Review of Etiologic Hypotheses for Feline Hyperthyroidism

Amy Lynn
Advisor: Dr. Nathan L. Dykes
Clinician: Dr. Richard E. Goldstein
Senior Seminar paper
Cornell University College of Veterinary Medicine
August 24, 2005

Review of Etiologic Hypotheses for Feline Hyperthyroidism

Summary

Feline hyperthyroidism (FH) was first reported in 1979 and is now recognized as the most common feline endocrinopathy. The pathogenesis of the disease remains unclear despite numerous epidemiological and molecular studies reported since that first case. Whether FH is a new disease, an epidemic of a rare disease, or can be attributed to an older cat population, increased veterinarian and owner awareness, or improved diagnostic testing is not known.

Several risk factors for FH have been identified but none has proven to be both necessary and sufficient to cause the disease. The cause of FH is likely multifactorial.

Introduction

FH was rarely diagnosed prior to 1979 but is the most common endocrinopathy of cats today. Reportedly, benign functional adenomatous hyperplasia of the thyroid gland is the most frequent diagnosis (98%) and is often (70-80%) bilateral[1]. The typical histopathological findings are comparable to the second most common thyroid disorder in people, toxic nodular goiter or Plummer's Disease. The cause of toxic nodular goiter is not well understood and most commonly affects older women[2,3]. Similarly, in cats, older animals are most commonly affected (range 4-22 years, mean 13 years), but a gender predilection is not recognized[1]. The pathogenesis of the feline disease remains unknown despite numerous epidemiological and molecular studies reported since 1988[4]. Whether FH is a new disease, an increased incidence of a rare disease, or can be attributed to the aging of the feline population, increased owner and veterinarian awareness, or improved diagnostic testing is still not known.

Environmental, genetic, and nutritional risk factors for FH have been identified but none has proven to be both necessary and sufficient to cause the disease. The cause of FH is most likely multifactorial.

Case Study

A 15 year old female spayed Domestic Shorthair cat was referred to Cornell University Hospital for Animals on 5/10/2005 for treatment with radioiodine. The referring veterinarian had examined the cat two weeks prior to evaluate an approximately 6 week history of weight loss, vomiting, and decreased activity. The cat is part of a multiple cat household making observation of appetite, thirst, and elimination habits difficult. Another cat in the house had been treated with radioiodine for hyperthyroidism in 2004.

During physical exam, the cat was alert and sociable. The body condition score was 2/5, a grade 3/6 systolic heart murmur was ausculted, and the thyroid glands were enlarged bilaterally. Results of laboratory examinations included a mild normocytic normochromic anemia (PCV=32%), minimal elevation of alanine aminotransferase (202 U/L; rr=29-186 U/L), and mildly elevated total thyroxine (TT4) (9.4 μg/dl; rr=1.5-4.0 μg/dl). A urinalysis and urine specific gravity (USG) were within normal limits (USG > 1.060). A 6-lead electrocardiogram was recorded and interpreted as normal. Thoracic radiographs were unremarkable. Thyroid scintigram depicted increased activity in both thyroid lobes of the thyroid gland (left more severely affected than the right). The findings ware attributed to feline hyperthyroidism with no contraindications to radioiodine treatment found.

Treatment with radioiodine (I-131; 5 mCi, SQ) was done on the 3rd hospital day and the cat was hospitalized until the radioactive exposure rate was less than 0.5 mRem/hr at one foot from the thyroid gland and less than 200 μCi remained in the body (as per NYS DOH and Cornell University Environment Health and Safety license regulations). The TT4 at discharge (15th hospital day) was 0.98 μg/dl. Three months later there was no vomiting, body weight was normal, and the TT4 was 2.8 μg/dl.

History of Feline Hyperthyroidism

FH was rarely recognized prior to 1979 but the incidence has steadily increased since then. A summary of several major studies of thyroid disease of companion animals prior to the first reported cases of FH in 1979 follows so that the emergence of the disease can be better understood.

An early study of thyroid disease in dogs and cats[5,6] examined 54 abnormal thyroid glands from cats who had presented to Angell Memorial Animal Hospital (AMAH) in Boston, MA over a 10 year period. Clinical signs of hyperthyroidism were described in only one cat and the age of the cats was not disclosed. Histopathologic examination of the glands diagnosed 5 adenomas. The authors concluded that the majority of the abnormal thyroid glands had normal function and that gross enlargement of the glands was rare.

In 1964, Lucke[7] studied 75 cat thyroid glands obtained at necropsy from cats in the Bristol, England area. Clinically, thyroid disease was not diagnosed in any cat, but histologically, 23 adenomas were found with only 3 glands grossly enlarged. Although the age of most of the cats was not reported, the 3 cats with gross thyroid enlargement were at least 13 years old. The clinical signs reported for at least 2 of these 3 cats were likely due to hyperthyroidism even though this disease was not on the differential diagnosis lists of the veterinarians at that time. Lucke concluded that although the majority of the thyroid lesions were of little clinical importance, not all of the thyroid lesions were incidental.

Leav et al[8] reported on a retrospective study of 52 thyroid tumors in cats presented to AMAH from 1949-1973 during which time 3,562 cats had been examined. He reported 47 adenomas and 5 adenocarcinomas of which 5 adenomas had been detected in the live cat. The average age of cats with adenoma was 12.4 years and 15.8 years for cats with adenocarcinomas. It was concluded that clinical signs were rare in cats with thyroid lesions, however no documentation was available for those cats that did exhibit clinical signs.

In 1979 Peterson et al[9] reported on 5 cats between the ages of 11-15 years undergoing hemithyroidectomy at the Animal Medical Center (AMC) in New York City. This is the first report of the disease as recognized today. All of the cats had elevated TT4 levels and displayed clinical signs consistent with FH. Histopathology of the removed thyroid lobes described adenomas in all samples. TT4 and clinical signs normalized in all cats post

surgery. Peterson concluded that functional thyroid tumors do occur in the cat and that surgery is an effective treatment.

Closely following Peterson's report, Holzworth et al[10] reported in 1980 on 10 cats between the ages of 10-14 years diagnosed with FH at AMAH from 1976-1978. All of the cats displayed clinical signs of FH and had elevated TT4. Histopathology of the removed tissue revealed benign adenomatous hyperplasia in 8 of the cats and adenocarcinoma in 2. The paper concluded that toxic thyroid tumors do occur in cats. An addendum to this report stated that within the 6 months following submission of the report and its publication, 16 more cases of FH were diagnosed at AMAH.

Discussion

The increased recognition of FH during a relatively short period caused investigators to ask whether the increased incidence of the disease might be due to increased veterinarian and owner awareness. The number of cats older than 7 years of age presenting to veterinarians did slowly increase from 1978-1986[4]. This may partially explain the increased reporting of FH since more veterinarians were examining older cats who are at increased risk of having FH.

Some argued that the increased reporting of FH could be due to the availability of improved diagnostic tests. The TT4 assay is considered the gold standard for diagnosing FH. The assay used in the cat is the same as that used for people and was developed in the early 1970's but was not applied to cats until the late 1970's[11], precisely the same time as the first reports of FH. The availability of a new test may partially explain the increased recognition of FH. However, many clinicians contend that the diagnosis of FH is not based solely on the results of the T4 assay but also in conjunction with the overt clinical signs that most hyperthyroid cats display[3].

Whether the increased incidence of FH is due to an aging of the cat population has been explored. Edinboro et al[3] looked at the incidence of 3 common diseases of older cats reported at 9 veterinary teaching hospitals from 1978 to 1997. The 3 diseases surveyed

included hyperthyroidism, diabetes mellitus, and renal disease, The incidence of FH increased significantly more than the incidence of diabetes mellitus and renal disease, suggesting that the increased incidence of FH is not due solely to the aging of the cat population.

Causes for new diseases or epidemics of an existing disease are many, and include infectious or environmental agents, changes in lifestyle or demographics, genetic mutations, or dietary excesses or insufficiencies. Numerous epidemiological and molecular studies have considered whether FH may be a new disease or an epidemic of an existing disease. Generally, the goal of epidemiological studies is not to find a cause for a disease but rather to identify risk factors associated with increased incidence of the disease that will help to guide future research.

No study since the first report of FH in 1979 has identified an infectious agent associated with FH[12]. Although occasional household clusters of disease are found, as in this case report, these disease clusters could also be caused by genetic, environmental, or nutritional factors[13], or be completely coincidental.

Although the first reports of FH came from the east coast of the United States (US), the Veterinary Medical Data Base (VMDB), which is a repository of diagnoses made at veterinary teaching institutions across North America, shows that in the early 1980s the veterinary teaching hospital at the University of California, Davis had the highest incidence of FH and the midsection of the country the lowest incidence[4,14]. Today, FH is commonly reported in Europe, Australia, and New Zealand[15]. In New Zealand, researchers have found that the risk factors associated with the disease in New Zealand cats are similar to those associated with FH in US cats even though cats in New Zealand are relatively isolated[2]. However, as of 2000, there have been only 2 reported cases of FH in Israel[16]. These chronological and geographical observances should be kept in mind as risk factors for FH are explored.

Several investigators have looked at the role that environment and lifestyle may have on the incidence of FH[2,4,17] . Researchers have looked at many possible risk factors including exposure to tobacco smoke, vaccination administration, and water source. None of these factors were found to increase the risk for developing FH, but an increased risk of developing FH has been associated with cats exposed to flea sprays and powders, and lawn fertilizers, pesticides and herbicides. An increased incidence of FH has also been found in cats who use cat litter and who live strictly indoors. Whether some of these risk factors are linked remains to be shown.

Siamese and Himalayan cats have been found to have a decreased risk of developing FH[2,4,17]. These are genetically related breeds, so this finding suggests there may be genetic risk factors. Two reports showed that female cats had an increased risk for developing FH[2,3], however, other investigators failed to show any gender predilection for the disease[4,17,18]. In people, hyperthyroidism affects 3-5 times as many women as men[3].

At the molecular level, Merryman et al[19] looked at the role proto-oncogenes may play in the development of FH. The researchers studied 18 thyroid glands from cats diagnosed with FH and found an overexpression of c-Ras in areas of nodular follicular hyperplasia and adenomas in all of the specimens. c-Ras is a G-protein that induces mitogenesis in cells. The authors concluded that overexpression of the c-Ras protein, presumptively due to a mutation in its gene, c-ras, may contribute to the development of FH.

Other investigators have looked at the stimulatory and inhibitory G proteins, G_s and G_i respectively[20,21]. It is generally believed that these proteins regulate the level of intracellular cyclic AMP (cAMP). cAMP regulates thyroid gland mitogenesis and hormone production with G_s increasing and G_i decreasing cAMP levels. Although no change in expression of G_s was found, a mutation was found in its gene. A decreased expression of G_i was found but its functionality was not examined. Decreased levels of G_i may lead to increased cAMP levels and thus to excess hormone production. Peeters et al[21] also studied the thyrotropin receptor (TSH R) and found no mutation in its gene. This

finding differs from human thyroid disease where mutations in the TSH R gene are common.

Because domestic cats are the only mammal other than humans to develop hyperthyroidism with any frequency and because the histopathology of the lesions associated with FH resemble those of toxic nodular goiter in people, many investigators involved in research on human thyroid disorders have looked to the cat as a potential animal model for human thyroid disorders. The fact that FH more commonly affects both thyroid lobes suggests that a circulating factor may be involved in the etiopathogenesis of the disease. This suggests that circulating factors may play a role in the development of FH because such factors have been identified in human thyroid diseases[22].

The most common human thyroid disease is Graves' disease. People with this disorder have circulating thyroid stimulatory immunoglobulins (TSIs) that mimic TSH and stimulate adenylate cyclase, thus increasing intracellular cAMP. In 1987, Peterson et al[23] showed that TSIs that increase intracellular cAMP levels are not present in hyperthyroid cats by showing that intracellular cAMP levels did not increase in rat thyroid cells when incubated with immunoglobulin extracted from hyperthyroid cat sera. Further research in this area in 1992[22] did reveal that circulating TSIs are present in some hyperthyroid cat sera but do not mediate growth via an adenylate cyclase mechanism. Further, the growth promoting effects of the TSIs in the cat sera were relatively weak and only identified by using very sensitive assays. These findings suggest that FH is similar to toxic nodular goiter in people, since it is believed that there is an immunological component involved in the development of the human disease.

Kennedy and Thoday[24] found circulating thyroid autoantibodies in 48% of hyperthyroid cat sera, although their pathogenic role, if any, is not understood and does not indicate that FH is an autoimmune disorder. This finding lends further credence to the belief that FH is similar to toxic nodular goiter in people since thyroid antibodies are commonly seen in the human disease.

Nutritional risk factors have been intensively investigated. An increased risk for developing FH has been identified in cats who eat canned food[4,17], eat a variety of flavors of canned cat food[2], eat specific varieties of canned food such as fish or liver and giblets[18], and who eat canned cat food from cans having a pop-top lid[3]. These findings suggest that there is something in the food or in the cans that is a risk factor for FH. Several researchers[3,25] investigated bisphenol A, a chemical used in the can coating process. Bisphenol A has been found in canned foods meant for human consumption with higher concentrations found in canned meat and fish[26]. Bisphenol A has been classified as an endocrine disrupter with estrogenic activity by the Environmental Protection Agency (EPA) and has been shown to reduce triiodothyronine (T3) binding to thyroid receptors in rat liver[3]. The EPA has set a maximum concentration for bisphenol A in food meant for human consumption. Kang et al[25] looked at 15 brands of canned cat foods and found that bisphenol A was present in all of the foods, though the level of bisphenol A was below the maximum level established for human foods by the EPA. An important point to consider is that bisphenol A is primarily eliminated via glucuronidation, a process known to be slow in cats[3].

Other dietary constituents explored and their possible association with FH include iodine, selenium, and soy. Both excessive and insufficient iodine intake causes goiter in people[27], but there is little data available for the recommended levels of iodine intake for cats[27, 28, 29,]. The iodine content in commercial cat foods has been shown to fluctuate widely. The iodine content of 28 varieties of canned and dry cat foods available in New Zealand was found to vary 100 fold, with many varieties either above or below the reference range. In the US, some commercial cat foods have been found to contain 10 times the recommended levels of iodine[29]. Although many commercial cat foods are supplemented with iodine[28], sources of additional iodine may be from artificial food dyes that release free iodine during processing and the inclusion of thyroid tissue from slaughtered animals[4,30]. In humans, the thyroid contains 70-80% of the body's store of iodine, so assuming this is true in farm animals, inclusion of offal containing thyroid gland in cat foods could significantly increase the iodine content of the food[30].

Tarttelin et al[31] fed cats food containing either high or low iodine content for a period of 2 weeks or 5 months. In the short term feeding trial, a dramatic thyroid response was seen. Free T4 (fT4) levels responded inversely with the iodine content consumed. In the long term feeding trial, no change in fT4 was found. This suggests that there are adaptive mechanisms in the cat that can act to maintain normal fT4 levels in chronic states of excessive or insufficient iodine intake. The investigators concluded by suggesting that long term feeding of food with varying iodine content may lead to thyroid activation and possibly FH[31,32].

Selenium (Se) is a vital component of glutathione peroxidase, an important antioxidant in the body, and is also a constituent of deiodinases, which are involved in the conversion of T4 to T3. Foster et al[33] assessed the Se status of cats in 4 geographic regions, 2 of which had a high incidence of FH (United Kingdom, eastern Australia) and 2 of which had a low incidence of FH (Denmark, western Australia). No difference in the plasma Se concentration was found among the cats in the study and the Se levels did not appear to affect the incidence of FH. One unexpected finding of the study was that cats have a plasma Se concentration 5 times greater than the concentration found in rats and humans. The investigators concluded that the Se concentration of cat foods be reassessed and possibly lowered[33].

Soy is a potential goitrogen in people[34] but only in its raw form[35]. White et al fed cats a high soy diet for a period of 3 months and was able to produce a measurable increase in serum fT4 and TT4 but no change in serum T3 levels. Hyperthyroidism developed in 4 of the 18 cats in the study (fT4 levels above the reference range)[34].

Because FH probably takes a long time to develop and because it still affects only a small percentage of the cat population, laboratory-based research is difficult to stage, fund, and justify. Rather, additional epidemiological studies could be undertaken in multiple geographic locations to investigate risk factors already identified and look for additional risk factors. The nutrient requirements of cats should be more critically defined so that

dietary excesses or insufficiencies can be eliminated in commercial cat foods. Molecular studies can offer understanding of FH at the cellular and genetic level.

Acknowledgements:
The author wishes to express her gratitude to the following individuals at Cornell University for sharing their expertise in the epidemiology, treatment, and etiology of FH: Nathan L. Dykes, DVM DAVCR, Chief, Section of Veterinary Imaging; Jeff Hobbs, LVT, Section of Veterinary Imaging; Janet M. Scarlett, DVM, MPH, PhD, Professor of Epidemiology; Francis A. Kallfelz, DVM, DACVN, James Law Professor of Medicine (Nutrition); Richard E. Goldstein, DVM, DACVIM, DECVIM, Assistant Professor, Small Animal Medicine; Elizabeth L. Buckles, DVM, MS, PhD, Assistant Professor, Pathology.

References

[1] Feldman EC, Nelson RW. Chapter 4 Feline Hyperthyroidism (Thyrotoxicosis). *Canine and Feline Endocrinology and Reproduction*. Third Edition 2004.152-218.

[2] Olczak J, Jones BR, Pfeiffer DU et al. Multivariate analysis of risk factors for feline hyperthyroidism in New Zealand. *New Zea Vet J.* 2004;53(1):53-58.

[3] Edinboro CH, Scott-Moncrieff JC, Janovitz E et al. Epidemiologic study of relationships between consumption of commercial canned food and risk of hyperthyroidism in cat. *J Am Vet Med Assoc.* 2004;224:879-886.

[4] Scarlett JM, Moise NS, Rayl J. Feline hyperthyroidism: A descriptive and case-control study. *Prev Vet Med* 1988;6:295-309.

[5] Meier H, Clark S. A clinico-pathological study of thyroid disease in the dog and cat. Part I: Thyroid pathology. *Zentralbl Veterinämed*. 1958;5:17-32.

[6] Meier H, Clark S. A clinico-pathological study of thyroid disease in the dog and cat. Part II: Clinical features. *Zentralbl Veterinämed*. 1958;5:120-128.

[7] Lucke VM. An histological study of thyroid abnormalities in the domestic cat. *J Sm Anim Pract* 1964;5:351-358.

[8] Leav I, Schiller AL, Rijnberk A et al. Adenomas and carcinomas of the canine and feline thyroid. *Am J Path.* 1976;83:61-93.

[9] Peterson ME, Johnson GF, Andrews LK. Spontaneous hyperthyyroidism in the cat. *Proc ACVIM*.. 1979:108.

[10] Holzworth J, Theran P, Carpenter JL et al. Hyperthyroidism in the cat: ten cases. *J Am Vet Med Assoc.* 1980;176:345-353.

[11] Schanbacher B. Endocrine laboratory, Animal Health Diagnostic Laboratory, Cornell University College of Veterinary Medicine. personal communication. 2005.

[12] White HL, Freeman LM, Mahony O et al. Effect of dietary soy on serum thyroid hormone concentrations in healthy adult cats. *Am J Vet Res.* 2004;65:586-591.

[13] Scarlett JM. Epidemiology of thyroid diseases of dogs and cats. *Vet Clin NA SA.* 1994;24(3):477-487.

[14] Gerber HG, Peter H, Ferguson DC et al. Etiopathology of feline toxic nodular goiter. Vet Clin NA SA. 1994;24(3):541-565.

[15] Ferguson DC. Pathogenesis of Hyperthyroidism. *Consultations in Feline Internal Medicine*. 1994;133-141.

[16] Goldstein, RE. Internal Medicine Service, Cornell University College of Veterinary Medicine. personal communication. 2005.

[17] Kass, PH, Peterson ME, Levy J et al. Evaluation of environmental, nutritional, and host factors in cats with hyperthyroidism. *J Vet Intern Med* 1999;13:323-329.

[18] Martin, KM, Rossing MA, Ryland LM et al. Evaluation of dietary and environmental risk factors for hyperthyroidism in cats. J Am Vet Med Assoc. 2000;217(6):853-856.

[19] Merryman JI, Buckles EL, Bowers G et al. Overexpression of c-Ras in hyperplasia and adenomas of the feline thyroid gland: an immunohistochemical analysis of 34 cases. *Vet Pathol* 1999;36:117-124.

[20] Hammer KB, Holt DE, Ward CR. Altered expression of G proteins in thyroid gland adenomas obtained from hyperthyroid cats. *Am J Vet Res*. 2000;8:874-879.

[21] Peeters ME, Timmermans-Sprang EP, Moi JA. Feline thyroid adenomas are in part associated with mutations in the $G_{s\alpha}$ gene and not with polymorphisms found in the thyrotropin receptor. *Thyroid*. 2002;12(7):571-575.

[22] Brown RS, Keating P, Livingston P et al. Thyroid growth immunoglobulins in feline hyperthyroidism. *Thyroid*. 1992;2(2):125-130.

[23] Peterson ME, Livingston P, Brown RS et al. lack of circulating thyroid stimulating immunoglobulins in cats with hyperthyroidism. *Vet Immunol Immunopathol*. 1987;16:277-282.

[24] Kennedy RL, Thoday KL. Autoantibodies in feline hyperthyroidism. *Res Vet Sci*. 1988;45:300-306.

[25] Kang J, Kondo F. Determination of bisphenol A in canned pet foods. *Res in Vet Sci*. 2002;73:177-182.

[26] Hammarling L, Gustavsson H, Svensson K et al. Migration of bisphenol-A diglycidyl ether (BADGE) and its reaction products in canned foods. *Food Add Cont.* 2000;17(11):937-943.

[27] Kyle AHM, Tarttelin MF, Cooke RR, et al. Serum free thyroxine levels in cats maintained on diets relatively high or low in iodine. *N Zea Vet J*. 1994;42:101-103.

[28] National Research Council. *Nutrient requirements of dogs and cats.* prepublication copy. 204-206.

[29] Johnson IA, Ford, HC, Tarttelin MF et al. Iodine content of commercially-prepared cat foods. *N Zea Vet J.* 1992;40:18-20.

[30] Mumma RO, Rashid KA, Shane BS et al. Toxic and protective constituents in pet foods. *Am J Vet Res.* 1986;47(7):1633-1637.

[31] Tarttelin MF, Ford HC. Dietary iodine level and thyroid function in the cat. *J Nutr*. 1994;124:2577S-2578S.

[32] Ranz D, Tetrick M, Opitz B, et al. Estimation of iodine status in cats. *J Nutr*. 2002;132:1751S-1753S.

[33] Foster DJ, Thoday KL, Arthur JR et al. Selenium status of cats in four regions of the world and comparison with reported incidence of hyperthyroidism in cats in those regions. *Am J Vet Res*. 2001;62(6):934-937.

[34] White HL, Freeman LM, Mahony O et al. Effect of dietary soy on serum thyroid hormone concentrations in healthy adult cats. *Am J Vet Res*. 2004;65(5):586-591.

[35] Kallfelz FA. Cornell University College of Veterinary Medicine. personal communication. 2005.