

**Feline Adrenal Disease**  
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### **Hyperadrenocorticism**

Hyperadrenocorticism develops most commonly in middle-aged to older cats (mean age = 10.4 years; range 6 - 15 years). Of the reported cases of feline Cushing's syndrome (78%) have been females. This female sex predilection resembles the human syndrome and contrasts with canine hyperadrenocorticism, where no sex predilection occurs.

The most common historical findings and clinical signs associated with feline hyperadrenocorticism are polyuria, polydipsia, and polyphagia. These signs likely correspond to the high incidence of concurrent diabetes mellitus (76%) found in cats with hyperadrenocorticism, and are consistent with the lack of overt signs preceding marked glucose intolerance observed in experimentally-induced disease. The typical "Cushingoid" pot-bellied appearance with hepatomegaly, weight gain, and generalized muscle wasting is common in cats as in dogs. Dermatologic abnormalities frequently recognized include an unkempt hair coat with patchy alopecia, and very thin skin prone to traumatically induced tears and secondary infections.

Hyperglycemia is the most common laboratory abnormality found on serum biochemistries. Cats appear more sensitive to the diabetogenic effects of glucocorticoid excess than dogs. Cats with concurrent diabetes mellitus often exhibit cortisol-induced insulin resistance, requiring high daily doses of insulin to control their hyperglycemia and glucosuria. Hypercholesterolemia is also common, and may relate to insulin resistance and increased lipolysis. Cats lack the steroid-induced isoenzyme of alkaline phosphatase found in the canine, and the half-life of the enzyme appears to be significantly shorter in the cat. Elevation of serum alkaline phosphatase (SAP) is present in only approximately one-third of cats compared to nearly 90% of dogs with hyperadrenocorticism. Increases in SAP and the hepatocellular enzyme ALT appear to correspond with the regulation of the diabetic state, rather than representing direct indicators of glucocorticoid excess. These enzymes frequently normalize with adequate regulation of diabetes, even without therapy directed towards the hyperadrenocorticism. Hematologic findings associated with hypercortisolemia (lymphopenia, eosinopenia, and neutrophilic leukocytosis) occur inconsistently in feline hyperadrenocorticism. Despite clinical polyuria and polydipsia, cats appear to maintain urine specific gravities of greater than 1.020 more frequently than dogs, and only occasionally exhibit dilute urine and decreased blood urea nitrogen concentrations commonly seen in dogs with hyperadrenocorticism.

Endocrinologic evaluation of cats suspected of hyperadrenocorticism involves

screening tests to confirm the diagnosis, and differentiating tests to distinguish pituitary-dependent disease (PDH) from adrenal tumors (AT). Adrenocorticotropin (ACTH) stimulation testing in adrenocortical hyperfunction is not as definitive as for hypoadrenocorticism. Fifteen to 30% of cats with confirmed hyperadrenocorticism have had normal cortisol response to ACTH administration (false negatives). In addition, stressed cats and those with non-adrenal illnesses may show an exaggerated response to ACTH in the absence of hyperadrenocorticism (false positives). A normal urine cortisol-to-creatinine ratio (UCCR) can be used to exclude the diagnosis of hyperadrenocorticism in cats as described in dogs. The UCCR is attractive due to the ease of sampling compared to other endocrine function tests, but is non-specific and will be elevated in a variety of non-adrenal illnesses. An exaggerated ACTH stimulation test or an elevated UCCR should be pursued with suppression testing prior to initiating any therapy.

Normal cats are more variable than dogs with respect to the degree and duration of adrenocortical suppression following dexamethasone administration. Intravenous doses of dexamethasone that have been evaluated in the cat range from 0.005 to 1.0 milligrams per kilogram. A dosage of 0.01 mg/kg of dexamethasone, commonly used in low-dose dexamethasone suppression testing in dogs, led to a significant drop in serum cortisol levels in ten normal cats, but 2 of the cats showed a slight escape from suppression by 8 hours after injection. Intravenous dexamethasone sodium phosphate (DSP), 0.01 and 0.1 mg/kg, produced equivalent reductions of plasma cortisol levels, but suppression was sustained below baseline longer with the higher dosage. Cats with various non-adrenal illnesses have also shown inadequate cortisol suppression after a low-dose (0.01 mg/kg) of DSP. The 0.1 mg/kg dosage of dexamethasone seems to more reliably suppress cortisol levels in normal cats and cats with non-adrenal illnesses. Elevated cortisol levels eight hours post-dexamethasone injection, using the 0.1 mg/kg dosage, appears to be a sensitive diagnostic test for feline hyperadrenocorticism (89%) similar to the low-dose (0.01 mg/kg) screening test in the dog.

The combined dexamethasone suppression/ACTH stimulation test has been used successfully to diagnose hyperadrenocorticism in the cat. Affected cats display inadequate suppression of cortisol 2-4 hours after an injection of 0.1 mg/kg of dexamethasone, and an exaggerated response 1-2 hours after ACTH stimulation. The ability of the combined test to discriminate PDH from AT is unclear. Several cats with confirmed pituitary disease failed to suppress 2-4 hours after dexamethasone. Extending the duration of post-dexamethasone monitoring, or using higher doses of DSP may improve the ability of the combined test to distinguish PDH from AT. Currently, the combined test does not appear to offer more clinical utility than either the ACTH stimulation or dexamethasone suppression test evaluated separately.

An ultra-high dose, 1.0 mg/kg, dexamethasone suppression test has been used to distinguish PDH from AT in the cat. Two cats with hyperadrenocorticism diagnosed by the combined high dose dexamethasone suppression/ACTH stimulation test had

exaggerated responses to ACTH with no cortisol suppression 2-4 hours after 0.1 mg/kg DSP. These cats did suppress following the ultra-high dose of dexamethasone, and were later confirmed to have PDH. Cortisol levels should be monitored at several time points following dexamethasone administration to determine if any suppression (a 50% or greater reduction in pre-test values) is occurring. Cats with PDH may show suppression 2, 4, or 6 hours into the test only to escape from the suppressive effects of dexamethasone by 8 hours. One cat with an adrenal adenoma failed to suppress following dexamethasone doses ranging from 0.1 to 1.0 mg/kg. As is the case in dogs, suppression following high doses of dexamethasone is diagnostic for PDH, but failure to suppress requires further testing to distinguish pituitary from adrenal disease.

Determination of plasma ACTH concentrations is an effective way of diagnosing PDH. The normal range of plasma ACTH is lower in cats than in dogs, and many normal cats may have concentrations of ACTH below the lower limits of the sensitivity of the assay. Cats with PDH will have normal to elevated ACTH concentrations while cats with adrenocortical adenomas or carcinomas will have undetectable plasma ACTH levels. Plasma ACTH samples need to be collected and handled carefully. Veterinarians should consult their diagnostic laboratory for specific instructions prior to performing the test. Incorrect sample handling can falsely lower measured values. Normal to elevated plasma ACTH levels support a diagnosis of PDH, whereas low concentrations may require additional diagnostic testing. As in the differentiation of canine hyperadrenocorticism, ACTH levels should only be used to distinguish PDH from AT after hyperadrenocorticism has been confirmed by other screening diagnostics.

Pituitary-adrenal function tests need to be interpreted in conjunction with historical, clinical, and clinicopathologic findings before any conclusions can be drawn. No single diagnostic test is infallible. Equivocal results or discordant findings should be reevaluated. Hyperadrenocorticism is an uncommon disorder in cats. Consequently, false positive test results should be anticipated. Interpretation of endocrinologic testing should incorporate all available information before any therapeutic intervention is attempted.

Diagnostic imaging can facilitate differentiation of PDH from AT when screening tests and clinical findings suggest hyperadrenocorticism. Approximately half of canine adrenal tumors are mineralized and can be recognized radiographically. The frequency of mineralization in feline adrenocortical tumors is unknown, but up to 30% of normal cats may have calcification of their adrenal glands. Abdominal radiographic findings in cats with hyperadrenocorticism included hepatomegaly (69%) and obesity. Ultrasonographic evaluation of adrenal size and morphology has been described for dogs and cats. Nonfunctional adrenal tumors can be incidental findings in humans undergoing abdominal imaging. The incidence of "silent" adrenal masses in the cat is unknown. The presence of unilateral adrenomegaly or distortion of adrenal architecture in a cat suspected of hyperadrenocorticism is strong evidence of AT. Abdominal computerized tomography (CT) and magnetic resonance imaging (MRI) offer

improved resolution for the detection of adrenal tumors or hyperplasia. CT and MRI detection of pituitary masses is also now feasible for small animal patients.

Adrenal tumors accounted for 22% of the reported cases of feline hyperadrenocorticism. Half of the adrenocortical tumors were found histologically to be adenomas and half carcinomas. The treatment of choice for adrenal tumors is surgical adrenalectomy. Two cats with adrenocortical adenomas responded well to unilateral adrenalectomy, with clinical signs resolving over 4 to 8 weeks. One cat with an adrenal adenoma removed surgically developed a recurrence of signs 12 months postoperatively. An adenoma of the contralateral adrenal gland was diagnosed. The cat survived a second adrenalectomy and was disease-free for over two years following the second procedure. Surgical therapy and long term follow-up for adrenocortical carcinomas in cats has not been reported.

Treatment options for pituitary dependent hyperadrenocorticism in the cat include both surgical and medical alternatives. Bilateral adrenalectomy followed by mineralocorticoid and glucocorticoid replacement therapy was performed in 11 cats. Nine cats responded well to surgery with cessation of polyuria and polydipsia, regrowth of hair coat, and marked improvement (4) or resolution (5) of diabetes mellitus. One cat developed acute signs of circling, wandering aimlessly, and apparent blindness 2 months post-operatively. An expanding pituitary tumor was suspected, but no necropsy was performed. Two cats died within one week of surgery from sepsis. Survival times for 6 cats with adequate follow-up after bilateral adrenalectomy for PDH ranged from 1 to 12+ months (median 5 months). Two cats are still alive, one year post-operatively. These results suggest that surgical complications of bilateral adrenalectomy may be less frequent in cats than in dogs.

Surgical treatment can also include transsphenoidal hypophysectomy which is performed at WLA for cats with pituitary masses extending above the sella (macroadenoma). Cats with functional tumors have similar success rates to those reported in dogs with PDH.

Four drugs (ketoconazole, mitotane, metyrapone and trilostane ) have been investigated for the medical management of spontaneous feline hyperadrenocorticism. Ketoconazole, an antifungal imidazole derivative, has been shown to inhibit adrenal and gonadal steroidogenesis in humans and dogs. One month of ketoconazole (15mg/kg orally twice daily) administration in 4 cats did not significantly reduce baseline plasma cortisol or ACTH responsiveness at doses 3 times greater than those effective in dogs. Two of 4 cats treated with 10 - 20 mg/kg/day of ketoconazole had adequate control of hypercortisolemia. One of the 4 cats developed severe thrombocytopenia after only one week of therapy and had to discontinue the medication. A cat with adrenocortical adenocarcinoma treated with 30 mg/kg/day for 3½ months showed improved regulation of diabetes and reduction in pu/pd despite no improvement in hyperresponsiveness to ACTH. The cat ultimately was euthanatized subsequent to a

non-healing skin laceration, chronic infections, and worsening insulin resistance. No evidence of hepatotoxicity or thrombocytopenia was seen at the 30 mg/kg/day dosage of ketoconazole, but the effectiveness and safety of this therapy remains questionable.

Mitotane, o,p'-DDD, is an adrenal cytotoxic agent and has been used successfully to treat dogs with PDH and AT. Use of mitotane in cats has been discouraged due to the feline sensitivity to chlorinated hydrocarbons. Three of 4 normal cats treated with o,p'-DDD at dosages ranging from 25 - 50 mg/kg, divided twice a day, tolerated the drug well, and remained clinically normal throughout treatment with mitotane. Only 2 of the 4 cats showed a decreased responsiveness to ACTH with mitotane. The cat with the largest reduction in post-ACTH cortisol levels developed vomiting, diarrhea, and partial anorexia lasting 2 weeks after a 50 mg/kg dosage of mitotane. Two cats with PDH treated with o,p'-DDD (25 mg/kg/day x 25 days, and 25 - 50 mg/kg/day x 59 days) tolerated the drug without apparent toxicity, but therapy was ineffective in controlling clinical signs in either cat. A cat with PDH treated with mitotane (50 mg/kg/day x 1 week, then 50 mg/kg/week) developed signs compatible with iatrogenic hypoadrenocorticism after 40 weeks of therapy with o,p'-DDD. At that time the cat was anorectic, lethargic, and exhibiting neurologic signs including mydriasis, pacing, and head pressing. Computerized tomography revealed a large pituitary mass extending above the sella turcica. Mitotane was discontinued, and the cat was treated with <sup>60</sup>Co teletherapy. Subsequent CT examinations revealed shrinkage and then disappearance of the mass 10 months post-irradiation. The cat was euthanatized for continued diabetes mellitus and post-irradiation cataracts 2 years after the initial diagnosis of hyperadrenocorticism. We have had 3 other cases where a positive response to mitotane was observed clinically.

Metyrapone, an inhibitor of the 11- $\beta$ -hydroxylase enzyme that converts 11-deoxycortisol to cortisol, has been used effectively in man to reduce the clinical signs of hypercortisolemia. A reciprocal rise in plasma ACTH levels occurs with falling cortisol concentrations and can eventually override the enzymatic block, allowing a return of clinical signs. In humans, metyrapone is utilized as an adjunctive therapy with pituitary irradiation or surgery. Dosages ranging from 195 - 250 mg/day have been used in cats with hyperadrenocorticism without observed toxicity. In a recent report, a diabetic cat with PDH and severe nonhealing skin wounds was treated with 65 mg of metyrapone orally 3 times a day. After 2 days of therapy the cat developed signs of glucocorticoid deficiency including depression, tremors, and ataxia. The cat improved rapidly following treatment with injectable steroids, and was discharged on twice daily metyrapone therapy. Cortisol response to exogenous ACTH was absent when evaluated on day 7. The cat was re-examined 24 days later after a hypoglycemic episode. The cat's skin wounds had resolved and hair regrowth was evident. A follow-up ACTH stimulation test revealed a slightly exaggerated response. The cat underwent successful bilateral adrenalectomy and was euglycemic, with a normal haircoat, 4 months post-operatively. Two of 3 other cats reported in the literature also showed clinical improvement with metyrapone therapy, but follow-up periods were short (less than 6 months). Whether

longterm therapy with metyrapone can control hypercortisolemia in cats, or whether rising ACTH levels eventually overwhelm enzymatic blockade has not been determined. Metyrapone appears to permit rapid correction of hyperadrenocorticism in some cats, and may be useful for pre-surgical stabilization prior to adrenalectomy.

We have recently evaluated the safety and efficacy of trilostane therapy (Vetoryl, Dechra Pharmaceuticals) in 15 cats with PDH. Clinical signs (13 of 15 cats) and ACTH stimulation testing results (13 of 15) improved with trilostane therapy. Diabetes mellitus was reported in 9/15 cases. Insulin requirements decreased by 36% within 2 months in 6/9 diabetic cats. Median survival time was 617 days for all cats (range 80-1,278 days). Complications included weight loss, urinary tract infections, chronic kidney disease, seizures, and recurrent pancreatitis. Hypocortisolemia was documented in 1 case. Cause of death occurred as a result of non-adrenal or non-diabetic illnesses (renal failure, seizures [caused by hypoglycemia or unknown]), or lymphoma. Trilostane ameliorates clinical signs of HAC in cats, is tolerated well in the long term, and can lead to improved regulation of diabetes. It should be considered first line therapy for cats undergoing medical management of PDH.

### **Hypoadrenocorticism**

Primary hypoadrenocorticism has been described in cats. Addisonian cats are middle-aged, with a median age of 4 years (mean 5.8 +/- 3.7 years) and range in age from 1.5 to 14 years. No sex or breed predilection is seen. The most common historical problems include lethargy, anorexia, and weight loss. Unlike dogs with adrenal insufficiency, diarrhea is not noted in Addisonian cats. Forty percent of cats have histories of episodic vomiting. Similar to hypoadrenocorticism in the canine, cats often have a waxing and waning clinical course, including temporary "remissions" associated with parenteral fluid and/or corticosteroid administration.

The most common findings on physical examination include depression, weakness, and mild to severe dehydration. Up to 40% present with in severe shock with weak pulses, slow capillary refill times, and extreme weakness or collapse. The duration of clinical signs preceding the diagnosis of hypoadrenocorticism ranges from 5 to 100 days, with a median of 14 days.

Clinicopathologic findings in cats with primary hypoadrenocorticism parallel the patterns seen in the dog. Serum electrolyte changes characteristic of mineralocorticoid deficiency are seen in most cats. Serum sodium:potassium ratios are less than 24 (range 17.9-23.7) with hyponatremia, hypochloremia, and hyperkalemia. All cats have had mild to severe azotemia (blood urea nitrogen 31-80 mg/dl, normal range 5-30 mg/dl; creatinine 1.6-6.0 mg/dl, normal range 0.5-1.5 mg/dl), and hyperphosphatemia (inorganic phosphorus 6.1-9.1 mg/dl; normal range 3.0-6.0 mg/dl). Hypercalcemia has been noted in one cat. Despite signs of dehydration and prerenal azotemia, urine

specific gravity was greater than 1.030 in only 40% of cats. The loss of renal medullary solutes, particularly sodium, is believed to result in impaired renal concentrating ability. Distinguishing hypoadrenocorticism from acute or chronic renal failure is critical to establishing an appropriate prognosis for clients.

Long-term management of cats with primary hypoadrenocorticism requires lifetime mineralocorticoid and glucocorticoid supplementation. Oral fludrocortisone acetate (0.1 mg/day) or intramuscular injections of desoxycorticosterone pivalate (DOCP; 10 -12.5 mg/month) have been successful in maintaining Addisonian cats. The dose of mineralocorticoid is adjusted as needed based on follow-up serum electrolyte concentrations monitored every one to two weeks during the initial maintenance period. Normal electrolyte parameters 2 weeks following DOCP suggests adequate dosing, but does not provide information concerning the duration of action of each injection. Eighty percent of dogs require DOCP more frequently than every 30 days (5% need to receive DOCP every 3 weeks), so frequent sampling during the early management period is recommended. Prednisone, 1.25 mg orally once a day, or intramuscular methylprednisolone acetate, 10 mg once a month, can be used to provide adequate long term glucocorticoid supplementation. Cats surviving the initial adrenal crisis can be managed successfully for many years. 60% of cats diagnosed with primary hypoadrenocorticism are alive a median of 2.75 years after diagnosis. With appropriate glucocorticoid and mineralocorticoid supplementation, cats with adrenocortical insufficiency should have a normal life expectancy.

### **Primary Hyperaldosteronism**

Feline primary hyperaldosteronism is diagnosed based on clinical signs, serum biochemistry, plasma aldosterone concentration, adrenal imaging and histopathology of adrenal tissue. Cats may present with blindness caused by systemic hypertension. Many will also present with weakness resulting from hypokalaemic polymyopathy. Elevated concentrations of plasma aldosterone and adrenocortical neoplasia have been documented in all cases. Seven cases had adrenal adenomas (unilateral in five and bilateral in two) and six had unilateral adrenal carcinomas. Three cases underwent medical treatment only with amlodipine, spironolactone and potassium gluconate; two cases survived for 304 and 984 days until they were euthanized because of chronic renal failure, while the third case was euthanized at 50 days following failure of the owner to medicate the cat. Ten cases underwent surgical adrenalectomy following a successful stabilization period on medical management. Five cases remain alive at the time of writing with follow-up periods of between 240 and 1803 days. Three cases were euthanized during or immediately following surgery because of surgical-induced hemorrhage. One cat was euthanized 14 days after surgery because of generalized sepsis, whilst the remaining cat was euthanized 1045 days after surgery because of anorexia and the development of a cranial abdominal mass. It is recommended that primary hyperaldosteronism should be considered as a differential diagnosis in middle-aged and older cats with hypokalaemic

polymyopathy and/or systemic hypertension and this disease should no longer be considered a rare condition.

In recent years, there has been renewed interest in primary hyperaldosteronism, particularly because of its possible role in the progression of kidney disease. While most studies have concerned humans and experimental animal models, a recent paper highlighted the occurrence of a spontaneous form of (non-tumorous) primary hyperaldosteronism in cats. At presentation, the main physical features of 11 elderly cats were hypokalemic paroxysmal flaccid paresis and loss of vision due to retinal detachment with hemorrhages. Primary hyperaldosteronism was diagnosed on the basis of plasma concentrations of aldosterone (PAC) and plasma renin activity (PRA), and the calculation of the PAC:PRA ratio. In all animals, PACs were at the upper end or higher than the reference range. The PRAs were at the lower end of the reference range, and the PAC:PRA ratios exceeded the reference range. Diagnostic imaging by ultrasonography and computed tomography revealed no or only very minor changes in the adrenals compatible with nodular hyperplasia. Adrenal gland histopathology revealed extensive micronodular hyperplasia extending from zona glomerulosa into the zona fasciculata and reticularis. In three cats, plasma urea and creatinine concentrations were normal when hyperaldosteronism was diagnosed but thereafter increased to above the upper limit of the respective reference range. In the other eight cats, urea and creatinine concentrations were raised at first examination and gradually further increased. Even in end-stage renal insufficiency, there was a tendency to hypophosphatemia rather than to hyperphosphatemia. The histopathological changes in the kidneys mimicked those of humans with hyperaldosteronism: hyaline arteriolar sclerosis, glomerular sclerosis, tubular atrophy and interstitial fibrosis. The non-tumorous form of primary hyperaldosteronism in cats has many similarities with "idiopathic" primary hyperaldosteronism in humans. The condition is associated with progressive renal disease, which may in part be due to the often incompletely suppressed plasma renin activity.

#### **References:**

Mellet, AM, Bruyette D, Stanley S: Trilostane therapy for spontaneous hyperadrenocorticism in cats: 15 cases (2004-2013). *J Vet Int Med* 27: 1471-77, 2013.

Bisignano J, Bruyette D: Feline Hyperaldosteronism. *J Vet Med* 19: 76-87, 2012.

Mamelak A, Owen T, Bruyette D: Transsphenoidal surgery for pituitary adenomas using a high definition video telescope in dogs with Cushing's disease. *Vet Surg* Jan 27: 1532-1543, 2014.



