidism generally have an increase of greater than 60%. The formula for calculating the percent increase is  $[(\text{post-TRH-T}_4 - \text{basal T}_4) / \text{basal T}_4] \times 100$ . If values are between 50% and 60% the diagnosis is suspect and needs to be repeated after some period of time (1 to 2 months?), or a T<sub>3</sub> suppression test performed. Advantages of the TRH stimulation test are the relatively short time of the test, versus having the cat send home and relying on owners to administer the medication for two days. The main disadvantage is that TRH induces signs of nausea, vomiting, tachypnea, hypersalivation and defecation in most cats when given intravenously. These signs resolve before the end of the test, however. At referral institutions, thyroid imaging with pertechnetate (<sup>99m</sup>Tc) will allow visualization of the hyperactive glands both as to location and as to size and bilateral or unilateral nature of the disease, and can be valuable in the rare case of malignant thyroid tissue.

The liver profile on hyperthyroid cats is often abnormal. Fifty to 75% of cats have elevations in either ALP (72%), or AST (61%), or ALT (51%). Hyperbilirubinemia has been reported in up to 21% of cats but is usually mild (< 3 mg/dl). The cause for these elevations is unknown, but they generally resolve with correction of the hyperthyroid state. Hyperphosphatemia may be

seen in 27% of cats with hyperthyroidism and is thought to be a result of a direct effect of thyroxine on bone resorption and secondary to muscle catabolism. Concomitant renal failure is a frequent finding in hyperthyroid cats (20 to 40%), but is usually mild (BUN 40 to 60 mg/dl). Occasional cats with coexisting renal failure and hyperthyroidism have decompensated their renal disease following surgical correction of the problem. Medical management of the condition for several weeks prior to surgical correction is warranted in cats with coexisting renal compromise and hyperthyroidism. This allows the cat to adapt to euthyroidism and monitoring of its renal function can be done to determine if the cat is a reasonable surgical candidate.

A cardiovascular work up will usually identify the cat to have a tachycardia (HR = 206-260), an increased R-wave amplitude in lead II supportive of left ventricular hypertrophy. Paroxysmal atrial and ventricular arrhythmias and interventricular conduction defects may also be identified. Thoracic radiographs may detect a valentine shaped heart typical of hypertrophic cardiomyopathy. Pulmonary edema or pleural effusions are occasionally identified as well. Echocardiograms usually detect findings typical for hypertrophic cardiomyopathy, but occasional dilated cardiomyopathy has been identified as well.

#### Therapeutic Options

Since the underlying cause for adenomatous hyperplasia of the thyroid gland is unknown and spontaneous resolution of the condition does not occur, lowering of the serum thyroxine concentration is required for correction of the disease. This is accomplished in one of three ways: surgical removal of the adenomatous or neoplastic thyroid tissue, radioactive  $^{131}\text{I}$  therapy, or chronic suppression of thyroid activity by the use of antithyroid drugs. The therapeutic choice must be individualized for each cat and no one best choice exists for all cats. Table 1 summarizes the advantages and disadvantages of each form of therapy. The treatment choice for any cat is dependent on the age of the cat, the presence of coexisting diseases (cardiac or renal), the cost of therapy, the availability of an experienced soft-tissue surgeon or access to radioactive iodine, for  $^{131}\text{I}$  therapy, and the willingness of individual clients to accept your therapeutic recommendations. Only surgery and  $^{131}\text{I}$  are curative. Antithyroid drug therapy must be given daily for the life of the cat for continued efficacy.

Antithyroid drugs-Two compounds are currently available in the United States for medical control of hyperthyroidism, methimazole (Tapazole) and propylthiouracil (PTU). Both of these oral drugs are actively concentrated in the thyroid gland where they act to inhibit the synthesis of thyroid hormones. Neither drug interferes with the ability of the gland to concentrate, inorganic iodine nor do they block the release of stored thyroid hormone into the blood. This therapy has the

advantage of being fairly inexpensive for owners, is readily usable by most clinicians, and carries very little risk for the patient. Of the two drugs, only methimazole can be recommended due to the large number of undesirable side effects to the use of PTU. Methimazole is the drug of choice for long term medical control of the disease or presurgical management of fragile cats. An initial starting dosage of 2.5 mg twice daily for two weeks is used to allow the cat to adapt to the drug and reduces the signs of anorexia and vomiting, then recheck a T<sub>4</sub>, if it is still elevated, increase the dosage of methimazole to 5 mg two to 3 times daily. Serum T<sub>4</sub> concentrations should become normalized within 2 to 3 weeks on this therapy. During the first 3 months of drug administration cats should be monitored for both T<sub>4</sub> concentrations and adverse side effects, both hematological, biochemical and dermatological. Initial side effects occurring in approximately 15% of cats are anorexia, depression and lethargy. These signs usually resolve with continued administration of the drug even if the dosage is not reduced. Severe GI signs persist in some cats necessitating cessation of the drug. In rare cats, self trauma to the face and neck will occur during the first 6 weeks of therapy that is only partially controlled by glucocorticoid therapy. In most of the cats with facial dermatitis, cessation of the drug will be required to correct the problem. In additional rare cats, severe hepatotoxic reactions to methimazole will occur that necessitates withdrawal of the medication. Anorexia, vomiting and lethargy coupled with severe elevations in ALT, ALP and bilirubin will occur. These enzyme abnormalities may require weeks to completely reverse after drug withdrawal. Complete blood counts, platelet counts, and T<sub>4</sub> concentrations should be monitored at 2 to 3 week intervals for 2 to 3 months. The most serious hematologic complications associated with methimazole are agranulocytosis, anemia and thrombocytopenia. All will reverse if the drug is stopped and the cat given supportive care. Most cats will develop a relapse of these problems if the drug is readministered, thus surgery or <sup>131</sup>I are the only therapeutic choices for these cats with serious drug toxicities. If the serum T<sub>4</sub> does not decrease to low normal in 2 to 3 weeks, the methimazole dosage should be increased in 5 mg increments i.e., from 10 to 15 mg/day for a week then rechecked. Nearly all cats will have hyperthyroidism suppressed if 25 to 30 mg are given daily. If methimazole is used presurgically, it need only be given for the 2 to 3 weeks necessary to normalize serum T<sub>4</sub> concentrations. Ultimately, the lowest maintenance dosage necessary to normalize the T<sub>4</sub> should be used. Most cats can be maintained on 7.5 to 10 mg/day once initial normalization of hyperthyroidism is accomplished. A few animals still require 15 to 20 mg daily for optimal control. Once a maintenance dosage is identified it may be given once daily if this is easier for the client and it does not induce GI upset. The drug must be given at least daily for maintenance of the euthyroid state. Hyperthyroidism will return in 24 to 72 hours after the last dose of the drug.

Thyroidectomy-Surgical removal of the hyperplastic thyroid tissue is the next most widely used method of reversing feline hyperthyroidism. Although the technique of thyroidectomy is not complicated, the high risk of these cats for surgical or post-operative complications makes this choice less optimal than drug therapy or  $^{131}\text{I}$ . All cats that are going to have surgery should receive methimazole for 2 to 3 weeks preoperatively and be euthyroid at the time of surgery. In addition, the use of 2.5 to 5 mg of propranolol every 8 hours for 2 to 3 weeks before surgery significantly reduces the cardiovascular manifestations of this disease. Propranolol should not be used if the cat has signs of congestive heart failure, however, as it has negative inotropic activity. It will significantly reduce the tachycardia and arrhythmias that bother some cats. The main complication associated with thyroid surgery is the removal of all functioning parathyroid tissue during bilateral thyroidectomy resulting in severe hypocalcemia within 1 to 3 days postsurgically. Other post surgical complications that may occur are laryngeal hemiplegia and Horner's syndrome due to damage to the vagosympathetic trunk during thyroidectomy. Since 70% of cats have bilateral disease, this has the potential to be a frequent complication. Every attempt must be made to preserve at least one of the external parathyroids with its cranial blood supply during surgery. Even if only a hemithyroidectomy is performed. If only one gland is obviously enlarged the contralateral gland should be left behind. If it is hyperplastic, signs of hyperthyroidism will generally reappear within 9 months following surgery. At that time, the other gland can be removed. Close monitoring of the serum calcium concentration for several days post surgery is mandatory. Therapy for hypocalcemia is not needed unless signs of hypocalcemia develop, such as tremors, weakness, tetany, or seizures. Therapy for hypocalcemic tetany initially involves the administration of I.V. calcium gluconate and following up with oral Vitamin-D and oral calcium salts. Intravenous calcium gluconate is given initially at a dosage of 1.0-1.5 ml/kg of 10% solution over 10 to 20 minutes if acute tetany develops. Once signs of tetany have been controlled, the rate is slowed to 2.0 ml/kg I.V. over 6-8 hrs. Calcium gluconate is repeated as signs dictate. Oral calcium gluconate may be started at 50-75 mg elemental  $\text{Ca}^{++}$ /kg/day = 500-750 mg/kg/day of the calcium salt, divided TID. If calcium lactate is given, it is dosed at 400 to 600 mg/kg/day, divided TID. The most effective form of vitamin D to give is synthetic Vitamin  $\text{D}_3$  - Dihydrocholecalciferol (Hytakeral) elixir. It has a rapid onset and dissipates more rapidly than Vit  $\text{D}_2$ . And dosage adjustments can be made rapidly due to its short half-life. An initial loading dose of 0.05 mg/kg/day is given for 2 days and then decreased to 0.02 mg/kg/day for 2 days, and then 0.01 mg/kg/day is given once daily thereafter. The required dosage is highly individualized in any cat and can only be determined by frequent serum calcium monitoring and appropriate dosage adjustments. You usually do not need calcium supplementation once they go home, if they are

on quality cat food. Vit D<sub>2</sub> is much less expensive, but slow in onset (4 wks) than Hytacherol. Initially, 4,000-6,000 IU/kg/day are given over the first 2 weeks to normalize serum calcium concentrations. Maintenance dosages of vitamin-D<sub>2</sub> are 1000-2000 IU/kg/day. This drug has a very long T<sub>1/2</sub> if hypercalcemic develops and it may be 2 weeks before normocalcemia returns if excessive vitamin D<sub>2</sub> has been administered. Even if hypoparathyroidism does develop postoperatively, it is not always permanent. In weeks to months some cats no longer require vitamin D or calcium supplementation. This can only be determined by slowly decreasing the vitamin D therapy and monitoring serum calcium concentrations.

Radioactive Iodine-Radioactive iodine (<sup>131</sup>I) may be the best alternative for therapy of hyperthyroidism if specialized facilities for obtaining and administering this isotope are available. The compound selectively irradiates the hyperplastic thyroid tissue killing the hyperactive tissue while preserving the normal thyroid gland. Because of radiation safety requirements for the handling of this agent, long hospitalization of animals may be required. This therapy is effective in correcting the hyperthyroid state in over 85% of cases with a single dose.

Hypothyroidism may develop following bilateral thyroidectomy or <sup>131</sup>I therapy. In most cases, even though the serum concentrations are low the cat has no signs of disease and it may not need to be treated. If therapy is desired, a replacement dosage for L-thyroxine is 0.1 to 0.2 mg/cat given once daily. Regardless of the mode of therapy used, annual measurement of the serum thyroxine concentration should be performed to determine if continued euthyroidism exists or whether reoccurrence of the disease has taken place.

Exacerbation of preexisting renal failure is a significant risk when treating hyperthyroidism in geriatric cats. It has been recommended not to use I<sup>131</sup> therapy until a trial of methimazole has been done with careful monitoring of the BUN and creatinine. With effective treatment of hyperthyroidism, the GFR may decrease, resulting in worsening of previously asymptomatic renal failure. In most cases, the BUN and creatinine rise following management are mild and not of clinical significance, but if renal failure is mild to moderate prior to treatment caution in management of the hyperthyroidism is warranted.