VetTalk

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Hyperadrenocorticism or Feline Cushing's Syndrome (FCS)
New Endocrine Series!

Introduction

The ACVP endocrine disorders newsletter species of discussion this month will be the cat. In the domestic feline, hyperadrenocorticism, or Feline Cushing's Syndrome (FCS), is a hormone disorder caused by an elevation in cortisol concentrations. The elevation of this endogenous steroid is usually derived from an adrenocorticotropic hormone (ACTH) secreting tumor of pituitary gland or a cortisol-secreting tumor of the adrenal cortex.

Prevalence

Though considered rare, Cushing's disease has been recognized as a clinical entity in domestic felines for approximately 30 years. FCS prevalence during this time has risen most likely due to awareness of the condition, feline medicine becoming more specialized, and the aging feline pet population is increasing. Current knowledge of the pathophysiology, epidemiology, diagnosis and treatment of FCS is based on scattered case reports and relatively small case series. There does appear to be a slight breed predilection in Siamese, Persians, Abyssinians, and domestic long hairs but a majority of cats that have been affected are domestic shorthairs with a trend towards females being affected more than males.

Pathophysiology/Etiology

As in the canine population, naturally occurring hyperadrenocorticism in the cat can be caused by either an adrenocorticotropic hormone-secreting tumor of the pituitary gland (PDH) or a cortisol-secreting primary tumor of the adrenal cortex (AT). Pituitary-dependent disease accounts for 80% of naturally occurring cases of feline Cushing's disease and despite the pathophysiologic consequences of excess ACTH, most are usually small benign adenomas. There is one case report that describes a cat with pituitary gland carcinoma so there is a small risk of this happening. Approximately 60% of adrenal tumors associated with FCS are benign adenomas and the remainders are malignant adenocarcinomas. Interestingly, cats are considered less prone to the deleterious effects of glucocorticoids than dogs and this may be one reason for their lower incidence of hyperadrenocorticism. One study demonstrated that cat skin and liver have decreased density of glucocorticoid receptors and lower binding affinity thus cats show a decreased sensitivity to the effects of glucocorticoids. Another cause of FCS is iatrogenic Cushing's syndrome where clinical case reports describe Cushing's disease in cats with abdominal enlargement, dermatologic abnormalities, and biochemical abnormalities similar to those seen in naturally occurring FCS. Experimentally induced iatrogenic Cushing's syndrome in cats demonstrates the effects of prolonged treatment with immunosuppressive doses of either prednisolone or dexamethasone.

Clinical Signs and Symptoms

The classical clinical signs are usually witnessed in middle-age to older cats or those on chronic corticosteroid medications. These cats will present with dermatologic abnormalities such as hair epilation and loss, skin atrophy and friability, abdominal enlargement, lethargy, panting, polyuria, polydipsia, and weight loss or gain. Cats with Cushing's may also exhibit hyperpigmentation, medially curled pinnae, and bruising. Curling of the ears is thought to be due to the catabolic effects of glucocorticoids on cartilage and has been reported in cats with iatrogenic Cushing's syndrome but not in cats with naturally occurring disease. Felines with hypercortisolism can have mild to moderate increases of serum liver enzymes but the degree of elevation is usually mild and attributed primarily to hepatic lipidosis commonly associated with the comorbid condition of diabetes mellitus. This secondary disease state presents in up to 90% of cats with FCS and occurs when cortisol interferes with the

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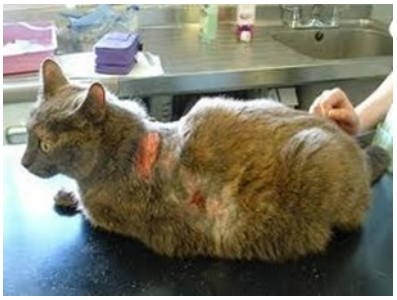
effects of insulin and can make treating diabetes (even with insulin) very difficult!

Summary of Clinical Signs in Cats

1. Seen in middle-age to older cats (range 5-16 years old) with an average of 10 years.
2. Possible female predilection
3. Insulin resistant diabetes mellitus
   a. Polyuria
   b. Polydipsia
   c. Polyphagia
   d. Weight loss/gain
4. Abdominal enlargement
5. Muscle atrophy
6. Unkempt dry hair coat
   a. Bilaterally symmetrical alopecia
   b. Coat epilates easily
7. Cutaneous fragility with tearing of skin even during routine grooming
   a. Recurrent abscess formation
8. Virilization and estrus-like behavior may occur in gonadectomized cats with adrenal tumors secreting steroids other than cortisol



Laboratory Abnormalities

Provided that the cat in question has not been on long-term corticosteroid administration, there are no consistent findings in a CBC that are typical and helpful for diagnosing a cat with naturally occurring FCS. However, the CBC remains important in determining any problems that might be associated with the disease state. The most consistent lab abnormality is an elevated blood glucose associated with diabetes mellitus. Anemia and evidence of chronic infections may also be noted. The alkaline phosphatase enzyme, very often elevated in HAC dogs, is only elevated in about 1/3 of cats and this elevation is most likely from their concurrent diabetes. Cats lack the specific steroid-induced isoenzyme found in the dog that produces the "normal" ALP increase seen on a CBC. The FCS cat may also have other liver enzymes and cholesterol that are elevated as well as glucose in their urine due to their poorly regulated diabetes. When diabetes is combined with the suppression of the immune system caused by the elevated cortisol levels, the cat is made very susceptible to urinary tract infections.

Diagnosis

The primary means of diagnosing a cat with FCS is by conducting a CBC, biochemical panel, and urinalysis. This UA will most likely reveal a cat with diabetes mellitus. Increased ALP, ALT, hypercholesterolemia, hyperglycemia, and low BUN are common. Increases in liver enzymes are often a result of FCS cats with diabetes who have hepatic lipidosis and more often ALT is seen increased but is not seen frequently with ALP. Hypercholesterolemia is reported in cats with Cushing's syndrome due to glucocorticoids inhibiting lipoprotein lipase activity and increasing the activity of hormone-sensitive lipase which combines to result in an increase in triglycerides and cholesterol. As expected, hyperglycemia and a low BUN are related to the concurrent disease state of diabetes in cats with FCS. Endocrine tests used for diagnosis of feline hyperadrenocorticism include the ACTH stimulation test, high dose dexamethasone suppression test, urine cortisol to creatinine ratio (UCCR) test, low dose dexamethasone suppression test with UCCR, and the endogenous ACTH test. Pituitary dependent hyperadrenocorticism occurs in 80% of cats with spontaneous or naturally occurring hyperadrenocorticism, while 20% have functional adrenocortical tumors. Abdominal ultrasound is the most useful diagnostic test for differentiation of PDH from AT. Either the high dose dexamethasone suppression test or measurement of endogenous ACTH concentration may also be helpful.

Diagnostic Algorithm

1. Assess history, physical exam, and clinical signs
2. Rule out iatrogenic disease
   a. Current or past medications like corticosteroids
3. Preliminary Lab Results
   a. CBC where the most consistent finding is inconsistency!!
      i. Lymphopenia
      ii. Eosinopenia
      iii. Monocytosis
      iv. Neutrophilia
      v. Leukocytosis
   b. Chemistry Profile
      i. Hyperglycemia
      ii. Hypercholesterolemia
      iii. ↑ liver enzymes-ALP, ALT
      iv. ↓ BUN
   c. Urinalysis
      i. Glucosuria
      ii. Proteinuria
      iii. Leukocyte esterase
4. Thoracic Radiography
   a. While useful in dogs, calcification of an adrenal tumor is unusual in FCS cats.
5. Abdominal Ultrasound
   a. Helps differentiate PDH from AT
   b. Helps identify the size and internal architecture of each adrenal gland and kidney
   c. Can detect diffuse hyperechoic changes in cat with hepatomegaly due to infiltrates from diabetes as well as pancreatitis
6. CT/MRI
   a. Imaging of the pituitary gland is not always readily available but it can be helpful in detecting pituitary masses
   b. Abdominal CT is often part of pre-surgical planning in cats undergoing adrenalectomy

Diagnostic Tests

1. <u>*Feline ACTH Stimulation Test*</u>*:* This test can be affected by a variety of chronic illnesses causing a false positive outcome and therefore is not highly recommended.
   1. Collect basal blood sample

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2. Inject 0.125 mg of synthetic ACTH (cosyntropin) IV*
3. Collect two further blood samples at one and three hours later
4. Label sample tubes clearly and request cortisol
5. Results: normal cats will increase from a normal level of 20-61 pg/ml to about 400nmol/L while cats with FCS will demonstrate an exaggerated response with a concentration >600nmol/L

** 0.25mg may be used in cats over 5kg*

2. *Feline High-Dose Dexamethasone Test (HDDST):* This test is pertinent for confirming the possible origin for the disease state.
   1. Collect basal blood sample
   2. Inject 1.0 mg/kg Dexamethasone IV
   3. Collect blood samples at 4 hours and then at 8 hours
   4. Label sample tubes clearly and request cortisol
   5. Results: Cats with pituitary-dependent FCS will exhibit 0%-69% suppression of serum cortisol. However, the other 50% will not be suppressed meaning that the diagnostic accuracy of this test is a coin toss. However, cats with adrenal tumors do not exhibit suppression of serum cortisol during the HDDST therefore serum cortisol suppression is useful but a lack of suppression is not.

3. *Feline High-Dose Dexamethasone and ACTH Test:* This test is unique because more than one diagnostic endpoint is assessed and so this test may be more accurate than an ACTH stimulation test alone. However, currently, the combined test does not appear to offer more clinical utility than either the ACTH stimulation or dexamethasone suppression test evaluated separately.

4. *Urine Cortisol/Creatinine Ratio Test (UCCR):* This is a very sensitive test to exclude FCS but must not be used to diagnose this disease as it is poorly specific since non-adrenal illness will commonly cause a positive result. Samples taken from a litter tray in home have a lower false positive than obtained from clinic animals. Litter should be non-absorptive material such as gravel or glass beads
   1. Morning urine sample is collected which reflects cortisol release over several hours
   2. In normal cats, the upper limit of normal for the UCCCR test is 2 X 10^{-6} to 36 X 10^{-5} noting that these values are considerably higher than the upper end of normal for dogs. However, in a FCS cat, the average is 122 X 10^{-6}

5. *Cortisol/Creatinine Ratio (CCR) with Low Dose Dexamethasone Suppression Test:* When Cushing's disease is strongly suspected, this test is useful for cats as they usually get very stressed at the vets office. The owner can do all the sampling at home via a litter box with washed and dried aquarium gravel and urine samples collected with a pipette. Wash the tray and gravel thoroughly between samples. Then send the samples together to the lab.
   1. Day 1, collect a first morning urine sample
   2. Mix the urine and add some to Sample Tube 1, place in the fridge until dispatch
   3. Day 2, collect a first morning urine sample
   4. Mix the urine and add some to Sample Tube 2, place in the fridge until dispatch
   5. Immediately after urine collection, note the time and give the cat the required number of Dexamethasone tablets (dose = 0.1mg/kg)
   6. 8 hours later give the cat a 2nd set of Dexamethasone tablets
   7. 16 hours later give the cat a 3rd set of Dexamethasone tablets
   8. Day 3, collect a first morning urine sample
   9. Mix the urine and add some to Sample Tube 3, place in the fridge until dispatch
   10. Send all 3 urine samples to the laboratory for CCR
   11. Results: FCS is suspected if the CCR is greater than the upper limit of normal in two consecutive morning urine samples and if the CCR in the 3rd urine sample is depressed by 50% of the mean CCR of the first two samples, PDH isthe likely diagnosis. If the suppression is less than 50%, an endogenous ACTH is suggested to confirm an adrenal tumor. PDH or ADH cats usually have a CCR greater than 50 x 10^{-6}

6. *Endogenous ACTH:* Endogenous ACTH may be used to assist in differentiating PDH and AT when hyperadrenocorticism has already been confirmed by ACTH stimulition test or low-dose dexamethasone screening test. It is not a diagnostic test for hyperadreno corticism. Special sample handling procedures apply.
   1. Contact lab regarding sample handling and collection. Use of the preservative (Aprotinin) allows for greater utilization of this test
   2. 95% of cats with pituitary dependent FCS had high plasma ACTH concentrations so if FCS is from adrenal tumor, then levels are low to undetectable

Treatment

In general, medical management of hyperadrenocorticism is less successful in the cat than in the dog. Moreover, cats with FCS are often poor surgical candidates especially when they have uncontrolled diabetes making overall treatment success very problematic. However, the decision to elect for surgery ultimately depends on the overall clinical picture of the presenting cat and whether or not the source of FCS is based in the pituitary or adrenal gland.

Vetoryl® (trilostane)

This medication is a synthetic hormonally inactive steroid analogue which is an enzymatic competitive in

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hibitor of the 3-β –hydroxysteroid dehydrogenase system. Essentially this drug blocks the production of many adrenal steroids including cortisol and aldosterone. It is currently the most effective drug for medical management of cats with PDH. The effective dose of trilostane ranges from 6mg/kg by mouth every 24 hours increased gradually to 10mg/kg by mouth every 24 hours. This approximates to 30mg to 60mg/day in order to see improvements in clinical signs. ACTH stimulation tests should be sued to titrate the dose, similar to the protocol for dogs. Vetoryl® (though not approved in cats) is available in capsule sizes of 10mg, 30mg, and 60mg. The lower recommended dosages require compounding as Vetroyl® is not available in capsules smaller than 10mg or in an oral suspension. Pharmacists compounding trilostane should start with Vetoryl® capsules and not the active pharmaceutical ingredient (bulk powder) as there are no USP standards for trilostane and FDA has prohibited compounding with bulk powder trilostane. ACTH stimulation testing should be performed 10, 30 and 90 days after start of treatment and 30 days after each dose adjustment. Treatment with this medication may improve clinical signs but cats typically remain diabetic. Trilostane is rapidly absorbed orally (peak concentrations within 1.5 hours) although suppression of plasma cortisol concentrations is short lived (< 20 hours). The drug is generally well tolerated and is reportedly effective in controlling polyuria, polydipsia, and dermatologic changes. Adverse effects that are usually mild and self-limiting include diarrhea, vomiting, and lethargy. Other possible effects include hyponatremia and hyperkalemia so monitoring of electrolytes is important especially if the cat is on a diuretic. Since trilostane can cause hyperkalemia through its aldosterone inhibiting effects, it is advised to use caution if given together with a potassium-sparing diuretic. The effect of angiotensin converting enzyme inhibitors might be potentiated (again due to its aldosterone inhibition) but no studies have yet been conducted. It has been shown that trilostane terminates pregnancy in rhesus monkeys at a dose of 50mg/monkey at various time points throughout pregnancy therefore the drug should not be used in pregnant animals or handled by pregnant cat owners. In a study of 5 cats treated with trilostane, 2 died after 16 days and 120 days respectively while the remaining cats were alive at 6, 11, and 20 months. Given the lack of other highly useful and well-studied medications, trilostane is a reasonable choice for treatment of FCS.

Metopirone (metyrapone)

This medication is an 11-β-hydroxylase inhibitor that blocks the conversion of 11-deoxycortisol to cortisol. It has been successfully used to treat hyperadrenocorticism in the cat. The recommended doses found in the literature are 43mg/kg twice daily up to 65 mg/kg by mouth every 8 to 12 hours. Side effects may include sedation, dizziness, and abdominal discomfort. While helpful, there are no reports of a completely successful cure with metyrapone as the sole treatment for FCS in the cat.

Lysodren (mitotane)

This medication is derived from the insecticide DDT and is a potent adrenocorticolytic agent. Mitotane therapy is designed to selectively destroy the 2 inner layers of the adrenal cortex (zona reticularis and zona fasciculata). Higher doses may also cause necrosis of the zona glomerulosa. Though this medication is a mainstay of medical therapy for dogs with HAC, its use in cats is questionable at best as it has shown disappointing results with only a partial response. Once case report showed a cat that improved after nearly 4 months of daily treatment with 37.5mg/kg dosing which is considered an extremely high dose in other species. Essentially this medication has been studied to a limited extent in normal cats and was ineffective or minimally effective at suppressing ACTH-stimulated serum cortisol concentration in 3 out of 4 cats. Though its use is not recommended, if given to a cat side effects may include gastric irritation, Addisonian crisis, fatty degeneration, centrilobular atrophy, congestion of the liver and occasionally neurologic signs. This drug should never be given to animals that are not eating well. Absorption of mitotane is increased if administered with fat or compounded into an oil suspension such that oil suspension are the most bioavailable and solid tablets are the least bioavailable. Glucocorticoids are not usually administered concurrently, but a small supply of prednisone should be made available to the owner for emergencies. Mitotane should be administered until depression, diarrhea, or vomiting is observed or until water intake or appetite decreases.

Nizoral (ketoconazole)

This medication is an azole antifungal that has also been used as an adrenal steroidogenesis inhibitor in other species though results are disappointing in FCS cats with only partial responses observed. This drug is interesting though because not only does it inhibit both 11-β-hydroxylase and cholesterol side-chain cleavage enzyme, which is the first step in the steroidogenesis cascade, but at high doses it also inhibits pituitary ACTH by inhibiting adenylyl cyclase activity in pituitary corticotrophs. There are no studies with ketoconazole used in cats with FCS, but one study which examined the long-term effects of high-dose ketoconazole in normal cats showed no suppression of basal serum cortisol concentrations after 30 days. However, the drug is well tolerated in cats so it may be reasonable to consider its use in the medical management of Cushing's in cats when other medical treatments haven't been establish as consistently effective just note that most results are disappointing with partial responses observed in only a few cats. Side effects are relatively unusual but can include an elevation of liver enzymes.

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Radiation therapy

This technique is another option besides oral medication, for treating cats with PDH. The amount of radiation used in photon radiation therapy is measured in gray (Gy), and varies depending on the type and stage of disease being treated. Radiosurgery describes a technique in which a large dose of radiation is delivered, in a highly conformal fashion to a defined target. One example of a dosing regimen is 5 Gy followed by four doses of 8 Gy and this protocol is based on that previously reported for treatment of tumors in dogs. An "ideal" protocol has not yet been established though the one aforementioned was well tolerated. Resolution of neurologic signs, improved clinical signs, and improved glycemic regulation with better response to insulin has been reported after radiation treatment. Improvement in endocrine function occurs within 1-5 months of completion of radiation therapy. Median survival time has been observed at 15 months and approximately 17.4 months after treatment. To note, a decrease in the size of the pituitary tumor has not been associated with an improvement of diabetic control in cats with FCS. Early treatment while tumors are small is most effective and improves prognosis and longevity of these cats. A modified radiosurgery approach has recently been offered by the Washington State University Veterinary Teaching Hospital. With their approach, a single, large dose of radiation is delivered in a non-conformal fashion by arcing a linear-accelerator-generated beam with a small field size around the patient's head with the pituitary mass at the center of the beam's rotation. Then, a small field is made that when arced, creates a cylindrical field shape. The doses they used were 15 and 20 Gy and had clinical improvement in 7 out of 11 cats. Complications of radiotherapy appear to be minimal in most cases and the disadvantages of this treatment include its high cost and limited availability. Mild otitis externa may develop in one or both ears during the 3rd week of treatment. A topical ear medication containing a corticosteroid can be used to decrease the inflammation. Transient lethargy and somnolence may be acute side effects during radiation treatment. The total dose of radiation that can be administered to a pituitary tumor is limited to the dose that normal tissues surrounding the tumor can tolerate without an unacceptable risk of late side effects. These late side effects occur months to years after treatment and are irreversible including hearing impairment as well as brain tissue necrosis and fibrosis.

Adrenalectomy

Given the lack of effective medical options for the treatment of FCS, this procedure is often considered the treatment of choice in cats with functional adrenal tumors although initial medical treatment may be necessary in severely debilitated cats. In fact, it is reasonable to try improving a cat's clinical condition by treating with a steroidogenesis inhibitor in preparation for adrenalectomy. Bilateral adrenalectomy is also effective in cats with PDH that do not respond to medical therapy. As in dogs, intravenous fluid supplementation and glucocorticoid administration are vital for successful post-operative management. Cats with diabetes mellitus require careful management of insulin requirements perioperatively. Cats undergoing bilateral adrenalectomy or with evidence of hypoadrenocorticism (hyperkalemia, hyponatremia) need supplemental mineralocorticoids (deoxycorticosterone pivalate or fludrocortisone acetate). Post-operative complications can be very severe including electrolyte abnormalities, skin lacerations, pancreatitis, hypoglycemia, pneumonia, venous thrombosis, and sepsis. In one review, 10 out of 10 cats experienced complications after bilateral adrenalectomy including pancreatitis, electrolyte abnormalities, and hypoglycemia. 5 weeks post-surgery, 3 of the 10 cats died. Diabetes mellitus, interestingly, resolved in 4 of the remaining cats.

Microsurgery

Although not widely practiced, microsurgical transsphenoidal hypophysectomy has been reported as a treatment for pituitary-dependent feline Cushing's disease in the cat. In that study, 5 of the 7 cats survived more than a month after surgery and had resolution of clinical sign of FCS. However, it should be noted that performing a hypophysectomy in small animals is very difficult and there are few veterinary surgeons skilled in this microsurgical technique at this time of writing so the cost of this procedure may be beyond what most owners can afford.

Prognosis

Once present, Feline Cushing's disease is a lifelong condition and the prognosis is generally poor. However, the long term prognosis for cats following an adrenalectomy is fair to good. In a recent study of 10 cats treated by adrenalectomy, 7 cats survived a median of 12 months.

Role of Veterinary Pharmacist

Treating cats with FCS is a unique opportunity for veterinary pharmacists. In addition to making compounded medications such a trilostane, we can also come up with creative ways to make medications taste better and be more appealing to our feline patients as they rarely like to take their pills. For this reason we can recommend pill pockets, placing the medication into soft food, or even compounding the medication into a liquid that tastes like fish or chicken. We also need to provide proper counseling to owners on how to administer these various medications to their felines and what side effects they may observe. It would also be helpful to talk to owners about keeping a journal to track the success of

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their cats treatment as many of the medications recommended for FCS aren't proven to be 100% efficacious. By keeping a journal, or even taking pictures once weekly, they can share with their veterinarians and pharmacists, how their cat is either improving or may need a change in therapy if no change is noted. Most owners are not going to be familiar with the disease state let alone the drugs used to help alleviate the symptoms so being familiar with FCS and its treatments gives us the perfect opportunity to use our knowledge as pharmacists to truly help out our cat owners**.**

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