FELINE HYPERTHYROIDISM
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Pathogenesis
Hyperthyroidism is one of the most common endocrinopathies of cats (Feldman and Nelson 2004). Ninety nine percent of cases result from benign nodular hyperplasia/adenoma (Peterson and others 1983; Peterson and Ferguson 1989), which results in the autonomous secretion of thyroxin (T4) and triiodothyronin (T3). These hormones produce a negative feedback affect on the pituitary gland, suppressing the release of thyroid-stimulating hormone (TSH), so any normal thyroid tissue atrophies. In 70% of the cats, both thyroid glands are affected (Peterson and others 1983; Peterson and Ferguson 1989; Feldman and Nelson 2004). In only 1% of cases is the disease caused by mild to moderately malignant thyroid carcinoma (Turrel and others 1988).

While the cause of the nodular hyperplasia/adenoma is unknown, it is believed to involve factors within the diet (possibly including iodine content, frequent changes, food additives) (Tarttelin and others 1992; Kass and others 1999; Martin and others 2000), environmental causes (possibly associated with cat litter, toxins, pollution, exposure to allergens) (Scarlett and others 1988; Kass and others 1999), genetic mutation (Merryman and others 1999), and/or abnormal immune and/or hormonal responses.

Clinical signs
Hyperthyroidism is seen mainly in middle-aged to older cats; with the age at presentation ranging from four to 23 years (mean 13 years) (Peterson and others 1983; Thoday and Mooney 1992). However, it has occasionally been seen in younger cats (including one kitten of eight months old) (Gordon and others 2003). There is no sex or breed predisposition (Peterson and others 1983; Thoday and Mooney 1992; Martin and others 2000), although Siamese and Himalayan (Colorpoint Persian) cats appear to be under-represented in some studies (Scarlett and others 1988; Kass and others 1999).

Most cats have a history of weight loss and polyphagia, usually occurring over several months (Thoday and Mooney 1992; Broussard and others 1995). In most cases clinical signs are insidious and progressive. Affected cats are frequently restless, aggressive, and stop grooming. They have commonly been vomiting and/or had diarrhea (the feces often become bulky); some have polyuria/polydipsia (Peterson and others 1983; Thoday and Mooney 1992; Broussard and others 1995). Less common clinical signs include dyspnoea, seizures, or severe muscle weakness (the latter being due to hypokalemic myopathy and/or low thiamine levels) (Nemzek and others 1994; Broussard and others 1995). The gastrointestinal signs may result from malabsorption and/or intestinal hypermotility, and may be associated with very low folate levels (which need to be treated for the diarrhoea to resolve). Polyuria/polydipsia may result from diuretic effects of T4, increased renal blood flow, associated renal insufficiency, or compulsive polydipsia. Associated cardiac hypertrophy may eventually result in congestive heart failure, with tachycardia, a gallop rhythm, systolic murmurs, dyspnoea, apathy, hind limb weakness due to aortic thromboemboli, or collapse (Liu and others 1984). Up to 85% of cats with hyperthyroidism...
may develop systemic hypertension. This may be detected as hypertensive retinopathy, including ocular hemorrhage (Stiles and others 1994), or cause clinical signs associated with cerebrovascular accidents, dementia, and/or renal failure. Approximately 10% of cats present with signs of inappetence, rather than polyphagia, and are often depressed and weak (so called apathetic hyperthyroidism) (Peterson and others 1983): this is frequently due to significant secondary or associated cardiac disease. Many hyperthyroid cats are presented for their routine vaccination with no owner complaints as their owner’s presume that the cat’s clinical signs are the normal result of ageing (Broussard and others 1995).

**Diagnosis**

Hyperthyroidism should be suspected when any older cat presents with weight loss, and especially when the weight loss is associated with a good appetite. However, inappetence should not rule out hyperthyroidism. Physical examination usually reveals rather poor body condition, an ill-kempt coat, and a thyroid nodule on either or both sides of the trachea in the ventral cervical region (80-90% of cases) (Peterson and others 1983; Thoday and Mooney 1992; Broussard and others 1995). Affected cats often have tachycardia, a gallop rhythm, and/or a systolic murmur. Cardiac effects result from a high output state, induced, in part, by a demand for increased tissue perfusion to meet the needs of increased tissue metabolism. In addition, thyroid hormones can have a direct effect on cardiac muscle. Cardiovascular changes include left ventricular hypertrophy, left atrial and ventricular dilation, increased myocardial contractility, and decreased peripheral vascular resistance (Liu and others 1984). Hyperthyroid cats are often agitated, difficult to examine, and become easily stressed (Peterson and others 1983; Broussard and others 1995).

Clinical pathology almost always reveals raised liver enzymes (serum alanine transferase [ALT], alkaline phosphatase [ALP], and aspartate transferase [AST]) (Peterson and others 1983; Thoday and Mooney 1992; Broussard and others 1995). The hepatopathy may be secondary to a direct toxic effect of the thyroid hormones, hepatic lipidosis, malnutrition, or hepatic hypoxia resulting from cardiac failure (Thoday and Mooney 1992). The ALP may also be raised because of increased bone metabolism (Horney and others 1994; Foster and Thoday 2000). In some cases, serum glucose concentration may be increased, or azotemia may be present (Peterson and others 1983). The latter may result from increased protein catabolism, reduced renal perfusion caused by associated cardiac insufficiency, renal damage induced by associated systemic hypertension, or be related to concomitant, but unrelated, chronic renal insufficiency. Hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism may be detected, irrespective of the presence of renal insufficiency, possibly resulting from T4-mediated alterations in bone metabolism and increased phosphate absorption (Peterson and others 1983; Barber and Elliott 1996). Hypokalemia may be present, or may develop apparently in response to the stress of the diagnostic investigations. When this occurs the resulting hypokalemic myopathy may be seen as severe muscle weakness and neck ventroflexion, and the serum CPK concentration will increase (Nemzek and others 1994).
Hematology may reveal erythrocytosis or, in very severe disease, mild anaemia. Leukocyte changes may include a mature neutrophilia, lymphopenia or lymphocytosis, eosinopenia or eosinophilia (Peterson and others 1983; Thoday and Mooney 1992). Unless there is concurrent renal insufficiency the urine is usually concentrated (Graves and others 1994; Thoday and Mooney 1992; Broussard and others 1995). Microalbuminuria may be present (Syme and Elliott 2003), and some cats develop significant proteinuria (i.e. urine protein to creatinine ratio >0.4), which is often associated with concurrent systemic hypertension (Syme et al 2006; Elliott and Syme 2006).

When investigating a cat for possible hyperthyroidism it is important to consider all possible differential diagnoses and to look for evidence of multiple interacting diseases. This is because hyperthyroidism is seen most often in older cats, and this group of patients is often affected by more than one disorder. Diabetes mellitus, renal disease, malassimilation syndromes (including inflammatory bowel disease, pancreatitis and/or exocrine pancreatic insufficiency, and early intestinal lymphosarcoma), acromegaly, and hyperadrenocorticism are perhaps the most important differentials.

A full cardiac investigation is recommended prior to considering treatment options for the hyperthyroidism. Thoracic radiography may reveal cardiomegaly, pulmonary edema or pleural effusion (Peterson and others 1983). Electrocardiography commonly reveals abnormalities, including sinus tachycardia, increased R-wave amplitude, atrial and ventricular arrhythmias and intraventricular conduction disturbances (Peterson and others 1982, 1983; Moise and Dietze 1986; Broussard and others 1995). Abnormalities are also seen frequently on echocardiography. These may include hypertrophy of the left ventricular free wall and interventricular septum, increased left atrial diameter at end diastole, and hyperdynamic wall motion (Moise and Dietze 1986; Bond and others 1988).

A definitive diagnosis of hyperthyroidism is based on detecting elevated serum concentrations of total T4 (and possibly T3) (Peterson and others 1983, 2001; Thoday and Mooney 1992). Measurement of T3 alone is not usually recommended, as it is less sensitive than T4 (Peterson and others 1987). Unfortunately, some cats with hyperthyroidism also have a T4 concentration that is within the normal range. This may be due to early or mild hyperthyroidism, daily variations in T4 concentrations, or the concurrent presence of severe systemic illness causing a reduction in T4 (euthyroid sick syndrome) (Peterson and Gamble 1990; Thoday and Mooney 1992; McLoughlin and others 1993; Mooney and others 1996a; Peterson and others 2001).

If hyperthyroidism is suspected despite a high normal T4 concentration:

- **Retest the cat:**
  Retest the cat, either immediately, or in a few weeks time (Peterson and Gamble 1990). Assessing free T4, as well as total T4, may help in confirming the presence of hyperthyroidism (Mooney and others 1996b; Peterson and others 2001).

- **T3 suppression test:**
Protocol: Collect a blood sample, give 25mg of T3 orally every eight hours for seven doses, then collect a blood sample two to four hours after the seventh dose (i.e. on day three). An increase in T3 concentration confirms successful medication. Suppression of the T4 concentration (below 50% of baseline, <1.5 ug/dl [<20 nmol/l]) does not occur in hyperthyroid cats (Peterson and others 1990; Refsal and others 1991). This is a useful test at ruling out but hyperthyroidism, but cannot reliably be used to confirm hyperthyroidism (Peterson and others 1990; Refsal and others 1991). In addition, unless the cat is hospitalized, relies on the owner being able to reliably administer the T3.

- **Thyrotropin-releasing hormone (TRH) stimulation test:**
  Protocol: Collect a blood sample, give 0.1 mg/kg TRH IV, and then collect a second blood sample four hours later. Assess both samples for serum T4 concentration. Stimulation to greater than 50% does not occur in hyperthyroid cats. Side effects of TRH include transient salivation, vomiting, tachypnoea, and defecation (Sparkes and others 1991; Peterson and others 1994). While this test is good at detecting mild or early hyperthyroidism (Peterson and others 1994), it is not so good at detecting hyperthyroidism in a cat with severe concurrent disease and euthyroid sick syndrome (Tomsa and others 2001).

- **Thyroid-stimulating hormone (TSH) response test:**
  This test is not recommended in the diagnosis of hyperthyroidism as cannot reliably differentiate between normal cats and cats with mild hyperthyroidism (Peterson and Ferguson 1989; Mooney and others 1996b; Peterson and others 1990). In addition, TSH is very difficult to obtain.

- **Nuclear isotope scanning:**
  This technique can be used to detect hyperactive thyroid tissue, and to determine whether one or both thyroid glands are overactive (Peterson and others 1983). The procedure is relatively safe and simple to perform, but requires access to a licensed facility.

- **Trial course of anti-thyroid therapy:**
  Administering a trial course of anti-thyroid therapy (see below), for approximately 30 days, and observing for changes in clinical signs, can help in trying to decide whether or not a cat is clinically hyperthyroid. However, there is a potential risk of side effects, and doing so requires monitoring of hematology and serum biochemistry.

**Treatment**

It is essential that the renal function is assessed prior to considering possible treatment options. This is because resolution of the hyperthyroid state is associated with an increase in blood urea nitrogen (BUN) and creatinine concentration, and a decrease in glomerular filtration rate (GFR) and effective renal blood flow. Because of this, some cats without prior evidence of renal insufficiency, or with only mild renal impairment, develop signs of uremia following treatment for hyperthyroidism (Graves and others 1994; Adams and others 1997). In order to ascertain what effect resolving the hyperthyroid state will have on any particular cat it is therefore recommended that all cats receive initial medical therapy with methimazole (or carbimazole), prior to considering radiotherapy or surgery (Graves and others 1994; Adams and others 1997). Cats that do show significant uremia or develop renal failure following radiotherapy or surgery should be given levothyroxin to maintain a euthyroid or mild hyperthyroid state (Graves and others 1994; Adams and others 1997).
Hyperthyroidism can be treated medically, surgically, or with radioiodine ($^{131}$I). Prior to deciding which treatment to use, the cat should be assessed for concurrent disease, especially renal disease, systemic hypertension and heart disease, all of which occur commonly in association with hyperthyroidism. The interplay between systemic blood pressure and renal function is complex. While systemic hypertension is detrimental to kidney function, a sudden fall in blood pressure (e.g., associated with a sudden fall in T4) can exacerbate renal dysfunction by causing a sudden fall in renal blood flow. Changes in T4 need to be made gradually so there are no sudden changes in renal blood pressure. By maintaining renal blood pressure, hyperthyroidism can mask low-grade renal insufficiency. It is essential to check serum urea and creatinine concentrations and urine specific gravity prior to inducing irreversible reduction of T4 (i.e., by thyroidectomy or $^{131}$I treatment). A short course of medical therapy may reveal the presence of masked renal insufficiency.

- **Medical therapy** tends to be given to stabilize the cat prior to surgical treatment, to check for masked renal disease prior to thyroidectomy or $^{131}$I treatment, or when neither $^{131}$I nor surgery are possible.

**Methimazole and carbimazole** block T3 and T4 synthesis. It takes 1-3 weeks before a significant decrease in T4 concentrations occur after beginning treatment. Carbimazole is broken down to methimazole in vivo. Unfortunately, bioavailability and volume of distribution of methimazole is highly variable between cats.

Dose for both is 2.5-5.0 mg PO every 8-24 hours initially, reducing to every 12-24 hours. If the cat has concurrent renal insufficiency, start with a low dose and monitor renal values as the dose is gradually increased. Preliminary studies with topical transdermal applications show promise but are not freely available.

When cat and owner compliance is good, the successful response rate is approximately 85% with medical treatment.

Poor compliance results from:
- The need for frequent medication.
- The need for frequent blood samples to look for possible side effects. Blood dyscrasias occur in 2-10% of cats and include eosinophilia, lymphocytosis, leukopenia, thrombocytopenia, and/or agranulocytosis, hepatopathy, jaundice, cutaneous reactions (typically pruritus of the head and neck), bleeding tendencies or, very occasionally, myasthenia gravis, or immune-mediated hemolytic anaemia (IMHA).
- Frequent side effects. Up to approximately 20% of cats develop anorexia, vomiting or lethargy. Mild side effects may resolve despite continued treatment.

**Other medical therapies include:**

**Propranolol** ($\beta$-adrenoceptor blocking agent) may be added to reduce tachycardia, arrhythmias, and hypertension (2.5-5.0 mg/cat PO every 8-12 hours).

**Stable iodine** helps to decrease T3 and T4 synthesis and reduce thyroid gland vascularity, but the effect can be transient and inconsistent. Give potassium iodide 30-100mg/cat/day PO for 10-14 days prior to surgery using 100g potassium iodide/100ml solution, or potassium iodate.
~20mg/cat every 12 hours PO.

*Calcium or sodium ipodate* is a radiopaque iodine agent that reduces T3 concentrations. Its effect can be transient, and it may be difficult to obtain (15 mg/kg PO every 12 hours).

- **Surgical thyroidectomy.** The success depends on the stability of the patient, the expertise of the surgeon (a bilateral thyroidectomy is usually performed), and the expertise of the anesthetist (e.g. do not give atropine).
  
  Successful response rate is > 95%. Ectopic overactive thyroid tissue is a cause of failure, as it is usually missed at surgery.
  
  Reduce the risks of surgery by making the cat euthyroid prior to surgery (see *medical therapy* above).
  
  Surgical risks include anesthetic risks in older patients (often with concurrent renal ± cardiac disease), iatrogenic damage to parathyroid tissue leading to transient or permanent hypocalcemia, or to the local nerves leading to laryngeal paralysis or Horner’s syndrome.

- **Radioiodine (I$^{131}$)** is taken up by and destroys the overactive thyroid tissue, but spares the normal tissue.
  
  Successful response rate is > 95%, but it may take a few weeks, or occasionally months, for the normal tissue to recover function.
  
  Availability of facilities and length of stay in hospital varies from 2 days to 4 weeks depending on country and state, as it often depends on the interpretation of radiation safety laws.
  
  Side effects are few and include transient dysphagia or dysphonia, or permanent hypothyroidism (~2%).

**Prognosis**

Without treatment, cats with hyperthyroidism will usually die of concurrent renal disease, heart disease, liver disease, or systemic hypertension.

With treatment, prognosis varies from very good to guarded, dependent on the presence of heart disease, renal disease, and systemic hypertension, whether or not any damage has become permanent prior to treatment of the hyperthyroidism, and which treatment options are available.
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