Endocrine Update:
There's More to Cats Than Thyroids and Diabetes

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Adrenal diseases in catshyperadrenocorticism (hac, cushings disease)

Cushings is a disease of middle-aged to older cats (7-12 years), and may be caused by a pituitary tumor (90% are adenomas) or hyperplasia, adrenal tumors or hyperplasia, by non-endocrine tumors (usually lung) or may be iatrogenic. Clinical signs in cats may include uncontrolled diabetes, pendulous abdomen, lethargy, thin skin, recurrent infections and poor muscle mass. Thin skin is the hallmark of feline hyperadrenocorticism and these cats may develop open wounds just by grooming themselves. Severe insulin resistance may be present. Changes expected in the bloodwork are non-specific but include hypercholesterolemia, hyperglycemia, mild leukocytosis and erythroid regeneration (nrbcs). SAP and ALT will be elevated not from a steroid effect rather due to concurrent lipidosis or pancreatitis. Overt diabetes mellitus may result from the insulin antagonism caused by hypercortisolemia in about 85% of cats with HAC. Urinalysis changes include glucosuria, possibly a low usg and a secondary bacteruria.

Diagnosis

Adrenal gland suppression is tested using a "Low-dose dexamethasone test" but the dose is higher than that used in dogs. Administer 0.1mg/kg dexamethasone sodium phosphate IV and sample plasma at times 0,2,4,6 and 8 hours after injection because cats may escape suppression earlier than 8 hours. Normal cats and cats with non-adrenal illnesses will consistently show cortisol suppression at this dose. However, unlike dogs, it may not suppress cats with pituitary dependent HA. Thus, we can't use it to discriminate between adrenal tumours and PDHA in cats. Rather, the feline "High-dose" dexamethasone test", i.e. 1.0mg/kg dexamethasone IV and sampling at times 0,2, 4, 6 and 8 hours will differentiate PDHA from adrenal tumours in most cases. In the rare cat who doesn't suppress even at this dose, endogenous ACTH levels, abdominal ultrasound, CT or MRI are required to confirm the location of the tumour. Feline ACTH stimulation test: collect plasma at time 0, administer 2.2 units of porcine ACTH gel/kg IM (Repository Corticotropin injection USP) and collect plasma again at 1 and 2 hours post injection or administer 0.125 mg synthetic ACTH/cat IV (Cortrosyn) and collect plasma again at 30 minutes and 1 hour after injection. Check that the reference laboratory has established feline reference ranges. There is controversy about the definitive test with some endocrinologists saying that ACTH stimulation test is the test of choice in cats. Most cats have pituitary dependent HA. Ultrasound is very helpful combined with endocrine tests to provide a diagnosis of PDHA. With PDHA, one will see 2 normal or enlarged adrenal glands. With adrenal tumors there will be atrophy of the contralateral gland. In cats, adrenal calcification is a normal aging change.

Treatment options

Control the diabetes with as much insulin as is required for glycemic control and because the immunosuppressive effects of glucocorticoids predispose an already prone individual to infections.

1. op-DDD (Lysodren): 25 mg/kg BID for 10 days. Check an ACTH stimulation test and if the values are below 5mcg/dl, then reduce the frequency of administration to once weekly. Retest ACTH stimulation after 4 weeks.
2. 2. Metyrapone, which blocks adrenal conversion of 11-deoxycortisol to cortisol may be used at 65mg/kg PO q12h. Clinical improvement is expected within 5 days of initiation of therapy. Monitor blood glucose closely as diabetic cats will be prone to becoming hypoglycemic rapidly.
3. 3. Recently, trilostane (Vetoryl), a steroid synthesis inhibitor, has been reported anecdotally for the treatment of PDHA at 6 mg/kg PO q24h. Retest ACTH stimulation after 4 weeks.

Medical treatment should be used to stabilize the patient prior to adrenalectomy. Cats recovering from bilateral adrenalectomy (PDHA) may develop sepsis, pancreatitis, thromboembolism, wound dehiscence, adrenal insufficiency and hypoglycemia. For patients who had a unilateral adrenalectomy, prednisolone 2.5mgPO q12h should be started in the evening after surgery, continued for several weeks before tapering. For bilaterally adrenalectized cats, lifelong mineralocorticoids will be required. Microsurgical transsphenoidal hypophysectomy has been described in 7 cats with PDHA; in five cats the hyperadrenocorticism disappeared. Alternately, pituitary tumour size may be reduced with external beam radiation therapy.

Hypoadrenocorticism (Addison's Disease)

This condition may be misdiagnosed as renal insufficiency. The clinical signs are similar to those in the dog and include lethargy, weakness, inappetance/anorexia, vomiting, diarrhea, PU/PD. On physical examination, the patient is depressed, dehydrated, has a slow capillary refill time, weak pulses (signs of dehydration and electrolyte imbalance), bradycardia and is hypothermic. The major differentials are renal insufficiency, shock and urethral obstruction. Laboratory findings show hyperkalemia, hyponatremia, hypochloremia, hyperphosphatemia (rarely hypercalcemia), and prerenal azotemia with a concurrent low urine specific gravity (caused by medullary washout). The CBC may show a lymphocytosis and eosinophilia with a mild, non-regenerative anemia. In cats, decreased Na:K ratios frequently occur in cats with diseases other than hypoadrenocorticism, especially any type of effusion. The diagnosis is made, after initiating treatment, using ACTH stimulation: a lack of response is diagnostic for

hypoadrenocorticism.Treatment consists of fluid therapy, glucocorticoids and mineralocorticoids. Florinef is administered at 0.1 to 0.2 mg PO q12h or DOCP at 1 mg/lb. IM or SQ every 21-28 days. Cats seem to due better on supplemental prednisolone especially in terms of eliminating GI side effects. Prednisolone also seems to be needed more in cats receiving DOCP, as DOCP has no glucocorticoid activity. Prednisolone doses are low: 1.25 to 2.5 mg once a day or q48h.More commonly cats develop the atypical form of hypoadrenocorticism. This is a glucocorticoid-deficiency state in which electrolyte disturbances are not present at the time of initial presentation. Hence, the cats appear in a similar state and may be thought to have renal or gastrointestinal disease but on evaluation of the minimum database, the characteristic hyperkalemia and hyponatremia are absent. Iatrogenic secondary hypoadrenocorticism is similar but has low endogenous ACTH. Atypical Addison's responds to oral prednisolone therapy.

Hyperprogesteronemia

There are several reports of cats with progesterone secreting adrenal gland tumours. Progestins have a similar structure to cortisol and can mimic the effects of glucocorticoids in cats resulting in the signs of hyperadrenocorticism by suppressing the hypothalamic-pituitary-adrenal axis. When insulin resistance is being evaluated in a cat, HAC, acromegaly and progesterone excess should be considered. If a diagnosis of HAC cannot be confirmed by measurement of cortisol during an dexamethasone suppression test or ACTH response test, adrenal sex hormone assays should be considered. Medical treatment using aminoglutethimide, a drug capable of inhibiting steroid hormone synthesis may be effective short-term; adrenalectomy is recommended for cure.

Hyperaldosteronism (Conn's Syndrome)

Primary hyperaldosteronism is probably the most common adrenocortical disorder in cats. It is caused by a unilateral neoplasm of the adrenal cortex producing excess mineralocorticoids. Cats present with systemic hypertension, muscle weakness from hypokalemia, and polyuria. Usually seen in geriatric cats, it can be mistaken for renal insufficiency. Treatment consists of potassium supplementation and control of hypertension. Some cats require very high doses of IV and oral K supplementation to resolve the hypokalemia. Doses as high as 60-80 mEq of KCl/liter of fluids may be required in some cats. The first clinical clue to the hypertension may be retinal detachment. Blood pressures are in 200-280 systolic range. Amlodipine is indicated to reduce the hypertension and doses are titrated to effect. The ratio of plasma aldosterone concentration to plasma renin activity (aldosterone:renin ratio) is currently the best screening test for feline primary hyperaldosteronism. repeated sampling for the ARR may be required, as a single ARR within the reference interval does not exclude primary hyperaldosteronism in cats. On ultrasound, a unilateral adrenal mass is found. These tumours are usually benign and surgery can be curative. If surgery is declined, then amlodipine and potassium supplementation will help to control the clinical signs. Spironolactone, a potassium-sparing diuretic works by antagonizing aldosterone receptors (2-4 mg/kg/d). Interestingly, almost all of the cats have had other endocrine disorders (esp. hyperthyroidism). It has also been seen with insulinoma, so this may be a feline example of multiple endocrine neoplasia (MEN)**.**

Acromegaly

Acromegaly has been studied in the last several years with an increased level of interest as it has been discovered that ¼-1/3 of cats with diabetes may have unrecognized acromegaly. This condition is usually caused by an adenoma in the pars distalis of the anterior pituitary gland that secretes excessive growth hormone (GH). Less commonly, pituitary hyperplasia is suspected to result in acromegaly. Insulin-like growth factor 1 (IGF-1) is produced in the liver in response to the GH. GH has catabolic and diabetogenic effects, while IGF-1 has anabolic effects. The characteristic signs of acromegaly are insulin resistance, believed to be caused by a GH-induced post-receptor defect in the tissues. Most are middle-aged to older, neutered male mixed breed cats. Physical changes consisting of prognathism and a broad face, large thickened limbs with clubbed paws and organomegaly may be subtle. Upper respiratory stridor associated with structural changes may be seen. Organomegaly is common as hypertrophic cardiomyopathy and renomegaly. In addition, arthropathies occur and, in some cases, there may be neurological signs from intracranial tumour expansion.

Classic signs of diabetes: PU/PD with polyphagia are present despite increasing doses of insulin. Uncharacteristic of diabetes, however, is concurrent weight gain. There are two populations of acromegalic cats: those who have been diabetic for some time and then deteriorate while the second group consists of those cats who appear to be acromegalic from the beginning of their diabetes. Other differentials for an insulin resistant or uncontrolled diabetic include treatment failure of compliance or comprehension, inappropriate insulin handling, resistance associated with concurrent, uncontrolled inflammatory or infectious conditions, hyperprogesteronemia or hyperadrenocorticism.

Insulin growth factor-1 is the screening test with confirmation of diagnosis by imaging the pituitary gland. If possible, GH measurements should be measured. No single antemortem test is 100% reliable as there may be false positives and negatives. Because GH is secreted in a pulsatile fashion, there may be false negatives, i.e., normal GH values in an acroegalic cat. IGF-1 is secreted continuously and is, therefore, theoretically more reliable. Contrast enhanced CT or MRI studies are used for diagnosis as well as for treatment planning, should radiation or stereotactic radiosurgery be a consideration. There are several therapeutic options. Conservative treatment with high doses of insulin as needed may be used, however the risk is that iatrogenic hypoglycemia may occur if the insulin dose is too high for the GH surge at the time. Thus, should this form of treatment be the one chosen, the client and veterinary team needs to work closely together to ensure that the client is able to assess blood glucose levels and trends. Medical

therapeutic options for people are of three kinds: 1. Somatotropin analogues control GH and IGF-1 secretion in about 50% of humans. Octreotride was effective in treating a small number of cats but did not result in normalization of GH after a single IV injection in one study. 2. Pegvisomant is a GH-receptor antagonist that is used in humans but does not appear to be effective in cats. 3. 70% of humans respond to dopamine antagonists such as bromocriptine and L-deprenyl (Selegiline). These have not been properly evaluated in cats. Currently the best treatment option is radiation therapy: by reducing the bulk and function of the pituitary mass, neurological signs associated with mass as well as insulin resistance improve. Adjustment of insulin doses is not straightforward as resolution of insulin resistance can occur immediately or months after radiotherapy. Hepatic IGF-1 hyperproduction does not always resolve, so while diabetic management may become significantly easier or diabetes may resolve, the anabolic effects (polyphagia, bone growth, organomegaly, etc.) may still cause problems. Stereotactic radiosurgery using a gamma knife to reduce the tumour mass is being investigated at Colorado State University. Another technique, transsphenoidal cryohypophysectomy has been attempted in two cats with favourable long-term results in one cat.

Because there are chronic, ongoing changes associated with the effects of the IGF-1, namely possible arthropathy, HCM, renal insufficiency and hypertension, these, along with quality of life must be addressed regardless of form of therapy.

Hyperthyroidism

Hyperthyroidism is the most common endocrine disorder in the cat. Since being first recognized in 1977, the incidence has increased steadily. This is, no doubt partly due to greater awareness and early screening, but certainly also due to a real increase in occurrence of this disease. The etiology and pathogenesis are not certain, but numerous epidemiological surveys have shown an increased incidence of this disease is seen in cats fed > 50% canned food in their diet, especially containing fish, living strictly indoors, using litter.

The disease has been reported in North America, Europe, Australia and New Zealand, but less frequently, or not at all, in other parts of the world. These risk factors implicate environmental, nutritional and genetic factors. It is also logical to assume, however, that cats who are well cared for and thus live longer, will be exposed to litter and canned foods.

Some of the goitrogens that have been studied include iodine and phyhalates (common in cat foods), resorcinol, polyphenols and PCBs, all of which may also be in diets, especially those containing fish, or in the environment. In the 1970's because the units for iodine supplementation were changed from amount/animal to amount/kg of diet, a wide variation exists in the amount of iodine a cat ingests. In addition, the variability in the bioavailaibility of different iodine sources compounds the problem further. As a result, it is possible that cats have been chronically iodine deficient for several decades. Another theory considers that nodular goiter development may be a normal age-related condition.

Most recently, attention has been directed towards brominated-flame retardants also introduced into household consumer products in the 1970-80's. Pet cats in the U.S. have been found to have high PBDE serum levels, which could be a result of exposure in cats living strictly indoors. Further, because cats groom their fur they may ingest any volatilized PBDE-like material or PBDE-laden dust that deposits on it.

Regardless of the cause(s), the condition of hyperthyroidism, is a multi-systemic disorder caused by excessive concentrations of circulating thyroglobulins, T_4 and T_3, produced most commonly by benign, hyperplastic adenomatous glands, but rarely by malignant, adenocarcinomatous glands. 97-99% of hyperplastic glands are benign and adenomatous. Approximately 70% of cases have bilateral disease and as many as 20% have multiple areas of intra- or extrathoracic hyperfunctional tissue, facts critical when considering surgical therapy.

Signalment

While hyperthyroidism is a disease of middle aged to old cats (4-22 years old), it has been reported in cats aging from eight months - 22 years of age. There is no sex predilection; two papers reported a decreased incidence in Siamese and Himalayans. **History**: Thyroid hormones regulate metabolic processes in virtually every tissue. Thus, increased appetite, weight loss, polydypsia, polyuria, vomiting, diarrhea, heat intolerance, hyperexcitability/nervousness, behavioural changes, tremour and tachycardia are classic findings in the hyperthyroid cat. The signs are gradual in onset and range from mild to severe. The only sign may be defecating outside of their litter box and/or large, voluminous stools. The frequency and severity of clinical signs has decreased since the condition was originally reported. This is likely due to screening, as clients often aren't aware that their cat is ill early in this disease. They may, in fact, be pleased with weight loss in a previously overweight cat or be proud of how alert and active their senior cat is.

Exam findings

The classic, advanced hyperthyroid cat is thin, active, has a bounding, rapid heart with a cardiac murmur (b-lub-dub), a palpably enlarged thyroid gland, and may be agitated and have an unkempt coat. Apathetic hyperthyroidism is a less common presentation (~5%) in which the cats are depressed, weak and may be anorectic or even obese.

Preliminary testing

baseline CBC, chemistry screen, urinalysis, total T4, blood pressure

Results: Elevations of the liver enzymes alanine aminotransferase (ALT) and serum alkaline phosphatase (SAP) are common findings in > 90% of hyperthyroid cats, although the cause for this is not clear. Histologic evaluation of the liver of these cats shows mild, non-specific changes. SAP has been hypothesized to increase due to increased metabolism of bone. Increases in ALT are harder to explain,

as ALT is an intra hepatocellular enzyme, yet there is no hepatocellular membrane damage seen with light microscopy. Thyroid hormones may have direct toxic effects on the liver, hypoxia, CHF, infection, malnutrition may all play a role, but the exact cause for increases in ALT and SAP are not understood. These enzyme values return to normal when euthyroidism is achieved.

The total T4 is the basic screening test for hyperthyroidism. Normal values may occur in hyperthyroid cats for a number of reasons including a) early in the course of disease, b) because of normal fluctuations of this hormone and c) when there is concurrent, non-thyroidal illness present ("euthyroid sick syndrome"). When one is suspicious of hyperthyroidism but T4 values are normal, one can use one of the alternative testing methods or repeat the T4 measurement at a later date.

Free T4 can be helpful in confirming a diagnosis of hyperthyroidism in a patient with high normal total T4 along with clinical signs suggestive of hyperthyroidism. It must be noted that nonthyroidal illness can, in up to 20% of cats, cause artificial elevations resulting in an incorrect diagnosis. Thus, use of this test should be restricted to cases where confirmation is needed. Equilibrium dialysis is the most reliable methodology.

Thyroid function tests

The principal behind using a thyroid function test is to stimulate the response pathway and negative feedback loop: Hypothalamus (TRH) => Pituitary (TSH)=> Thyroid (T4 => T3) => negative feedback to hypothalamus.

Thyrotropin releasing hormone (TRH) stimulation test

This test is easily performed. Collect a baseline serum sample prior to administration of Relefact TRH (0.1 mg/kg IV to a maxiumum of 1 vial/cat), then collect a second serum sample 4 hours. Run T4 on both samples. Common side effects include panting, vomiting, salivation and defecation; pretreatment with maropitant may help. Hyperthyroid cats, because of the autonimity of their thyroid gland function, experience less, if any elevation in their post TRH serum T4 values.

Triiodothyronine (T3) suppression test

The protocol for this test is slightly more involved, but still very simple. Draw a serum sample to determine baseline T3 *and* T4, separate the serum by centrifugation, then refrigerate or freeze the serum. Clients are instructed to administer T3 (Cytomel: 25 mcg) PO q8h for two days; on the morning of the third day, a 7th dose of T3 is administered, and serum is collected within 2-4 hours for T3 and T4 determinations. Both the basal (day 1) and post T3 serum samples should be submitted to the laboratory together to eliminate inter-assay variation. Because the hyperplastic thyroid gland is autonomous from superior control, we expect to see no suppression of the T4. T3 assays must be run to ascertain that the client was successful in administering the Cytomel to the cat. While Cytomel is much less expensive than Relefact, this test may be more prone to inconclusive results than TRH.

Technetium scanning

Thyroid imaging is a safe, easy and reliable adjunct in diagnosing hyperthyroidism in cats. It has the advantage of determining the extent of involvement, namely whether both lobes are involved and whether metastasis is present.

Thyroid Stimulating Hormone (TSH) Response Test

This test is currently unavailable and not validated in cats.

Hyperthyroidism and chronic kidney disease

Concurrent renal dysfunction is also fairly common in untreated hyperthyroid cats, and may be masked due to increased cardiac output and renal blood flow. Therefore, it is essential to continue to monitor these renal parameters during therapy. It is well recognized that amelioration of the hyperthyroid state by any method (i.e. medical therapy, 131I treatment or surgery) can result in decreased GFR, elevations in BUN and creatinine, and, in some cases, overt azotemia. The decline in GFR stabilizes by approximately four weeks.

Numerous studies have attempted to identify predictive parameters. GFR can be measured using plasma clearance of exogenous creatinine exo-iohexol or endo-iohexol; N-acetyl-beta-D-glucosaminidase index and retinol-binding protein have been assessed as possible biomarkers. Of the common clinical measures, cats with hypertension and/or an increase urine protein: creatinine ratio are more likely to develop problems while cats with elevated plasma globulins, a high usg and PCV are less likely to.

A practical approach is to treat cats with methimazole until the serum T4 is adequately controlled when the effect of permanent therapy can be assessed. If renal failure does become overt after definitive correction of hyperthyroidism, exogenous thyroid hormone can be supplemented to support the kidneys. A balance must then be struck between creating iatrogenic hyperthyroidism and maintaining renal function as iatrogenic hypothyroidism appears to contribute to azotemia and decreased survival.

Therapeutic options

Medical

Methimazole disrupts synthesis of thyroid hormones by inhibiting thyroid peroxidase. Initially dose at 2.5 mg/cat PO BID, recheck T4 after 10-14 days and adjust dose accordingly. Side-effects include an acute, allergic facial pruritis, with red wheals on the ears (uncommon). Gastrointestinal upset (anorexia, vomiting) and lethargy are more common (up to15%), but these are transient and resolve when the drug is stopped and then started again at a lower dose. Hepatotoxicity may arise and is a serious side effect if it

occurs. Severe thrombocytopenia and leukopenia (agranulocytosis) or development of ANA titers may occur and will require cessation of the drug. Because of these potential effects, as well as the renal precautions discussed above, and the possible growth of the tumour, regular monitoring of CBC, T_4, BUN, creatinine and a usg should be done at 3-4 month intervals. Transdermal methimazole has been shown to be absorbed but may take four weeks of use to get therapeutic serum levels.

Other options include carbimazole, propothiouracil and iopanoic acid. The major disadvantage of medical therapy is that it must be continued (along with monitoring) lifelong.

Nutritional

Dietary therapy (Hill's y/d) has recently become available and operates on the rpemise that a reduction in iodine as a substrate for thyroid hormone production corrects the hyperthyroid state. The diet was tested on cats with minimal clinical signs of hyperthyroidism so how well it will work in cats with concurrent cardiac or hypertensive complications is unknown. Cats being treated with this diet may not have any other food or treat. The manufacturer recommends that medical therapy be reduced by 50% one week after the cat has been transitioned completely onto y/d, that the medication be discontinued after one week at this lower dose and that the T4 levels should be checked 3-4 weeks after a complete transition onto the diet to verify euthyroidism and compliance.

Surgical

Thyroidectomy is an easy procedure. Ideally, a technicium scan should be preformed ahead of time to determine the extent of involvement and lilelihood of cure. Evaluation of cardiac function by echocardiography is recommended prior to anaesthesia. It is important to achieve pre-operative euthyroidism and cardiac stability by treating with methimazole and atenolol for 4-6 weeks prior to surgery. These cats are significant anaesthetic risks and the choice of anaesthetic regimes needs to be considered carefully. Avoid xylazine and atropine; be aware of the predisposition to catecholamine-induced arrhythmias and choose agents accordingly. Ketamine may be contraindicated because of its propensity towards creating hypertension.

When a bilateral procedure has been performed, serum calcium should be monitored at 48 and 72 hours post- operatively. A cat with hypocalcemia will present with facial twitching (early), muscle weakness and spasms, progressing, if untreated, to full-blown seizures and death.

Radioiodine therapy

Is "the gold standard". Renal parameters (BUN, Creatinine, usg) as well as T4 should be monitored at 1 and 3 months after treatment.Monitoring: Regardless of form of therapy the T4 should be checked every 4-6 months, as the condition may recur either due to incomplete surgical removal, an inadequate 131I dose, or growth of the tumour necessitating a higher dose of methimazole. In the case of nutritional management, inadequate control of T4 may be from growth of the tumour or from ingestion of iodine-containing substances.