The Many Faces of Hyperthyroidism

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Introduction

Hyperthyroidism is the most common endocrine disorder of cats.[1,6] This disease affects older cats with the average age being 13 years.[1] The most common cause of feline hyperthyroidism is functional adenomatous hyperplasia of the thyroid gland or a thyroid adenoma which leads to excessive secretion of thyroid hormones T3 and T4..[1,6] It is most commonly a bilateral disease, with approximately 70% affecting both thyroid glands.[7] Thyroid carcinoma is the main cause of hyperthyroidism in dogs, but accounts for only 1-2% of feline hyperthyroid cases.[1] Although the exact pathogenesis for thyroid adenomas is not known, many risk factors have been hypothesized including environmental and dietary factors.[1,7]

Common clinical signs include weight loss, polyphagia, hyperexcitability, polyuria and polydipsia. GI signs including vomiting and diarrhea are also commonly seen.[9] Feline hyperthyroidism is associated with hypertension in about 80% of cases and affects ocular, cardiovascular, and renal systems.[1,5] Feline hyperthyroidism has also been associated with a reversable from of hypertrophic cardiomyopathy that occasionally leads to congestive heart failure in severe cases.[10]

Diagnosis is typically based on clinical signs and elevated thyroid hormone concentration.[1] Many treatment options exist for this endocrine disease. These include antithyroid medication, radiation therapy, surgical thyroidectomy, and diet modification. Treatment choice depends on multiple factors such as concurrent disease, ease of oral medications, and client financial limitations.[10] Some cases may need concurrent treatment for cardiovascular or renal disease. Prognosis is good with effective treatment and lifetime monitoring for recurrence and complications.[10]

History and Presentation

L.C. is a 17 year old, spayed female DSH who presented to MSU-CVM community veterinary services on 12/12/18 due to ataxia in her hindlimbs. The previous evening her owner noticed that she was ataxic and had trouble jumping up to use the litter box. She noticed that L.C. was running into things and was splaying her back legs. She has a history of an abscess on her neck on December 2017. She has previously been diagnosed with a grade II-III/VI systolic heart murmur.

On physical exam, L.C. was bright and alert. She was thin with a body condition of 4 out of 9 and had lost 1 kg of body weight since her visit one year prior to this visit. Her pulse was 112 beats per minute and her respiratory rate was 54 breaths per minute. Her mucous membranes were pale pink in color with a CRT of 2 seconds. No ocular or nasal discharge was seen. Ear debris and moderate dental tarter were noted. Her lungs auscultated normally and a grade III-IV/VI systolic heart murmur was noted parasternally, but louder on the left side. L.C.'s abdomen was soft when palpated, and she did not seem painful. Her skin appeared normal. All of her peripheral lymph nodes palpated normally. General ataxia and a head tilt to the left were seen as she walked. A horizontal nystagmus with fast phase to the right was noted on ocular exam. She was noted to have decreased conscious proprioception in the left hindlimb. Based on her clinical evidence of vestibular dysfunction and presence of proprioceptive deficits she was classified as having a left central vestibular lesion. The rest of her physical exam was uneventful. Our rule outs at this time included a vascular event secondary to underlying cardiac or endocrine disease, neoplasia, or infectious/inflammatory disease.

Diagnostic Approach

Presenting complaints for cats with hyperthyroidism include weight loss, polyphagia, diarrhea, vomiting, hyperactivity, polyuria and polydipsia.[1,3] In some cases, alopecia and poor hair coat may be seen.[10] Vomiting and GI signs can occur due to rapid eating or stimulation of the chemoreceptor trigger zone.[8] Physical exam can reveal a palpable thyroid slip, tachycardia with a murmur or gallop rhythm, poor body condition, and thin hair coat.[5] CBC may reveal polycythemia due to dehydration or increased erythropoietin production.[1,8] Occasionally neutrophilia, lymphopenia, and eosinopenia are seen.[8] A serum chemistry will typically show elevated liver enzymes ALT, ALP, and AST. In 90% of hyperthyroid cases, at least one of these liver enzymes is elevated.[6] Bone and liver contribute to increased ALP.[1] Elevated BUN and creatinine can be seen due to underlying renal disease.[1] Hyperphosphatemia is also common due to increased bone turnover.[1,6] Serum fructosamine can be increased due to the effect thyroid hormones have on protein metabolism.[1,9] Serum cobalamin levels are also lower in hyperthyroid cats when compared to normal cats.[2] One study measured cobalamin levels in 76 hyperthyroid cats and revealed that cobalamin concentration was elevated in 40.8% of hyperthyroid cats compared to 25% in the control group. This study suggests that cobalamin uptake or excretion is affected in hyperthyroid patients.[2]

Thyrotoxic cardiomyopathy, a form of reversable hypertrophic cardiomyopathy is frequently seen with feline hyperthyroidism.[5] In these cases, 20-30% will have cardiomegaly on radiographs. Many also have tachycardia and increased R wave amplitude on ECG.[1,6] Around 5% of patients with thyrotoxic cardiomyopathy will present with failure and can have pleural effusion and pulmonary edema.[1] Hypertension is also a common complication of this disease and can manifest as ocular signs such as hyphemia, retinal detachment, and retinal hemorrhage that may be seen on physical exam.[1,6] Hypercoagubility is a common side effect seen with

cardiomyopathy and hypertension, which causes thrombi formation. This can lead to pulmonary emboli and cerebral vascular events. [6]

The first screening diagnostic test is a total T4 concentration.[1,8] In rare cases, underlying disease will cause euthyroid sick syndrome and hyperthyroid patients will have a normal T4. Once the underlying disease is controlled, T4 levels will rise to be abnormal.[1] In cats with clinical signs but a normal T4, a free T4 by equilibrium dialysis can be measured. Free T4 concentration has a higher sensitivity but lower specificity than total T4 concentration. Therefore, it should only be used in combination with a total T4 in cats that have clinical signs of hyperthyroidism but normal total T4 concentration, and not used as a sole diagnostic test.[1] TSH is almost always undetectable in hyperthyroid cats and can sometimes be used to rule out the disease if it is able to be measured.[8] In cats that are clinical but have normal total T4 and fT4 levels, a T3 suppression test can be performed.[8] For this test, first baseline T3 and T4 concentrations are measured. Then, 25 mcg/cat of T3 is administered orally every 8 hours for 7 doses. Four to six hours after the last dose, T3 and T4 measurements are taken. Hyperthyroid cats do not suppress, where euthyroid cats will have a T4 of less than 50% of the baseline.[8]

The final diagnostic test for hyperthyroidism is radioactive thyroid scintigraphy.[8] This is helpful in diagnosing ectopic thyroid tissue. The most common isotope used is Technetium-99m because it has a rapid uptake by thyroid tissue. Hyperthyroid cats will have a rapid uptake. This test is also used to determine dosing for I-131 therapy.[8]

On the day L.C. presented to MSU-CVM, a CBC, chemistry, total t4, and urinalysis were performed. The CBC revealed no abnormal findings. The chemistry showed an elevated ALP and CK and a low globulin. Urinalysis showed 2+ protein with a specific gravity of 1.041. Total T4 was also elevated and indicative of hyperthyroidism. A doppler blood pressure was 130

mmHg. A neurological consult was performed with the MSU-CVM Neurology department and it was determined that L.C. was showing signs of left-sided, central vestibular disease. Potential causes for this disorder are a vascular event, infectious/inflammatory cause, or neoplasia. Unfortunately, this patient has historically limited veterinary care so it is unknown if the left pelvic limb proprioceptive deficit is historical or truly secondary to central vestibular dysfunction. Based on the severity of deficits, acute onset of neurological dysfunction, and lack of known issues with limb reported by owner it was assumed to be a new clinical finding. However, without definitive knowledge of previous neurological condition a left peripheral vestibular syndrome cannot be fully excluded for which differentials include inflammatory/infectious etiologies (otitis media/inerna), neoplasia, and idiopathic vestibular disease. Additional diagnostics including advanced imaging such as a CT or MRI would be required to further diagnose the cause of her symptoms. However, these were not performed due to financial constraints.

Pathophysiology

Feline hyperthyroidism occurs when the thyroid lobe excretes excessive amounts of thyroxine (T4) and triiodothyronine (T3) due to benign adenomatous hyperplasia.[7] This results in an increase in metabolic rate. Thyroid hormones play a role in growth and development, regulation of heat, metabolism of protein, carbohydrates, and fats, and increase the tone of the sympathetic nervous system.[8] In normal animals, the hypothalamus secretes thyrotropin releasing hormones (TRH) which causes thyroid stimulation hormone (TSH) to be released from the anterior pituitary which then causes release of T3 and T4 from the thyroid glands.[10] Thyroid hormones are formed from thyroglobulin and iodine obtained from the diet. In normal animals,

these hormones have a negative feedback effect on the pituitary to prevent overproduction of thyroid hormone.[10]

While the exact etiology of hyperthyroidism is unknown, possible environmental and dietary factors have been hypothesized. One study found that cats that eat mostly fish flavored canned food were at increased risk.[1] It also found that Siamese and Himalayan breeds had a decreased risk for developing the disease.[1,5] The study also suggested a 3 fold increase in risk among cats that use litter when compared to those who do not.[1] The expression of G(i) protein has been found to be significantly decreased in thyroid glands of hyperthyroid cats as opposed to euthyroid cats. It's been hypothesized that a decrease in this protein causes a reduction in the negative inhibition of cAMP resulting in hyperplasia.[1] The oncogene c-Ras has also been found to be overexpressed in thyroid adenomas, suggesting a role in the pathogenesis of hyperthyroidism.[1,8]

Thyrotoxic cardiomyopathy is a common occurrence in hyperthyroid cases. Excessive T4 hormones have direct ionotropic effects on cardiac muscles which cause hypertrophy of the left ventricle and interventricular septum, leading to systolic murmurs, tachycardia, and arrhythmias.[5,6] In addition, excessive thyroid hormone causes increased beta-adrenergic activity of the sympathetic nervous system, leading to hypertension, tachycardia and increased cardiac output.[6]. Hypertension is seen in 80% of cats with hyperthyroidism.[5] Hypertension can have ocular signs such as blindness from retinal detachment and lead to thromboembolism formation.[1,5]

Hyperthyroidism increases GFR and can therefore mask underlying renal disease.[4,6] In some cases, azotemia and signs of renal disease appear after effective treatment of hyperthyroidism.[6] One study of 36 cats compared IRIS stages of kidney disease before and after

treatment to determine the effects treating hyperthyroidism had on IRIS kidney stage.[4] They found that progression to the next level of CKD stage was common after treatment and that urine specific gravity was useful in predicting which patients would progress to the next stage. 79% of cats with post treatment creatinine of 1.5 mg/dl (stage 2 or 3) had a pretreatment USG of < 1.040, while 18% of cats with post treatment creatinine < 1.5 had USG of >1.040.[4]

Treatment and management

Many treatment options exist including antithyroid medication, nutritional management, radiation therapy, and surgical thyroidectomy.[3] Methimazole, a thioureylne drug, is the most commonly used antithyroid medication. It is commonly used in patients that have concurrent disease, with clients that have financial limitations, or as the first step to a permanent solution.[8] Methimazole is available as an oral or transdermal medication. Dosing starts at 2.5 mg/kg orally every 12 hours and cats typically return to normal thyroid hormone levels in 2-3 weeks.[8] Methimazole controls the overproduction of thyroid hormones but does not correct the underlying disease. Therefore, the thyroid adenoma may continue to increase in size and require dosing adjustments later in the patient's lifetime.[8] Adverse reactions are seen in 20% of patients taking Methimazole and include vomiting, anorexia, lethargy, and facial excoriations. Hematological side effects such as leukopenia and lymphocytosis can also be seen. CBCs should be checked periodically as these hematological complications are typically seen in the first 3 months of therapy.[8] Total T4 concentrations must be checked every 2-3 weeks initially until T4 is normalized to adjust dose as necessary, and then every 3-4 months as an increase in dose may be indicated as the thyroid adenoma grows in size.[8] Due to the possibility of hyperthyroidism masking underlying kidney disease, kidney values should be checked periodically. The dose of

Methimazole may need to be adjusted to lowest dose that controls the symptoms but maximizes renal fution.[6]

Dietary management is another treatment possibility. It consists of an iodine restricted diet of <.32 ppm of iodine.[8] One study showed a decrease to normal thyroid levels and improvement in clinical signs in 4 weeks after diet modification.[3] An example of an iodine restricted diet is Hill's y/d.[8] The biggest challenge to this treatment option is poor owner compliance. Contributing factors to poor compliance include other cats in the household eating different food, treats or flavored medications, human food, and prey caught from hunting.[8] This diet should not be fed in conjugation with antithyroid medication or hypothyroidism can result.

A more permanent solution to feline hyperthyroidism is surgical thyroidectomy. A bilateral thyroidectomy is usually performed due to the high incidence of bilateral disease.[8] Typically oral medical therapy is initiated before surgery to control thyrotoxicosis and check for underlying kidney disease. If renal disease is present, a permanent solution may not be the best solution because a balance between control of clinical signs and maximum renal function must be met.[8] Prior to surgery, radioactive thyroid scintigraphy is performed to determine which lobes are affected and to rule out ectopic thyroid tissue.[8] Possible complications include hypothyroidism, which is usually temporary, and hypoparathyroidism due to close proximity to the parathyroid glands. Therefore, calcium levels should be checked 3-5 days post-surgery and if hypocalcemia is present, it may require lifetime treatment.[9] T4 levels should also be checked periodically every 6-12 months, due to the possibility of recurrence that happens in 5-12% of thyroidectomy patients.[8]

The gold standard for treatment of feline hyperthyroidism is radioactive iodine, or I131 therapy.[9] I131 destroys functional thyroid tissue by emitting B particles.[8] This therapy is

especially useful in cases with ectopic thyroid tissue or thyroid carcinomas. However, it should be avoided in cases with concurrent renal disease. The success of returning to normal thyroid hormone levels is 90% in 5-10 days.[8] The downfall to this therapy is that the cats must remain in isolation for weeks after therapy until they are no longer emitting radioactive iodine in their urine.[8] This treatment is only available in select locations such as Washington State.

L.C. was given a subcutaneous injection of 0.34 mLs of Cerenia (Maropitant Citrate) and sent home on oral Methimazole 0.5 tablets every 12 hours for 30 days. It was recommended that L.C. return in one week to check for improvement in her neurologic signs and that she return in 2 weeks to check her thyroid levels and kidney values and adjust the dose of Methimazole as needed. Additional testing to determine the cause of her neurologic signs and heart murmur were offered but declined due to financial restraints.

Case Outcome

On December 19th L.C. presented for a recheck of her neurologic signs. L.C's neurological signs had improved since her last visit. She was less ataxic and no longer had a nystagmus, although she still had a head tilt to the left. Her previously noted proprioceptive deficits had resolved, which further supports our suspicion of a centralized vestibular lesion. She now had a grade II/VI systolic heart murmur.

She presented January 7 to recheck T4 levels and bloodwork to assess kidney values. Her CBC showed no abnormalities. Her serum chemistry showed a mildly low glucose, a moderately elevated ALP, and a mildly low globulin. Her ALP had decreased since her visit on December 12. L.C.'s T4 was mildly elevated but significantly lower than her visit on December 12. At this visit, she had a grade III-IV/VI systolic heart murmur. L.C. had been doing well at home but had

a few episodes of vomiting. Because GI upset is a side effect of Methimazole, her dose was decreased, and she was sent home with Cerenia and Omeprazole.

L.C. presented again on February 11 to recheck her thyroid hormone levels. Her T4 was mildly elevated. Her owners report she had been doing well at home and had no more episodes of vomiting. Her heart murmur held steady at a grade III-IV/VI. L.C. was kept at the same dose of Methimazole (Give 0.5 tablet orally in the morning, and then give 0.25 tablet orally in the evening) due to her improvement in clinical signs and T4 levels slowly returning to normal.

References

1. Bruyette, David., "Feline hyperthyroidism: Diagnosis and treatment" *Atlantic Coast Veterinary Conference*. 2012. https://www.vin.com/doc/?id=5540703
2. Cook AK, et al., "The prevalence of hypocobalaminaemia in cats with spontaneous hyperthyroidism." *Journal of Small Animal Practice.* 2011. Vol 52. No. 2 pp. 101-06. DOI:10.1111/j.1748-5827.2021.01027.x
3. Grossi, Giorgio. Et al., "Iodine-restricted food versus pharmacological therapy in the management of feline hyperthyroidism: A controlled trial of 34 cats." *Open Veterinary Journal*. vol. 9, no. 3, 02 Dec. 2019, pp. 196–204., http://dx.doi.org//10.4314/ovj.v9i3.3.
4. Harley LS., et al: "IRIS Stage of Chronic Kidney Disease Before and After Treatment with Radioiodine in Cats with Hyperthyroidism". *American College of Veterinary Internal Medicine*. 2011. https://www.vin.com/doc/?id=4902178.
5. "Hyperthyroidism Associated Cardiomyopathy." *Ethos Veterinary Health*. 2019. https://www.ethosvet.com/blog-post/hyperthyroidism-associated-cardiomyophathy/

6. Mooney, Carmel., “Complications and Consequences of Feline Hyperthyroidism.” *World Small Animal Veterinary Association.* https://www.vin.com/doc/?id=3850082.
7. Mooney, CT. “Pathogenesis of Feline Hyperthyroidism.” *Journal of Feline Medicine and Surgery*, vol. 4, no. 3, 1 September 2002, pp. 167–169., doi:10.1053/jfms.2002.0177.
8. Shell, Linda G. “Hyperthyroidism” *Vincyclopedia of Diseases*. 2014. https://www.vin.com/Members/Associate/Associate.plx?DiseaseId=895.
9. *The Merck Veterinary Manual*. Tenth edition. Merck & Co. Inc., 2010. pp. 512 – 513.
10. Walker, Jamie. “Feline Hyperthyroidism: An Overview.” *Veterinary Ireland Journal*. Vol. 5, No. 8, 1 August 2015, pp. 381-383.