FELINE ADRENAL DISORDERS
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Feline Cushing’s (hyperadrenocorticism or HAC) Syndrome (FCS) is a disorder of excessive cortisol secretion by the adrenal glands. Spontaneous FCS is caused by over production of cortisol by the adrenal glands. Approximately 85% of felines suffer from bilateral adrenocortical hyperplasia resulting from pituitary hyperplasia or tumor (PDH). The remaining 15% have an adrenal tumor (ATH) half of which are benign and half malignant. Regardless of the cause, FCS is usually (80%) accompanied by diabetes mellitus (DM).

FCS is caused by a pituitary adenoma with subsequent corticotrophic hyperplasia and excess adrenocortical cortisol secretion. Also found in cats with FCS are autonomously functioning benign adenoma (50%) or malignant adrenal carcinoma (50%). Iatrogenic FCS due to glucocorticoid administration is rare. Differential diagnoses include diabetes mellitus, insulin resistance, acromegaly, hepatic disease, sex hormone-secreting adrenal tumors and hypothyroidism.

There is no known breed or sex predisposition but is most often diagnosed in middle-aged to older cats. Clinical signs include olyuria (PU), polydipsia (PD), polyphagia (PP), fragile (bruising, tearing, thin) skin, weight loss, and muscle weakness. Obesity, hepatomegaly, alopecia, diarrhea, vomiting, abdominal enlargement, curled ear tips and unkempt appearance are also seen. Lethargy (dullness) has been reported due to muscle weakness or the effects of a pituitary mass. Excess sex hormones can cause signs such as penile barbs and behavioral changes (sexual behavior)

Common laboratory abnormalities include stress leukogram, hyperglycemia, hypercholesterolemia, mild increased alanine aminotransferase (ALT) due to poorly-regulated concomitant DM. Elevated serum alkaline phosphatase not as common as dogs because cats do not to have corticoid-induced isoenzyme. Less common are azotemia, proteinuria and hyperglobulinemia.

Screening Tests

Urine Cortisol-to-Creatinine Ratio (UC:CR) is sensitive (useful for its negative predictive value, i.e. if a normal UC:CR is obtained, FCS is unlikely), inexpensive and easy to perform and interpret. Home collection (non-stressed) of urine is preferred. Low-Dose Dexamethasone Suppression Test (LDDST) is extremely sensitive. It requires 10 times the dose used in dogs: 0.1 mg/kg IV. Plasma obtained for cortisol before, 4 and 8 hours after dexamethasone administration. Failure to suppress is consistent with FCS. ACTH stimulation test, mainly a test of adrenal reserve, requires little time, is easy to interpret, is relatively inexpensive, and specific for FCS when results are abnormal.

Differentiating Tests

High Dose Dexamethasone Suppression Test (HDDST): 1 mg/kg dexamethasone, protocol as with LDDs. An at-home version using multiple UC:CR’s and oral dexamethasone is easier to perform and interpret than the in-hospital protocol. Plasma Endogenous ACTH measurement is high normal or greater with PDH compared to low plasma ACTH levels with ATH (<10 pg/ml). The normal range for cats is 0 to 60 pg/ml. Blood is collected in EDTA, spun immediately, the plasma transferred to plastic and frozen. Abdominal ultrasound preferred to visualize adrenal glands. Although subjective, ultrasonography can be an excellent tool to discern PDH from ATH. Symmetric adrenal glands of normal or enlarged size are suggestive of PDH, whereas unilateral enlargement supports ATH. CT/MRI (computed tomography/magnetic resonance imaging) allows visualization of pituitary macroadenomas.

TREATMENT
Medical pretreatment is beneficial prior to surgery to prevent complications from fragile skin, infections and bruising. Pituitary Cobalt Radiation of PDH has the potential to become a part of FCS
treatment. Adrenalectomy for ATH (unilateral for ATH, bilateral for PDH) appears to be the most successful treatment option. Desoxycorticosterone pivalate (DOCP) and depo-medrol may be required.

MEDICATIONS

**DRUG(S)**

Mitotane (Lysodren; o,p'-DDD) causes selective destruction of cortisol-secreting adrenocortical cells. Doses of 50 mg/kg/day divided have been used but even doubled sometimes failed to demonstrate improvement.

Trilostane reversibly inhibits 3 beta-17-hydroxysteroid dehydrogenase, which blocks steroid synthesis. In a small number of FCS with PDH, trilostane reduced clinical signs and improved endocrine testing. Doses up to 60 mg/cat twice daily have been used.

**Suggested Reading**


Feline Addisons Disease

The diagnosis and treatment of hypoadrenocorticism (Addison’s disease) can be one of the greatest challenges faced by veterinary practitioners. The purpose of this review is to describe the clinical diagnosis and treatment of hypoadrenocorticism in dogs and cats.

Hypoadrenocorticism is a result of deficient secretion of both mineralocorticoids (aldosterone) and glucocorticoids. Naturally-occurring primary hypoadrenocorticism is usually caused by immune-mediated destruction of the adrenal cortex in both cats and dogs, however, lymphomatous infiltration of the adrenals has been reported as a cause of hypoadrenocorticism in cats. Secondary hypoadrenocorticism, in which the pituitary gland produces inadequate amounts of adrenocorticotropic hormone (ACTH), can be caused by chronic steroid therapy or less commonly by tumors, trauma, or congenital defects of the pituitary gland. Secondary hypoadrenocorticism is rare in both dogs and cats. Hypoadrenocorticism, which is glucocorticoid deficient only, has been termed “atypical” Addison’s disease. Secondary hypoadrenocorticism is always atypical and primary hypoadrenocorticism is atypical in the early stages of the disease prior to destruction of the zona glomerulosa.

Signalment, Clinical Signs and Laboratory Abnormalities

Canine hypoadrenocorticism is most often diagnosed in young cats of any breed or sex can also develop hypoadrenocorticism. Historical findings compatible with hypoadrenocorticism include intermittent vomiting, diarrhea, weight loss, lethargy, depression, anorexia, and weakness. There may be a history of vomiting or diarrhea responsive to non-specific treatment, such as intravenous fluids, only to have signs reoccur several days to weeks later. Often the clinical signs come and go (waxing and waning) periodically. As the disease progresses, the animal may present with collapse, hypothermia, shaking, polyuria, and polydipsia. Hair loss and melena are unusual historical findings. Differential diagnoses for the common clinical signs consistent with hypoadrenocorticism include inflammatory bowel disease, intestinal parasitism, bilious vomiting syndrome, and renal disease. A comparison of clinical signs hypoadrenocorticism in cats and dogs is shown in Table 1 and a comparison of typical and atypical hypoadrenocorticism in dogs is listed in Table 2.

Physical examination of animals in an acute Addisonian crisis reveals weak pulses, bradycardia, prolonged capillary refill time, severe mental depression, and profound muscle weakness. Clinical features which should heighten the index of suspicion of hypoadrenocorticism include a normal or slow heart rate in the face of circulatory shock, previous response to corticosteroid or fluid therapy, and a “waxing and waning” course of disease prior to collapse.

Classic electrolyte abnormalities, such as hyponatremia, hyperkalemia, hypochloremia, and sodium to potassium ratios of less than 20 to 1, are highly suggestive of primary hypoadrenocorticism.
However, gastrointestinal disease, acute renal failure, post-renal azotemia and abdominal/thoracic effusions are additional differential diagnoses. Azotemia and hyperphosphatemia also attend primary hypoadrenocorticism making it difficult to differentiate from acute renal failure. Azotemia associated with hypoadrenocorticism may be prerenal as a result of dehydration, hypovolemia or gastrointestinal hemorrhage.

Hypercalcemia may be observed in up to 30% of cats with hypoadrenocorticism as a result of hemoconcentration. Metabolic acidosis results from decreased hydrogen ion secretion in the renal distal tubule, increased generation of acids secondary to reduced tissue perfusion, and renal retention of organic acids. Animals with glucocorticoid deficiency only, will not show classic electrolyte imbalances, but may present with hypoglycemia as a result of impaired gluconeogenesis and glycogenolysis.

Hematological findings include mild normocytic normochromic (non-regenerative) anemia; however, if the animal is dehydrated the underlying anemia may be masked. The absence of a stress leukogram is a subtle but important feature of atypical hypoadrenocorticism. The presence of a normal or elevated eosinophil or lymphocyte count in a stressed animal should be viewed with suspicion for hypoadrenocorticism, particularly atypical Addison's disease. Eosinophilia and lymphocytosis are seen in 20% and 10% of animals with primary hypoadrenocorticism, respectively.

Urine specific gravity is frequently low and is attributed to medullary washout (inadequate medullary gradient due to sodium depletion) and decreased medullary blood flow. Dilute urine in the face of azotemia and hyperkalemia may easily be mistaken for acute renal failure. Hormonal assays are required to confirm the presence or absence of adrenal disease and to differentiate between hypoadrenocorticism and renal failure.

Electrocardiography and radiographic findings

If bradycardia is present, an electrocardiogram may be helpful in the diagnosis of hypoadrenocorticism. Classic electrocardiographic findings reported with hyperkalemia include prolonged QRS complexes, decreased R wave amplitude, increased T wave amplitude (“spiked” T waves), and prolonged or absent p waves. Sinoatrial standstill is the most common arrhythmia noted. Radiographs may demonstrate signs associated with volume depletion or decreased tissue perfusion, such as microcardia, narrowed vena cava, and hypoperfused lungs. Megesophagus has been reported uncommonly in dogs, but not cats with both typical and atypical hypoadrenocorticism.

Diagnostic testing

Diagnosis of primary hypoadrenocorticism is based on clinical signs, classic electrolyte imbalances, and confirmation with an ACTH response test. To perform the test, a serum sample is obtained before, 30 minutes (cats) and 1 hour (cats and dogs) after intravenous administration of synthetic ACTH (cosyntropin; 0.5 mg/kg). Endogenous plasma ACTH may be measured to determine if the hypoadrenocorticism is primary or secondary. This specimen must be collected in an EDTA tube, spun within an hour of sampling and stored in plastic prior to the administration of any corticosteroids.

Cats with primary hypoadrenocorticism will exhibit a subnormal response to ACTH administration. The baseline cortisol concentration is usually low or undetectable and the post-ACTH cortisol concentration is also low or undetectable. Endogenous plasma ACTH concentrations are dramatically increased in animals with primary hypoadrenocorticism (> 100 pg/ml) as a result of loss of negative feedback to the pituitary caused by decreased serum cortisol concentrations. In the case of secondary hypoadrenocorticism, which is caused by a pituitary deficiency of ACTH, the endogenous ACTH concentrations are typically decreased (<20 pg/ml). The response to exogenous ACTH is diminished, but not as dramatically as for primary hypoadrenocorticism. Baseline cortisol and post-ACTH cortisol concentrations may be in the normal range.

Therapy: Acute adrenal crisis

Acute adrenocortical insufficiency is a life-threatening emergency; therefore, therapy must be initiated immediately. Treatment of the Addisonian crisis consists of four parts: 1) fluid therapy and electrolyte stabilization, 2) glucocorticoid replacement therapy 3) treatment of gastrointestinal hemorrhage, and 4) mineralocorticoid replacement therapy.
Of primary importance is rapid administration of large volumes of intravenous fluids; 0.9% NaCl is the fluid of choice. Fluid delivery is accomplished using a jugular catheter. Blood samples for a complete blood count (CBC), chemistry profile, and resting cortisol level can be obtained through the catheter prior to initiating therapy. Rapid administration of intravenous fluids restores blood volume and improves renal perfusion which decreases serum potassium concentration via dilution and promotion of renal potassium excretion. However, if hyperkalemia persists, serum potassium can be rapidly decreased by intravenous administration of regular insulin and glucose (0.03 to 0.06 units/lb; for every unit of insulin given, 4 ml 50% dextrose) or intravenous administration of 10% calcium gluconate (0.4 to 1 mg/kg over a 10 - 20 minute period) to counteract the effects of elevated potassium on the heart.

Glucocorticoid therapy, using ultra-short acting corticosteroids such as dexamethasone sodium phosphate (2-4 mg/kg) or prednisolone sodium succinate (15-20 mg/kg), should be instituted immediately. Dexamethasone may be preferred in animals that require immediate glucocorticoid administration as it will not interfere with the cortisol assay; in addition, a single dose of short-acting corticosteroid will not suppress the hypothalamic pituitary adrenal axis.

Rapid correction of hyovolemia with 0.9% NaCl is usually sufficient to correct most electrolyte abnormalities, however, oral mineralocorticoid supplementation with fludrocortisone acetate (Florinef®) can be instituted as soon as vomiting ceases. Metabolic acidosis often resolves after fluid therapy; however, severe acidosis (pH < 7.1) may be treated with sodium bicarbonate. Hypoglycemia, if present and symptomatic, should be treated with a slow intravenous bolus of 50% dextrose (0.5 - 1.0 ml/kg).

Maintenance therapy and Prognosis

Mineralocorticoid supplementation, using oral fludrocortisone (0.1 mg/10 lbs PO q 24 hr) or deoxycorticosterone pivalate (DOCP, 2 mg/kg q 25 days) should be initiated after the results of dynamic adrenal testing have been received. Cats with hypoadrenocorticism are managed with injectable corticosteroids such as Depo-Medrol (10 mg/cat q 3-4 weeks) and DOCP (12.5 mg/cat q 3-4 weeks). Addisonian animals should be monitored every 3 weeks until the dosage and interval of administration is determined. Most dogs require DOCP every 25 days and most cats require DOCP every 30 days. Electrolytes should be used to determine the optimal dosing interval.

Prognosis

The long-term prognosis for animals with hypoadrenocorticism, once an adrenal crisis is controlled, is excellent. With appropriate glucocorticoid and/or mineralocorticoid replacement therapy, dogs should be expected to live a normal life. The importance of life-long therapy must be emphasized to the owners, as well as the potential for increasing glucocorticoid supplementation during stressful situations.
References


