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Hyperthyroidism in cats: An overview

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Abstract

Hyperthyroidism, primarily due to functional thyroid adenoma, is the most common endocrinopathy of older cats worldwide. Even though the etiopathogenesis of feline hyperthyroidism is not yet fully understood, the four common therapeutic modalities that can be implemented individually or in combination for management are surgical thyroidectomy, radioactive iodine, pharmaceutical therapy and dietary therapy using a limited-iodine diet. Regular monitoring of a hyperthyroid cat is important to assess therapeutic efficacy, to detect iatrogenic hypothyroidism and to confirm comorbidities that become evident with resolution of the hyperthyroidism.

Thyroid gland is an endocrine gland located at the neck area. In cats, this gland has two lobes connected by an indistinct isthmus. The functional unit of the gland is the thyroid follicle and the three hormones produced are triiodothyronine (T3), thyroxine (T4) and calcitonin. Secretion of T3 and T4 are regulated by the thyroid-stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH) produced by the pituitary gland and hypothalamus, respectively. Ectopic or accessory thyroid tissue is relatively common in many species including cats and may be located anywhere from the larynx to the diaphragm. Hyperthyroidism is characterized by the overproduction of thyroid hormone and a subsequent increase in metabolic rate.

Incidence

The most common endocrinopathy in cats is hyperthyroidism. It became evident first about four decades ago (Peterson *et al.*, 1979; Holzworth *et al.,* 1980). The prevalence of feline hyperthyroidism has steadily increased worldwide since those first reports and is now diagnosed in 1.5 to11.4 per cent of older cats around the world (Miyamoto *et al.*, 2002; Wakeling *et al.*, 2005; Sassnau, 2006; De Wet *et al*., 2009; Peterson, 2012). Among middle-aged or older cats in the United States of America, its prevalence is up to 10 per cent (Peterson, 2012; Vaske *et al*., 2016).

The most common pathologic abnormality associated with hyperthyroidism in cats is functional thyroid adenoma involving one or both thyroid lobes (Holzworth *et al.,* 1980; Hoenig *et al.*, 1982; Gerber *et al.*, 1994). Most hyperthyroid cats have bilateral disease and studies indicated that removal of a functional adenoma might be followed by the development of a contralateral

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one. Scintigraphic evidence suggested that the adenoma could continue to grow if ablative surgery or radioiodine were not chosen for management of the initial mass (Peterson, 2012; Peterson and Broome, 2012; 2015). Malignant carcinoma was found at the time of initial diagnosis only in two per cent of hyperthyroid cats (Turrel *et al.,* 1988; Hibbert *et al*., 2009).

Etiopathogenesis

A clear picture of the various causes of hyperthyroidism in cats is not yet fully understood. Multiple factors play a role, but the relative importance of each is unknown (Scarlett *et al*., 1988; Kass *et al*., 1999; Wakeling *et al*., 2009; 2011). Genetics may influence susceptibility to hyperthyroidism. In one study, Siamese and Himalayan breeds were found to have diminished risk of developing hyperthyroidism (Kass *et al*.,1999). Changes in cat husbandry over the past several decades, including a higher percentage of indoor cats, increased utilization of commercial cat foods and longer lifespans, may influence the prevalence (Scarlett *et al*., 1988; Kass *et al*., 1999; Wakeling *et al*., 2009).

The occurrence of bilateral thyroid disease strengthens the hypotheses of dietary and environmental etiologies than mutational causes alone (Hammer *et al*., 2000). Lifelong exposure to environmental thyroid disruptor chemicals or goitrogens through food or water may lead to euthyroid goiter and then to autonomous adenomatous hyperplasia, thyroid adenoma and hyperthyroidism (Peterson, 2012). Epidemiologic studies have identified a list of compounds like phenols and halogenated hydrocarbons having association with the incidence. The use of deodorized litter material and/or canned food that may contain bisphenol A and phthalates also have been associated with feline hyperthyroidism (Kang and Kondo, 2002; Edinboro *et al*., 2004; Peterson, 2012). Soy isoflavones, a component of many cat foods and the common environmental contaminant fire-retardant polybrominated diphenyl ethers may act as goitrogens via TSH stimulation or as direct mitogens (Court and Freeman, 2002; Guo *et al*., 2012; Mensching *et al*., 2012; Norrgran *et al*., 2012). Variable iodine content of cat foods also seems to have an influence on the development of the disease (Edinboro *et al*., 2010; 2013; Wedekind *et al*., 2010). So far, prospective evaluation of the effect of lifelong exposure to a specific compound in development of hyperthyroidism in cats has not been studied in detail and hence all associations are assumptions (Carney *et al*., 2016). A recent study to identify associations between coat phenotype and feline hyperthyroidism by investigation of breed, coat colour and hair length as risk factors, identified decreased risk of hyperthyroidism in the Tonkinese, Abyssinian and British shorthair breeds. It also identified an association between risk of hyperthyroidism and hair length and confirmed decreased risk in Burmese, Siamese, and Persian breeds (Crossley *et al*., 2017).

Clinical symptoms

The common signs of feline hyperthyroidism include progressive weight loss in spite of a ravenous appetite (polyphagia), polyuria, polydipsia, increased vocalization, aggressive behavior, agitation, restlessness, hyperactivity, tachypnea, tachycardia, periodic vomiting, diarrhea, weakness, depression and a poor unkempt hair coat (Bruyette, 2013; Carney *et al*., 2016).

Diagnosis

Diagnosis of feline hyperthyroidism is based on presence of one or more clinical signs and increased serum total T4 concentration. However, up to 10 per cent of all hyperthyroid cats and 40 per cent of those with mild disease have serum T4 values within the reference range (Broussard *et al*., 1995; Peterson *et al*., 2001). Hyperthyroidism should not be excluded based on a single normal serum T4 value especially in a cat with typical clinical signs, a palpable thyroid nodule and serum T4 in the upper half of the reference range (Peterson *et al*., 1987). In these cases, serum free T4 (fT4) measured by equilibrium dialysis may provide an alternative approach to diagnosis. Studies document that up to 20 per cent of sick euthyroid cats can have increased fT4 concentrations (Wakeling *et al*., 2008). Therefore, it is appropriate and reliable to interpret the total T4 and fT4 values together. Mid to high serum total T4 (grey zone)

and increased fT4 concentration are consistent with hyperthyroidism. A definitive diagnosis of feline hyperthyroidism requires demonstration of persistently elevated thyroid hormone concentrations (T4, or T4 plus fT4) occurring concurrently with one or more of the typical clinical signs. Differential diagnoses for cats with clinical signs similar to hyperthyroidism should include diabetes mellitus, gastro-intestinal malabsorption or maldigestion, neoplasia, chronic kidney disease and parasitism (Carney *et al*., 2016).

Management options

Being a life-threatening disease, hyperthyroidism in cats requires prompt veterinary attention. The choice of therapy often depends on factors such as age of the affected cat, comorbidities like renal, heart disease and hypertension, cost of the treatment, availability of treatment options and the clinician's recommendations and expertise. The goal of therapy is to restore euthyroidism, avoid hypothyroidism and minimize side effects of treatment. As a rule, treat all cats diagnosed with hyperthyroidism and monitor them prudently (Carney *et al*., 2016).

In general, there are four methods for managing feline hyperthyroidism. One is a permanent solution through thyroidectomy. This has more than 90 per cent cure rate if both glands are removed and 35 to 60 per cent cure rate if one gland is removed. It cures disease within one to two days post-surgery and the relapse rate is about five per cent in bilateral procedure and 30 per cent in unilateral procedure. The disadvantages of surgical thyroidectomy include increased risk involved in general anesthesia of a cat with a compromised cardiovascular system, damage to parathyroid gland and subsequent transient or permanent calcium crisis. The procedure requires hospitalization, is not reversible and most hyperthyroid cats require stabilization first with medication prior to the surgery. The voice or purr of the cat may change after the surgery (Carney *et al*., 2016).

The gold standard treatment for feline hyperthyroidism is radioactive iodine. After administration, it is actively concentrated by the thyroid gland, with a half-life of eight days. Even though, it emits both beta-particles and gamma-radiation, the beta-particles are responsible for most of the local tissue destruction traveling a maximum of two millimeter. Therefore, no significant damage to adjacent parathyroid tissue, atrophic thyroid tissue, or other cervical structures is expected (Bruyette, 2013). It kills abnormal cells in any locations and the cure rate is more than 95 per cent. This is the most successful treatment for thyroid carcinoma and the relapse rate is only five per cent. The treatment is simple consisting of one injection or oral capsule and serious side effects are rare. Limited testing is needed after successful treatment with minimal risk of permanent hypothyroidism. The main limitation to widespread use of radioactive iodine is the requirement for special licensing from the local regulatory authority and isolation of the cat after treatment, which can range from several days to several weeks depending on local radiation regulations and the dose administered. (Mooney, 2010; Carney *et al*., 2016).

Medical management of hyperthyroidism through daily administration of antithyroid medications *via* oral or transdermal route is the most widely used. These drugs can be used long term as a sole treatment or short term to stabilize the patient before any surgery or anesthesia or if radioiodine therapy is not immediately available (Mooney, 2001; Trepanier, 2007). Two pharmacologically active ingredients are available as licensed veterinary drugs for treatment of hyperthyroidism, methimazole and carbimazole (Carney *et al*., 2016). Methimazole acts by blocking thyroid peroxidase, thus inhibiting biosynthesis of thyroid hormones (Trepanier *et al*., 1991). Methimazole is thought to accumulate in the thyroid glands of cats as in humans (Trepanier *et al*., 1991; Okuno *et al*., 1987). Oral methimazole is well absorbed in healthy cats and the pharmacokinetic parameters are not significantly altered by hyperthyroidism (Trepanier *et al*., 1991). Carbimazole is a metabolite of methimazole that has a similar mechanism of action as well as side effects (Frénais *et al*., 2009). The most severe, but rare, side effects observed with

methimazole are hepatopathy and marked blood dyscrasias such as severe leucopenia, anemia and thrombocytopenia. Gastro-intestinal upset, lethargy and facial pruritus occur at variable frequency. Occurrence, frequency and severity of side-effects have not been shown to be dose related (Peterson *et al*., 1988; Hill *et al*., 2011). Gastro-intestinal upset may be less frequent with transdermal preparations (Hill *et al*., 2011). Most side effects appear within the first four to six weeks of therapy and are less common after two or three months of treatment (Peterson *et al*., 1988). The advantages of medical management include a response rate of more than 95 per cent while on medication in the form of small pills, liquid or topical gel. This does not require hospitalization and there is no risk of permanent hypothyroidism. Medication can be discontinued or dosage can be reduced if kidney function declines. Disadvantages include a relapse rate 100 per cent when the medication is off, daily medication for the rest of the cat's life and frequent laboratory tests to monitor effectiveness and safety. Drug reactions in the form of facial itching, vomiting, liver failure, abnormal blood cell levels and bleeding episodes may occur in up to 25 per cent of cats. Even with the treatment, the tumour continues to grow and may become malignant (Carney *et al*., 2016).

Limited iodine diets can also be given to normalize thyroid hormone concentrations and alleviate clinical signs of hyperthyroidism. Production of thyroid hormone requires sufficient dietary iodine. The only known function for ingested iodine is for thyroid hormone synthesis (Peterson, 2008). This observation led to the hypothesis that limiting dietary iodine intake could be used to control thyroid hormone production and potentially manage hyperthyroidism in cats. This option is simple and straightforward requiring only a change in diet. The response rate is more than 82 per cent while on the diet and is safe in cats with renal insufficiency. Absolutely the only food the cat can eat for the rest of its life will be limited iodine diets and has to be fed with low iodine treats and water as well. The relapse rate is cent per cent when the cat is off the special diet (Carney *et al*., 2016).

Conclusion

Hyperthyroidism, the most common endocrine disorder in cats, first became evident about four decades ago. Its prevalence has steadily increased over the past years reaching about 10 per cent among the older cat population. Even though, thyroid adenoma involving one or both lobes being the most common pathologic abnormality associated with feline hyperthyroidism, the etiopathogenesis is not yet fully understood. Being a life-threatening disease in cats, it requires prompt veterinary attention. Surgical thyroidectomy, radioactive iodine treatment, pharmaceutical therapy and dietary therapy using limited-iodine diet are the four common therapeutic modalities that can be implemented individually or in combination for management of feline hyperthyroidism.

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