ATYPICAL CUSHING’S DISEASE
(Abstracted from ACE endocrine course 2015, Dr. Rhett NICHOLS)

The majority of dogs with classical Cushing’s disease screened with an ACTH response or LDDST and will have at least one positive test.

Noncortisol steroid hormones are commonly elevated in dogs with classic HAC and nonadrenal illness and therefore, elevated levels are not specific for ACD.

Current reference ranges and cut-off levels may be misleading and need to be re-evaluated.

Cut-offs and the LDDS: The cut-off for the 8 hour cortisol following the administration of a low dose of dexamethasone can be quite variable from one veterinary laboratory to another. For example, the cut-off for the 8 hour cortisol at Antech Diagnostics, Michigan State University, and UC Davis ranges from 1.4 ug/dl, 1 ug/dl, and 0.6 ug/dl respectively.

Cut-offs and the ACTH response test: At Antech Diagnostics and Michigan State University diagnostic laboratories a post-ACTH cortisol concentration above 20 ug/dl is consistent with HAC, while at the University of Tennessee Endocrine diagnostic laboratory the reference range for cortisol in healthy dogs is different depending on whether the dog is a female or an intact or neutered male. For example, a post-ACTH cortisol > 10.85 ug/dl in an intact male is consistent with HAC, while a post-ACTH cortisol > 10.85 but < 17.5 ug/dl would be considered normal for an intact or spayed female and therefore not consistent with HAC.

Summary impact point: The cut-off values previously established for screening tests may be misleading, especially with milder cases and cases worked up at clinics with low disease prevalence. In other words, because the cut-offs are too high, ACD may be in actuality misdiagnosed cases of classic Cushing’s disease.

Summary impact point: Because ACD in dogs is often associated with adrenal hyperplasia, elevated 17-OHP and androstenedione concentrations, and occasionally low to low-normal cortisol concentrations post-ACTH administration, it has been suggested that ACD may be a congenital adrenal hyperplasia-like syndrome.

What is food-induced Cushing’s disease? The dogs with food-induced Cushing’s disease have signs and symptoms consistent with HAC, ultrasound evidence of bilaterally enlarged adrenal glands, normal ACTH response and LDDS tests, suppressed endogenous ACTH levels, and an increase in the urine cortisol:creatinine ratio > 50% following a meal (10).

TREATMENT CONSIDERATIONS FOR ATYPICAL CUSHING’S DISEASE

Mitotane may be the treatment of choice in dogs, especially in Scottish Terriers, that have extremely high concentrations of both androstenedione and 17-OHP. It is theorized that these dogs as adults have a congenital adrenal hyperplasia-like syndrome whereby elevated 17-OHP acts as an androgen precursor and fuels the rise of androstenedione which may be a risk factor for hepatocellular carcinoma.

FELINE ADRENAL DISORDERS
Deborah S. Greco DVM, PhD, Dip ACVIM
Nestle Purina Petcare, St Louis MO

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, hepatopathy, renal 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. In the IV protocol, plasma is obtained for cortisol analysis before, 4 and 8 hours after dexamethasone administration. Failure to suppress is consistent with FCS. In the UCCR low dose dexamethasone suppression test, a UCCR is collected on days 1 and 2 in the morning. After the second urine collection, oral dexamethasone soln (1 mg/kg) is given in 3 doses 6 hrs apart and the final urine is collected on the morning of the third day. Failure to suppress is consistent with FCS.

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 in cats but even doubling the dose failed to provide 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 Addison's 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

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, hypovolemic 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. Megaesophagus 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.1,2,9,11

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.1,2,11 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.1,11

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.11 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.2

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).11

**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).9 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.

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**Table 1.**

<table>
<thead>
<tr>
<th>Key Drug</th>
<th>Drug Class</th>
<th>Dose Range</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications</th>
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<td>Q 24 hr</td>
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<td>Hypoadrenocorticism</td>
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<td>Mineralocorticoid</td>
<td>12.5 mg/cat</td>
<td>Monthly</td>
<td>IM</td>
<td>Hypoadrenocorticism</td>
</tr>
<tr>
<td>Depo Medrol</td>
<td>Steroid</td>
<td>10 mg/cat</td>
<td>Monthly</td>
<td>IM</td>
<td>Hypoadrenocortism</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Corticosteroid</td>
<td>0.1 mg/cat</td>
<td>Q 24 hr</td>
<td>PO</td>
<td>Hypoadrenocorticism</td>
</tr>
</tbody>
</table>
References


HYPOADRENOCORTICISM IN SMALL ANIMALS

Deborah S. Greco DVM, PhD, Diplomate ACVIM

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 (hypercortisolemia), has been termed “atypical” Addison’s disease. Secondary hypoadrenocorticism is always atypical and primary hypoadrenocorticism can be 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 female dogs (70%) of any breed. However, hypoadrenocorticism has been reported in families of Leonbergers and standard poodles suggesting a genetic basis in some breeds. 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. Signs of megaesophagus, such as regurgitation and weight loss, have been reported uncommonly in dogs with both typical and atypical hypoadrenocorticism. Differential diagnoses for the common clinical signs consistent with hypoadrenocorticism include inflammatory bowel disease, intestinal parasitism (trichuriasis), 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.

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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 (trichuriasis), acute renal failure, post-renal azotemia and abdominal/thoracic effusions (third space) are additional differential diagnoses. Azotemia and hyperphosphatemia also attend primary hypoadrenocorticism. 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 dogs 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. Hypoalbuminemia has been described in association with hypoadrenocorticism; however, a cause and effect relationship has not been defined. 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 dogs with primary hypoadrenocorticism, respectively.

Urinary 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, ultrasound and radiographic findings**

If bradycardia is present, an electrocardiogram may be helpful in the diagnosis of hypoadrenocorticism, especially when serum electrolytes are not immediately available. 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. Electrocardiographic changes should not be used to determine the exact serum potassium concentrations because serum potassium concentrations do not directly correlate with specific EKG changes; however, the EKG is useful in an emergency setting. Radiographs may demonstrate signs associated with volume depletion or decreased tissue perfusion, such as microcardia, narrowed vena cava, and hypoperfused lungs. Megaesophagus has been reported uncommonly in dogs with both typical and atypical hypoadrenocorticism. Ultrasound cannot be routinely used to identify “small” adrenals, particularly since the right adrenal may be difficult to image in normal animals.

**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). Administration of a single dose of dexamethasone sodium phosphate prior to obtaining baseline or one hour post ACTH cortisol samples will not interfere with the test. However, administration of prednisolone will interfere with the ACTH response test because prednisolone will cross react with the cortisol assay. If corticosteroids have already been administered, one can wait 24 hours and perform the ACTH response test after the short-acting corticosteroids have dissipated. 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.

Dogs and 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.

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Of primary importance is rapid administration of large volumes of intravenous fluids; 0.9% NaCl is the fluid of choice. Fluid delivery is best accomplished using a jugular catheter. Blood samples for a complete blood count (CBC), chemistry profile, and resting cortisol level can be obtained through a central jugular 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 (crystalline) 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.1,18

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.18 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.2 Some Addisonian dogs may hemorrhage into the gastrointestinal tract because because of poor intestinal perfusion caused by shock..2,15 Treatment of anemia secondary to severe gastrointestinal hemorrhage should include blood transfusion coupled with gastrointestinal protectants. Metabolic acidosis often resolves after fluid therapy; however, severe acidosis (pH < 7.1) may be treated with sodium bicarbonate.18 Hypoglycemia, if present and symptomatic, should be treated with a slow intravenous bolus of 50% dextrose (0.5 - 1.0 ml/kg).1,18

**Maintenance therapy and Prognosis**

Mineralocorticoid supplementation, using oral fludrocortisone (Florinef®, 15-20 µg/kg/day PO q 24 hr) or deoxycorticosterone pivalate (DOCP, 2.2 mg/kg q 25 days) should be initiated after the results of dynamic adrenal testing confirm a diagnosis of hypoadrenocorticism. Glucocorticoid supplementation (0.22 mg/kg) must be given with DOCP as this drug has no glucocorticoid activity.19 Fludrocortisone, on the other hand, does provide some glucocorticoid activity; therefore, additional prednisolone supplementation is only required in about 50% of dogs.1, 19 All dogs should receive additional corticosteroids during periods of stress (i.e. elective surgery).

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).4 Most dogs require DOCP every 25-35 days and most cats require DOCP every 30 days.19 Monitoring of serum electrolytes should be used to determine the optimal dosing interval. Addisonian animals receiving DOCP should be monitored every 3 weeks until the dosage and interval of administration is determined and dogs receiving fludrocortisone should be monitored weekly until electrolytes become normal. In patients with normal potassium, but low sodium concentrations, sodium chloride tablets supplementation has been recommended in the past; however, the cause of the hyponatremia should be investigated and a thorough thyroid evaluation (TT4, cTSH) should be undertaken (see polyendocrine gland failure in small animals). Signs of DOCP toxicity include hypokalemia, hypernatremia, polydipsia and polyuria; however, DOCP toxicity is very difficult to induce.20

The practitioner may want to consider cost and size issues with regard to choosing between Florinef and DOCP.19 In large breed dogs (> 25 kg), the new formulation of DOCP (Dechra) may be a more economical choice. In a recent study looking at the response of Addisonian dogs to treatment, it was found that fewer than 20% of the dogs required the manufacturer’s recommended dose (2.2 mg/kg q 25 days) of DOCP. Therefore, if cost is a consideration, an initial dose of 1.5 mg/kg q 25 days can be administered and the response to therapy monitored. In the same study, adverse effects (iatrogenic Cushing’s) occurred in almost one third of the dogs receiving fludrocortisone and necessitated a change to DOCP.19

**References**


Table 1. Clinical Signs and Abnormal Laboratory Findings in Dogs and Cats with Primary Hypoadrenocorticism (Addison's disease).1,9

<table>
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<tr>
<th>Clinical signs</th>
<th>Cats (%) n=10</th>
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<td>Lethargy</td>
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Laboratory Findings

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</tr>
<tr>
<td>Azotemia</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>-----</td>
<td>40</td>
</tr>
<tr>
<td>Elevated ALT/AST</td>
<td>-----</td>
<td>30</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>-----</td>
<td>20</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>-----</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Urine specific gravity &lt;1.030</td>
<td>--</td>
<td>75</td>
</tr>
</tbody>
</table>
Table 3. Protocols for dynamic adrenal function testing in dogs and cats.

<table>
<thead>
<tr>
<th>Screening Tests for Hypoadrenocorticism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin (ACTH) Stimulation Test</td>
</tr>
<tr>
<td>Cosyntropin®</td>
</tr>
<tr>
<td>Protocol: 0.5 U/kg aqueous corticotropin IV or IM, serum samples at 0 and 1 hr (dog)</td>
</tr>
<tr>
<td>Protocol: 1/2 vial aqueous corticotropin IV or IM, serum samples at 0, 30 and 60 min (cat)</td>
</tr>
<tr>
<td>ACTH gel</td>
</tr>
<tr>
<td>Protocol: 2.2 U/kg corticotropin gel IM (max 20 units/dog), serum samples at 0 and 2 hrs</td>
</tr>
<tr>
<td>Protocol: 2.2 U/kg corticotropin gel IM, serum samples at 0, 1 and 2 hrs (cat)</td>
</tr>
<tr>
<td>Normals:</td>
</tr>
<tr>
<td>Pre: 1-4 μg/dl (28-110 mmol/L)</td>
</tr>
<tr>
<td>Post ACTH: &lt; 20 μg/dl (55-166 mmol/L)</td>
</tr>
</tbody>
</table>

LDDS:
DOSE: 1 mg/kg IV or PO
Sampling: IV—0, 4, 8 hr or PO (1mg/kg q 6 hrs, 3 doses)
Normal: Low UCCR baseline, suppression after dexamethasone

Endogenous ACTH
Protocol: Single plasma sample (may be collected prior to screening test and frozen for later analysis). Collect in EDTA vacutainer (with aprotinin), centrifuge and store in plastic, ship at 4°C (0-8°C)
Normals: 20-80 pg/ml (4.4-8.8 pmol/L)
FELINE HYPERALDOSTERONISM

- Primary hyperaldosteronism (PHA) or low-renin hyperaldosteronism is an adrenocortical disorder characterized by excessive, autonomous secretion of aldosterone leading to systemic hypertension and/or hypokalemia.

- This disorder is also referred to as Conn’s syndrome. In cats, the inappropriate aldosterone secretion is caused from either unilateral or bilateral neoplasia or bilateral nodular hyperplasia of the adrenal zona glomerulosa.

SIGNALMENT

- Median age of 13 years (range 5-20 years).
- There is no apparent sex or breed predilection.

HISTORY AND PHYSICAL EXAMINATION FINDINGS

- **History**
  - Loss of vision
  - PU/PD
  - Anorexia
  - Weight loss
  - Depression
  - Inability to jump

- **Physical Exam**
  - Mydriasis
  - Hyphema
  - Retinal detachment
  - Intraocular hemorrhages.
  - Muscle weakness- episodic or acute
  - Plantagrade stance of the hindlimbs
  - Cervical ventroflexion
  - Lateral recumbency
  - Collapse
  - Pendulous abdomen

LABORATORY ABNORMALITIES

- Hypokalemia (< 3.5 mEq/L)
- Arterial hypertension (> 170/100 mmHg)
- Elevated BUN and creatinine
- Elevated creatine kinase (CK)
- Hyperglycemia (less common)
- Hypophosphatemia (less common)
- Plasma aldosterone concentration (PAC) is increased
- Plasma renin activity (PRA) is below or within the reference interval

SCREENING TESTS FOR PHA IN CATS

- The ratio between the plasma aldosterone concentration (PAC) and plasma renin activity (PRA), termed the aldosterone-to-renin ratio (ARR), has been widely accepted as the screening test of choice for PHA in cats.
The combination of a high-normal or elevated PAC and a low PRA indicates persistent aldosterone synthesis in the presence of little or no stimulation by the renin-angiotensin system.

In addition, the potassium concentration should also be considered when evaluating the PAC. In the presence of hypokalemia, even a mildly elevated aldosterone level can be regarded as inappropriately elevated.

CONFIRMATORY TESTS FOR PHA IN CATS

The suppression test with the greatest utility in cats is the fludrocortisone suppression test.

- Fludrocortisone is administered at a dose of 0.05 mg/kg q12h for 4 days.
- A basal UACR < 7.5 x 10^-9 excludes PHA and a value of >45.9 x 10^-9 confirms it, while for values between 7.5 x 10^-9 and 45.9 x 10^-9 suppression by < 50% also confirms the diagnosis of PHA.

DIAGNOSTIC IMAGING

Diagnostic imaging techniques such as ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) are used to identify adrenal abnormalities and, in the case of neoplasia, to evaluate possible extension into the caudal vena cava and the presence of distant metastasis.

TREATMENT AND PROGNOSIS

Surgery

- Unilateral adrenalectomy is the treatment of choice for confirmed unilateral PHA,
- Preoperative and perioperative hypokalemia should be controlled as well as possible by oral and intravenous supplementation.

Medical therapy:

- Potassium supplementation
- Angiotensin receptor blocker (ARB) such as spironolactone. The initial dose is 2mg/kg BID, increased as needed to control hypokalemia. A dose in excess of 4 mg/kg may cause anorexia, vomiting, and diarrhea.
- Persistent arterial hypertension is often treated successfully with the calcium channel blocker amlodipine, at an initial dose of 0.1 mg/kg once daily.
- In PHA due to bilateral normokalemia can be sustained for long intervals with spironolactone alone or combined with lose doses of potassium

PROGNOSIS

- After complete removal of a non-metastasized aldosterone producing tumor, the prognosis is excellent.
- Cats that survive the immediate postoperative period have continue to be clinically asymptomatic for one to several years.

References


