When It Looks Like Cushing's But Doesn't Test Like Cushing's

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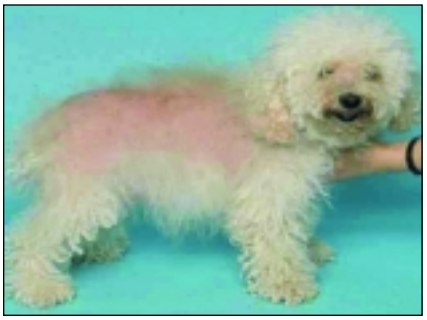
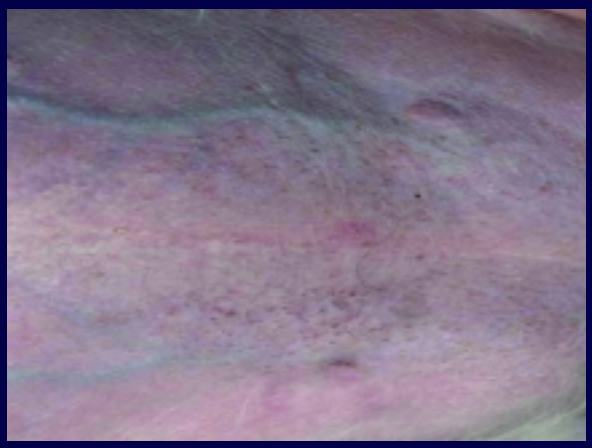


The Patient

Pumpkin, a 9-year-old, castrated, male miniature poodle had a 6-month history of "endocrine" alopecia. He had received multiple courses of antibiotics and one course of corticosteroids. No polydipsia or polyuria was observed. Pumpkin had evidence of external skin lesions as shown in ***Figure 1***, and he was panting on presentation. Results of the clinical pathology workup are shown in ***Tables 1 and 2***.



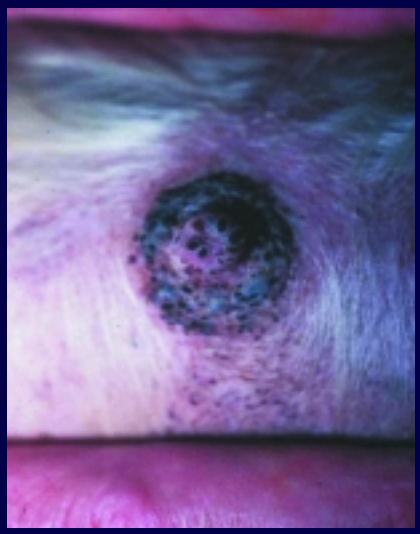


Figure 1. Skin lesions observed on Pumpkin at the time of presentation.

SPOT CHECK

What initial screening tests do you want to run?

	Seminar veterinarians said: NAVC / WVC
1. UCCR	***20% / 15%***
2. ACTH stimulation test	***31% / 36%***
3. Low-dose dexamethasone suppression test	***30% / 26%***
4. Thyroid T_4, TSH, FT_4D	***14% / 16%***
5. Bile acids	***5% / 7%***

Answer: 1, 2, or 3

TABLE 1. CLINICAL PATHOLOGY RESULTS: PUMPKIN

ALP	968
ALT	234
Cholesterol	425
NRBCs	
Stress leukogram	
Polycythemia	
Bile acids	25.9
Urine specific gravity	1.046
Sediment	Inactive
Culture	Negative

TABLE 2. ENDOCRINE TESTING: PUMPKIN	
T_4	1.8 µg/dL
TSH	0.2 ng/mL
FT_4D	24 nmol/L
UCCR	Positive, 85
Endogenous ACTH	75 pg/mL
LDDS	
Baseline	3.4 µg/dL
3-hour	1.7 µg/dL
8-hour	1.2 µg/dL

SPOT CHECK

What is the correct interpretation of the endocrine tests?

	Seminar veterinarians said: NAVC / WVC
1. The tests are diagnostic for hyperadrenocorticism.	***13% / 16%***
2. The tests are diagnostic for hypothyroidism.	***1% / 1%***
3. The tests are inconclusive.	***83% / 76%***
4. The tests definitively rule out hyperadrenocorticism.	***3% / 6%***

Answer: 3

Physical Examination

At a follow-up visit 3 months later, the owners were concerned that Pumpkin was still panting and that the alopecia was still present. Physical examination disclosed a small (4 mm) mass adjacent to the anus, but the rectal examination was normal. The mass was aspirated (see ***Figure 2***).

SPOT CHECK

What is your interpretation of the cytology (see Figure 2)?

	Seminar veterinarians said: NAVC / WVC
1. Perianal adenoma	***68% / 67%***
2. Anal sac carcinoma	***13% / 15%***
3. Lymphoma	***9% / 9%***
4. Sebaceous adenoma	***11% / 9%***

Answer: 1

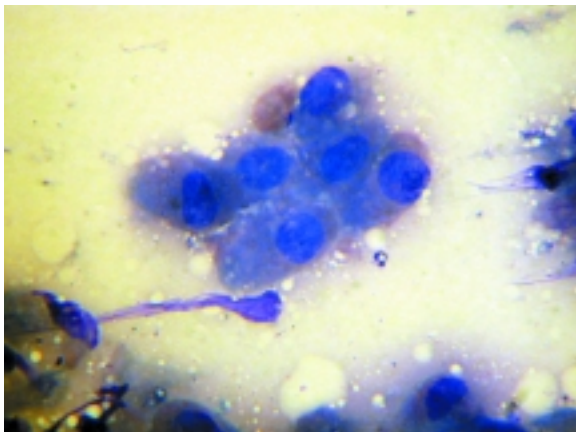


Figure 2. Aspiration cytology. Pumpkin returned for a follow-up visit after 3 months at which time on physical examination a 4 mm mass was detected adjacent to the anus and an aspiration sample was collected. His rectal examination was otherwise normal.

SPOT CHECK

What is your next step?

	Seminar veterinarians said: NAVC / WVC
1. Abdominal ultrasound	***45% / 41%***
2. Repeat the LDDS test	***16% / 22%***
3. High-dose dexamethasone suppression test	***11% / 5%***
4. ACTH stimulation test with sex steroid analysis	***28% / 30%***
5. Treat	***2% / 2%***

Answers: 1 and 4

Abdominal ultrasonography is a sensitive method of identifying adrenal tumors. ***Figure 3*** shows results following ultrasonography of Pumpkin's abdomen. A sex steroid analysis was also done, and results are shown in ***Table 3***.

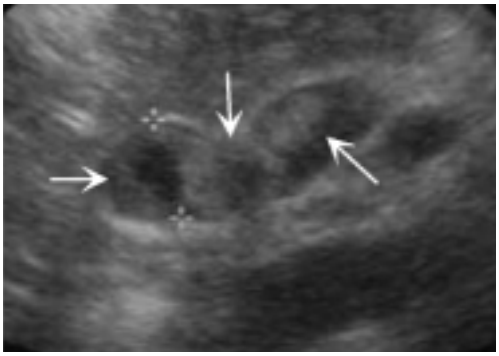


Figure 3. Hyperechoic nodules are evident on each pole (arrows), and there is a 1.35 cm cyst in the cranial pole. Abdominal ultrasonography is a sensitive method of identifying adrenal tumors.

TABLE 3. SEX STEROID ANALYSIS: PUMPKIN

	Pumpkin (ng/mL)	*Normal (ng/mL)*
Cortisol, baseline	41.5	7-65
Cortisol, postprandial	131.0	104-151
17α-OH progesterone, postprandial	5.2	0.4-1.2
Androstenedione, postprandial	48.5	2.7-8.0
Progesterone, postprandial	5.3	0-1.2
DHEAS, postprandial	16.7	0.3-12.0

SPOT CHECK

How should this dog be treated?

	Seminar veterinarians said: NAVC / WVC
1. Surgery	***71% / 61%***
2. Radiation	***1% / 5%***
3. Medical	***28% / 34%***

Answer: 1

SPOT CHECK

If you chose medical, which treatment would you use?

	NAVC seminar veterinarians said:
1. Mitotane	***74%***
2. Trilostane	***2%***
3. Ketoconazole	***9%***
4. Anipryl	***15%***

Answer: 1

Case Management

Pumpkin's adrenal tumor was surgically removed. He was prepared for surgery with a low dose (5 mg intramuscularly) of methylprednisolone acetate (Depo-Medrol—Pfizer Animal Health). Following his recovery from the surgical procedure, Pumpkin was sent home on a regimen of 2.5 mg of prednisolone once daily for 2 weeks, then every other day for 2 weeks.

Hyperadrenocorticism/Cushing's Syndrome

Diagnosis of hyperadrenocorticism, or Cushing's syndrome, in dogs may be challenging. The following sections review the etiology[1-3], common signalment[1,2], clinical signs[1,4-12] and laboratory findings[1-16] associated with the disease and then explore medical, surgical, and radiation treatment options.

Etiology

Hyperadrenocorticism (HAC) may be divided into two broad categories. One category, ***pituitary-dependent hyperadrenocorticism***, arises from adenomatous enlargement of the pituitary gland resulting in excessive adrenocorticotropin (ACTH) production. The other category, ***adrenal-dependent disease***, is associated with functional adenomas or adenocarcinomas of the adrenal gland. Ectopic ACTH secretion has not been reported in dogs; however, in humans ectopic ACTH secretion is associated with certain lung tumors. Iatrogenic HAC results from chronic excessive exogenous steroid administration. ***Figure 4*** illustrates the various forms of HAC.

Signalment

Hyperadrenocorticism is found in middle-aged to older dogs (7 to 12 years of age); approximately 85% have pituitary-dependent hyperadrenocorticism (PDH), and 15% suffer from adrenal tumors. Breeds in which PDH is commonly seen include the miniature poodle, dachshund, boxer, Boston terrier, and beagle. Large-breed dogs often suffer from adrenal tumors, and there is a distinct female (3:1) predilection.

History and Clinical Signs

The most common clinical signs associated with canine HAC are polydipsia, polyuria, polyphagia, heat intolerance, lethargy, abdominal enlargement or "pot belly," panting, obesity, muscle weakness, and recurrent urinary tract infections.[1,4-9] Dermatologic manifestations of canine HAC can

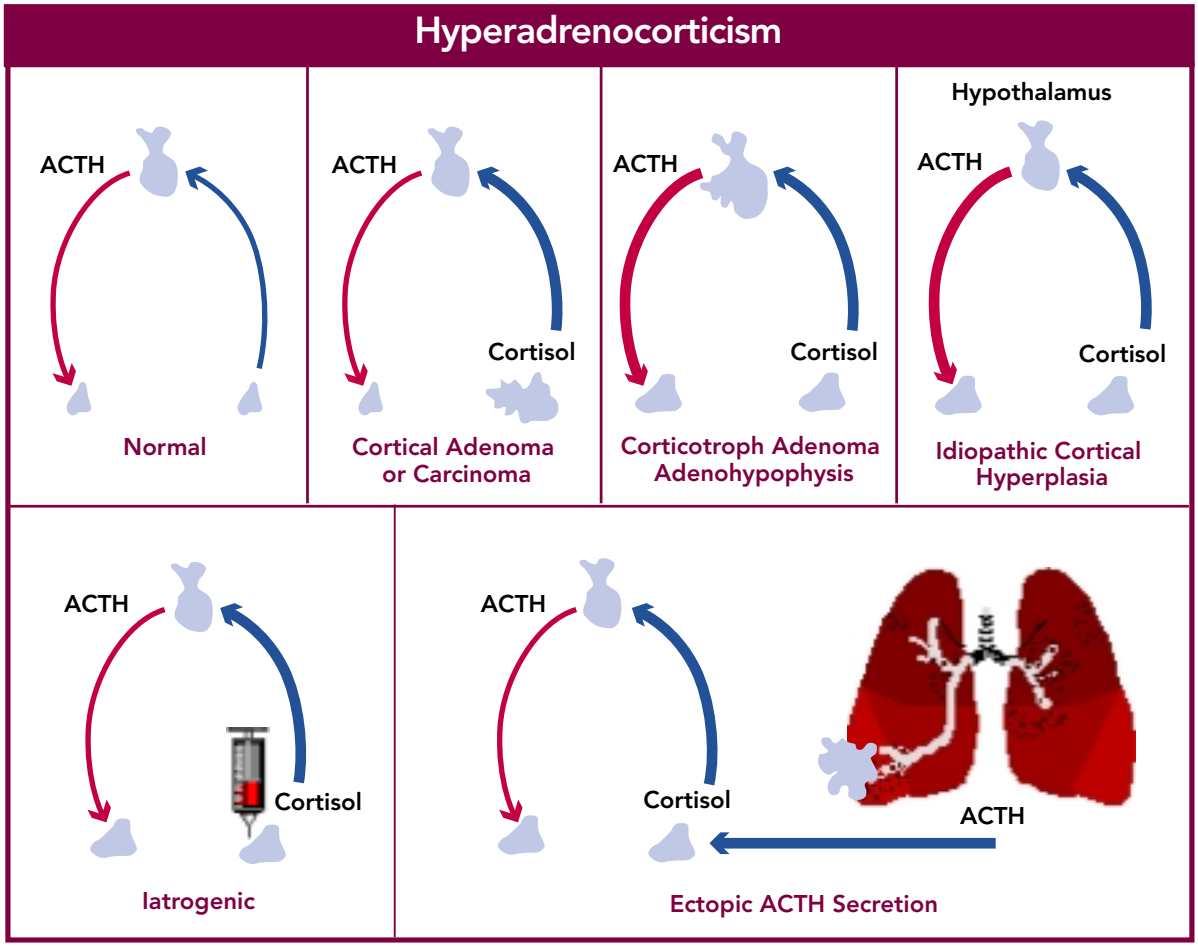


Figure 4. Various etiologies of canine and feline hyperadrenocorticism.

include alopecia (especially truncal), thin skin, phlebectasias, comedones, bruising, cutaneous hyperpigmentation, calcinosis cutis, pyoderma, dermal atrophy (especially around scars), secondary demodicosis, and seborrhea.[9]

Uncommon clinical manifestations of HAC in the dog can include such signs as hypertension, pulmonary thromboembolism, bronchial calcification or congestive heart failure and neurologic signs, such as polyneuropathy/myopathy, behavior changes, blindness, or pseudomyotonia. Evidence of hypercortisolemia may be evident as weakening of collagen manifesting as cranial cruciate rupture (small dog) or corneal ulceration (nonhealing). Finally, reproductive signs of HAC can include perianal adenoma in a female or castrated male, clitoral hypertrophy in females, testicular atrophy in intact males, or prostatomegaly in male castrated dogs.[4,5,10-12]

Laboratory Abnormalities

CLINICAL CLIPBOARD

The most common clinical signs associated with canine HAC are polydipsia, polyuria, polyphagia, heat intolerance, lethargy, abdominal enlargement or "pot belly," panting, obesity, muscle weakness, and recurrent urinary tract infections.

In dogs, serum chemistry abnormalities associated with hypercortisolemia include increased serum alkaline phosphatase (ALP), increased alanine transferase (ALT), hypercholesterolemia, hyperglycemia, and decreased BUN.[14,15] The hemogram is characterized by evidence of regeneration (erythrocytosis, nucleated red blood cells [NRBCs]) and a classic stress leukogram (eosinopenia, lymphopenia, and mature

leukocytosis). Basophilia is occasionally observed.[1,5,9] Many dogs with HAC have subclinical urinary tract infection without pyuria (bacteriuria and positive culture) but lack pyuria or proteinuria, which is likely to be caused by glomerulosclerosis.[1,5,13,16]

Thyroid status is often affected in animals with HAC, as evidenced by decreased basal thyroxine (T_4) and triiodothyronine (T_3), usually caused by euthyroid sick syndrome, and decreased endogenous thyroid-stimulating hormone (TSH) secretion, which can result from overcrowding of pituitary thyrotrophs.[17] Although less common in dogs than in cats, overt diabetes mellitus may result from the insulin antagonism caused by hypercortisolemia in about 25% of dogs with HAC.[15] Rarely, HAC can be a cause of insulin resistance and poor glycemic control in diabetics.

Diagnostic Approach

The diagnosis of HAC should be based on appropriate clinical signs (first and foremost) followed by supporting minimum database abnormalities (high cholesterol, SAP, etc) and confirmed via an appropriate screening test for HAC.[1,18,19] If screening test results are inconclusive (borderline, etc), or if laboratory abnormalities associated with HAC (increased SAP, etc) are noted in a dog without clinical signs of HAC, the dog should be retested at a later date (3 to 6 months) rather than be subjected to treatment for HAC without a definitive diagnosis. In particular, the diagnosis of sex steroid–induced Cushing's disease may be especially difficult.

SCREENING TESTS: DOES THE DOG SUFFER FROM HYPERADRENOCORTICISM?

CLINICAL CLIPBOARD

The diagnosis of HAC should be based on appropriate clinical signs (first and foremost) followed by supporting minimum database abnormalities (high cholesterol, SAP, etc) and confirmed via an appropriate screening test for HAC.

Serum alkaline phosphatase (SAP) isoenzyme is a screening test available to the practitioner. The advantages of SAP isoenzyme measurement are wide availability and low cost[20-23]; however, even small elevations in serum cortisol, such as those that occur with exogenous steroid administration in ocular preparations, can induce SAP isoenzyme. This test has a very low specificity (<44%) because it is affected by stress and by nonadrenal disease.[22] Another disadvantage is that this test cannot differentiate between endogenous and iatrogenic HAC.

CLINICAL CLIPBOARD

If screening test results are inconclusive or if laboratory abnormalities associated with HAC are noted in a dog without clinical signs of HAC, the dog should be retested at a later date (3 to 6 months) rather than be subjected to treatment for HAC without a definitive diagnosis.

The **urine cortisol to creatinine ratio (UCCR)** is highly sensitive in separating normal dogs from those with HAC, but the test is not highly specific for HAC because dogs with moderate to severe nonadrenal illness also exhibit elevated ratios.[23-28] Therefore, the UCCR test should be performed on a free-catch urine sample collected at home by the client. Even the stress associated with transportation to the veterinarian's office or restraint for cystocentesis, or both, can be enough to elevate a dog's cortisol level and cause a falsely elevated UCCR. Any abnormal UCCR should be confirmed with an ACTH stimulation test, an intravenous low-dose dexamethasone suppression (LDDS) test, or an oral LDDS test.[26-28]

The **LDDS test** is considered the screening test of choice for canine HAC when it is properly used.[1,24,29] It is an extremely sensitive test (92% to 95%); only 5% to 8% of dogs with PDH exhibit suppressed cortisol concentrations at 8 hours (ie, 5% to 10% false negatives).[19,30] In addition, 30% of dogs with PDH exhibit suppression at 3 or 4 hours followed by "escape" of suppression at 8 hours; this pattern is diagnostic for PDH making further testing unnecessary.[19] The major disadvantage of the LDDS test is the lack of specificity in dogs with nonadrenal illness. Kaplan and Peterson recently reported that more than 50% of dogs with nonadrenal illness will have a positive LDDS test.[31] It is recommended that a dog be allowed to recover from the nonadrenal illness prior to testing for HAC with an LDDS test.[19]

The **adrenocorticotropin (ACTH) stimulation test**

CLINICAL CLIPBOARD

The LDDS test is considered the screening test of choice for canine HAC. The major disadvantage of the LDDS test is the lack of specificity in dogs with nonadrenal illness. It is recommended that a dog be allowed to recover from the nonadrenal illness prior to testing for HAC with an LDDS test.

is used to diagnose a variety of adrenopathic disorders, including endogenous or iatrogenic HAC and spontaneous HAC.[8,29,32-34] As a screening test for the diagnosis of naturally occurring HAC, the ACTH response test has a diagnostic sensitivity of approximately 80% to 85% and a higher specificity than the LDDS test.[29,34] In the study by Kaplan and Peterson, only 15% of dogs with nonadrenal disease exhibited an exaggerated response to ACTH stimulation.[31] Adrenal tumors may be particularly difficult to diagnose using an ACTH stimulation test.[1,19]

WHEN THE SIGNS INDICATE CUSHING'S BUT THE TESTS DON'T: DOCUMENTING ADRENAL SEX STEROID EXCESS

Dogs suffering from adrenal sex steroid excess may have normal ACTH stimulation and LDDS tests because serum cortisol concentrations are normal. This may be due to excess cortisol precursors (***Figure 5***). Increases in progesterone, 17α-OH-progesterone, androstenedione, testosterone, and estrogens may require dynamic adrenal testing using the ACTH stimulation test and measurement of sex steroids in addition to cortisol.[35]

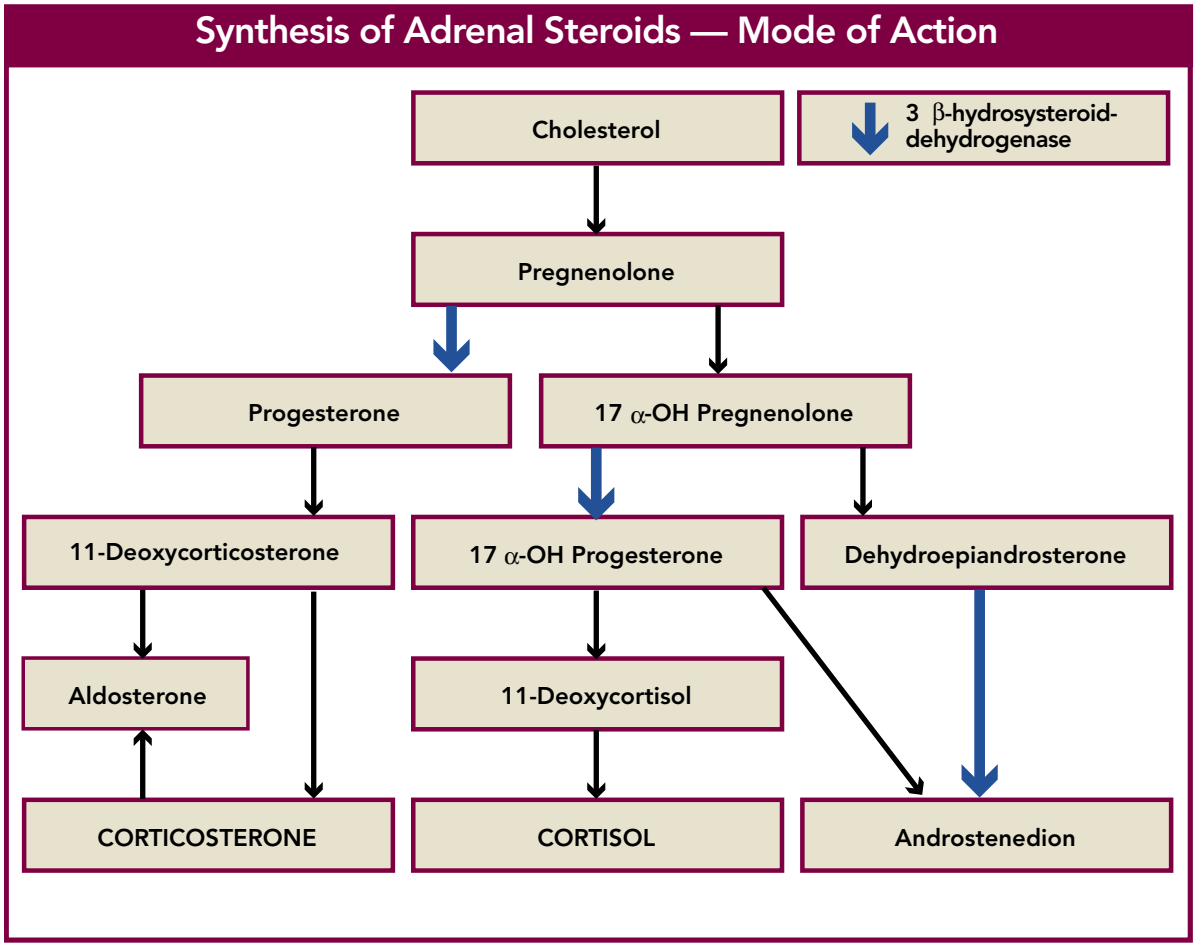


Figure 5. Steroid synthesis pathway.

DIFFERENTIATION TESTS: DOES THE DOG HAVE PITUITARY-DEPENDENT HYPERADRENOCORTICISM OR AN ADRENAL TUMOR?

After the diagnosis of HAC has been confirmed, differentiation of pituitary-dependent versus adrenal-dependent disease may be necessary. Although the majority of dogs with HAC suffer from PDH, certain cases that are atypical (eg, the anorectic dog with HAC) should alert the clinician to the fact that a differentiation test is appropriate. In particular, differentiation of PDH (often macroadenomas) from adrenal tumor is often necessary in large-breed dogs.

The **high-dose dexamethasone suppression (HDDS) test** works on the principle that autonomous ACTH hypersecretion by the pituitary can be suppressed by supraphysiologic concentrations of steroid. Dogs with autonomous cortisol-producing adrenal tumors have maximally suppressed ACTH production via the normal feedback mechanism; therefore, administration of dexamethasone, no matter how high the dose, cannot suppress serum cortisol concentrations in these dogs.[1,4] In dogs with PDH, however, the high dose of dexamethasone is able to suppress ACTH and, hence, cortisol secretion. One important caveat is that dogs with pituitary macroadenomas (15% to 50% of dogs with PDH) fail to suppress on the HDDS test.[1]

Measurement of endogenous plasma ACTH concentrations is the most reliable method of discriminating between PDH and adrenal tumor.[36] Dogs with adrenal tumors have low to undetectable ACTH concentrations; in contrast, dogs with PDH exhibit normal to elevated ACTH concentrations.[36] Recently, researchers have found that the addition of the protease inhibitor, aprotinin, to whole blood in EDTA tubes inhibits the degradation of ACTH.[37] Samples may be collected, spun in a nonrefrigerated centrifuge, and kept for up to 4 days at <4° C.[37]

CLINICAL CLIPBOARD

Dogs with adrenal tumors have low to undetectable ACTH concentrations; in contrast, dogs with PDH exhibit normal to elevated ACTH concentrations.

Diagnostic imaging of the pituitary and the adrenal glands can be accomplished via abdominal radiography, ultrasonography, computed tomography, or magnetic resonance imaging.[38,39] Abdominal radiographs should be performed in all dogs that fail to suppress on an HDDS; approximately 30% to 50% of dogs with adrenal tumors exhibit a mineralized mass in the area of the adrenal glands.[38] A more sensitive method of identifying adrenal tumors is via abdominal ultrasonography.[38] In addition, liver metastasis or invasion into the vena cava may be demonstrated in dogs with adrenal carcinomas.

Either computed tomography or magnetic resonance imaging, or both, of the brain or abdominal cavity in dogs that fail to suppress on the HDDS may demonstrate unilateral adrenal enlargement (50%), pituitary macroadenoma (25%), or pituitary microadenoma (25%).[39-41]

There is no single test or combination of tests that performs with 100% accuracy for making a diagnosis of HAC. The sensitivity and specificity of individual tests or combinations of tests to make an accurate diagnosis of HAC are increased when they are applied to a patient population that is likely to have HAC. Most of the tests used in the diagnosis of HAC are markedly affected by the presence of other, perhaps unrelated, disorders; and, as a result, these tests perform poorly when applied to dogs with nonadrenal illness. Proper patient selection is essential in order to get useful diagnostic information from such tests as the LDDS and UCCR, both of which have a high false-positive rate when applied to the general population of sick patients. Similarly, the results of the HDDS test are more meaningful when considered in light of results of imaging studies, a finding that underscores the need for an integrated diagnostic strategy in most patients.

CLINICAL CLIPBOARD

There is no single test or combination of tests that performs with 100% accuracy for making a diagnosis of HAC. The sensitivity and specificity of individual tests or combinations of tests to make an accurate diagnosis of HAC are increased when they are applied to a patient population that is likely to have HAC.

Treatment When It looks Like Cushing's But Doesn't Test Like Cushing's

MEDICAL THERAPY

Three treatment options are available for canine HAC. Medical, surgical, and radiation therapy have all been used, and all three treatment modalities have met with varying degrees of success.[1]

Mitotane

Medical therapy has been successful in most dogs with HAC. The majority of dogs respond to mitotane (Lysodren (o′p′ DDD)—Bristol-Myers Squibb).[1] An outline for the standard treatment of Cushing's syndrome with mitotane is shown in ***Figure 6***. Other methods of treatment with mitotane include creating hypoadrenocorticism by administration of 50 mg/kg/day for 30 days and administration of a low dose (25 mg/kg) weekly for 1 month. Monitoring consists of ACTH response tests; the post-ACTH cortisol level should be in the normal range.

Ketoconazole

Ketoconazole is a steroid inhibitor used to reversibly treat dogs with HAC. A dosage of 15 mg/kg/day divided into twice-daily dosing is used initially, and the dose is increased slowly (over 3 weeks) to 30 mg/kg/day divided to twice daily dosing. Ketoconazole is **not often used** in dogs because of expense and because severe anorexia may result from the drug itself. The primary use of ketoconazole in HAC is to prepare the dog for surgical adrenalectomy or radiation therapy. Cortisol levels after ACTH stimulation should be in the normal range.

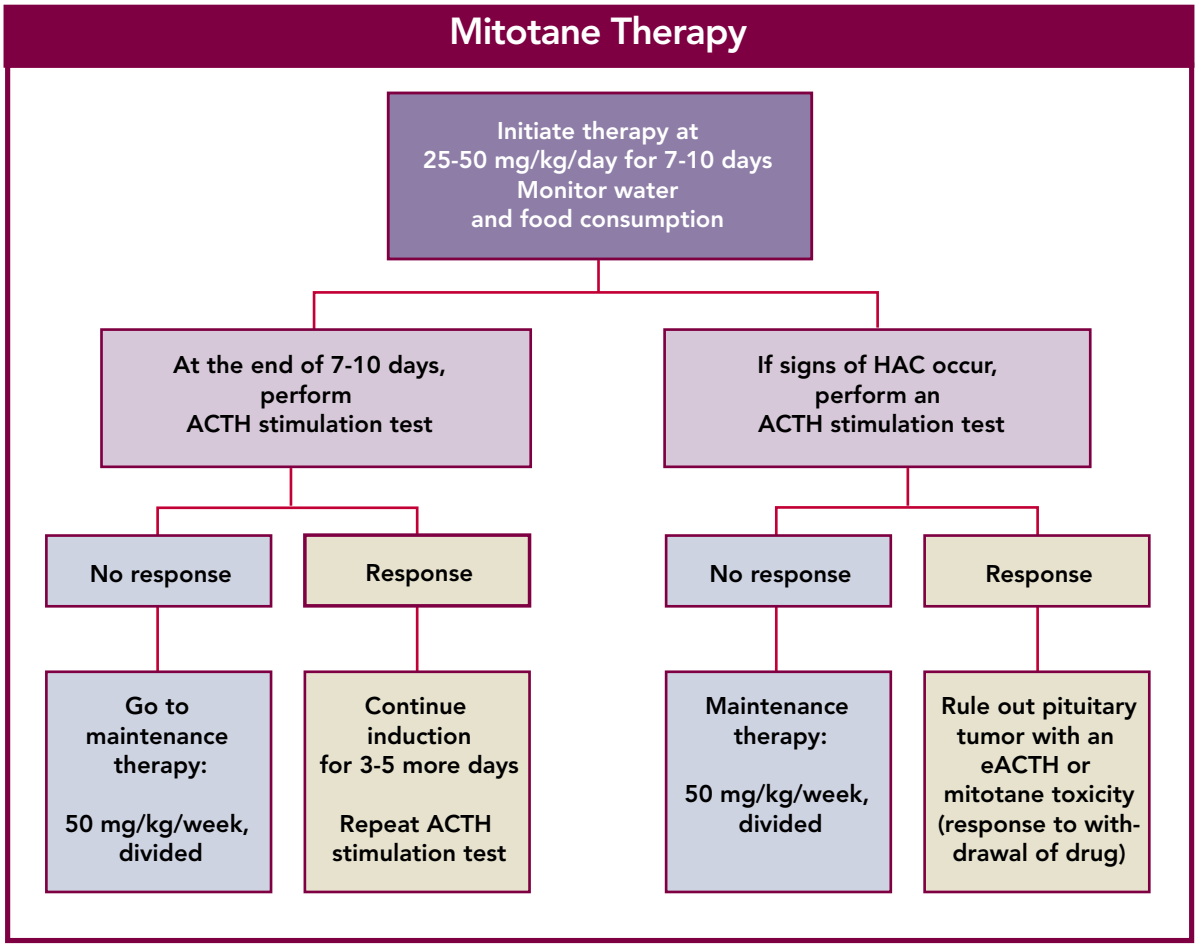


Figure 6. Treatment of hyperadrenocorticism in dogs with mitotane: an algorithm.

Deprenyl

There are no large studies looking at the efficacy of deprenyl (selegiline; Anipryl—Pfizer Animal Health) in dogs with PDH compared with placebo. As a monoamine oxidase type B (MAO-B) inhibitor, deprenyl would be expected to work on the minority of dogs with PDH and suffering from pars intermedia tumors because these tumors are thought to be under the regulation of dopamine. The authors limit the use of this drug to patients with mild HAC (skin disease only) or patients that do not tolerate mitotane or ketoconazole.

Trilostane

Trilostane is an orally administered competitive inhibitor of 3 beta-hydroxysteroid dehydrogenase, the enzyme that mediates the conversion of pregnenolone to progesterone and, hence, its end products (cortisol, aldosterone, and androstenedione) in the adrenals. Studies in dogs with HAC have shown that trilostane is an effective steroid inhibitor that is associated with minimal side effects.[42,43] Although currently unavailable in the United States, trilostane may prove to be a reasonable alternative to mitotane therapy for HAC in dogs, particularly those suffering from sex steroid imbalance.

SURGICAL THERAPY

Surgical treatment of HAC consists of unilateral or bilateral adrenalectomy. The reader is referred to surgical texts for an explanation of the surgical procedure; however, medical management of the dog during the operative and postoperative period is essential for a good outcome. Mineralocorticoid (desoxycorticosterone pivalate [DOCP] at 2.2 mg/kg intramuscularly every 25 days) and glucocorticoid (prednisone orally at 0.2 mg/kg daily) supplementation should be initiated immediately before adrenalectomy to prevent corticosteroid withdrawal syndrome. Complications following adrenalectomy include dehiscence, poor wound healing, Addisonian crises, and enlargement of the pituitary tumor, which may result in blindness or seizures (Nelson's syndrome).

RADIATION THERAPY

As 85% of all dogs with HAC have PDH, radiation therapy is another treatment option for many patients; however, radiation therapy is expensive ($1,500 to $2,000) and time-consuming (3 weeks' duration). Results of radiation therapy in dogs at Colorado State University Veterinary Teaching Hospital show that it is an effective method of treatment and associated with low morbidity, but signs of PDH may take several months to subside in treated animals. Eventually, though, treated dogs do well long-term (years) because the primary disease process (pituitary tumor) has been addressed.

CLINICAL CLIPBOARD

Results of radiation therapy in dogs show that it is an effective method of treatment and associated with low morbidity, but signs of PDH may take several months to subside in treated animals. Eventually treated dogs do well long-term (years) because the primary disease process has been addressed.

Wrap-up

The diagnosis of hyperadrenocorticism can be challenging because many diseases cause clinical signs that are similar to those caused by Cushing's disease. It is important to make every effort to ensure that hyperadrenocorticism is correctly diagnosed and to avoid overdiagnosis.

The authors advise clinicians to remember these simple rules when approaching the diagnosis of hyperadrenocorticism:

- ✔ The laboratory tests are most useful when applied to dogs with presenting complaints, clinical signs, and physical examination findings that are consistent with Cushing's disease.
- ✔ Postpone testing in dogs with significant nonadrenal illness.
- ✔ When signs are mild or inconsistent with hyperadrenocorticism, or when laboratory results are inconclusive, reevaluation in 3 to 6 months is justified, so long as the dog's clinical condition is stable and serious illness has been ruled out.

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UPDATE ENDOCRINOLOGY: ADRENAL DISEASE

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 the 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.

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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, 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

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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.[1] Naturally-occurring primary hypoadrenocorticism is usually caused by immune-mediated destruction of the adrenal cortex in both cats and dogs;[1,2,3] however, lymphomatous infiltration of the adrenals has been reported as a cause of hypoadrenocorticism in cats.[4] Secondary hypoadrenocorticism, in which the pituitary gland produces inadequate amounts of adrenocorticotrophic hormone (ACTH), can be caused by chronic steroid therapy or less commonly by tumors, trauma, or congenital defects of the pituitary gland.[1,4] Secondary hypoadrenocorticism is rare in both dogs and cats. Hypoadrenocorticism, which is glucocorticoid deficient only, has been termed "atypical" Addison's disease.[4] 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.[4,9] Historical findings compatible with hypoadrenocorticism include intermittent vomiting, diarrhea, weight loss, lethargy, depression, anorexia, and weakness.[1-6] 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.[1,2] 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. [1,2] 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. [10] 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.[9] Animals with glucocorticoid deficiency only, will not show classic electrolyte imbalances, but may present with hypoglycemia as a result of impaired gluconeogenesis and glycogenolysis.[1,5]

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.[5] 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. [1-6]

Urine specific gravity is frequently low and is attributed to medullary washout (inadequate medullary gradient due to sodium depletion) and decreased medullary blood flow.[1] 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.[1] 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. [1,2]

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). [1,2,10] 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. [2]

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. [1,2] 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). [1] 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.

Table 1.

Key Drug	Drug Class	Dose Range	Frequency	Route	Indications
Florinef	Minieralocorticoid	0.1 mg/cat	Q 24 hr	PO	Hypoadrenocorticism
DOCP	Mineralocorticoid	12.5 mg/cat	Monthly	IM	Hypoadrenocorticism
Depo Medrol	Steroid	10 mg/cat	Monthly	IM	Hypoadrenocorticism
Prednisolone	Corticosteroid	0.1 mg/cat	Q 24 hr	PO	Hypoadrenocorticism

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

Clinical signs	Cats (%) n=10	Dogs(%) n=225
Lethargy	100	95
Anorexia	100	90
Weight loss	100	50
Dehydration	88	45
Weakness	75	75
Slow capillary refill	63	30
Weak pulse	50	20
Vomiting	25	75
Polyuria/polydipsia	25	25
Bradycardia	13	18
Diarrhea	-----	40
Waxing/waning course	-----	40
Previous response to therapy	---	35
Hypothermia	----	35
Shaking	----	27
Melena	----	15
Painful abdomen	----	8
Hair loss	----	5
Laboratory Findings		
Hyperkalemia	100	95
Hyponatremia	100	80
Hypochloremia	100	40
Azotemia	100	85
Hyperphosphatemia	88	85
Metablic acidosis	----	40
Elevated ALT/AST	----	30
Hyperbilirubinemia	----	20
Hypercalcemia	13	30
Hypoglycemia	----	17
Anemia	25	25
Eosinophilia	20	13
Lymphocytosis	38	10
Urine specific gravity <1.030	--	75

Table 3. Protocols for dynamic adrenal function testing in dogs and cats.

Screening Tests for Hypoadrenocorticism
Corticotropin (ACTH) Stimulation Test Cosyntropin® Protocol: 0.5 U/kg aqueous corticotropin IV or IM, serum samples at 0 and 1 hr (dog) Protocol: 1/2 vial aqueous corticotropin IV or IM, serum samples at 0, 30 and 60 min (cat) ACTH gel Protocol: 2.2 U/kg corticotropin gel IM (max 20 units/dog), serum samples at 0 and 2 hrs Protocol: 2.2 U/kg corticotropin gel IM, serum samples at 0, 1 and 2 hrs (cat) Normals: Pre: 1-4 □g/dl (28-110 mmol/L) Post ACTH: < 20 □g/dl (550 mmol/L) 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), centriguge and store in plastic, ship at 4□C (or frozen if not collected in aprotinin) 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 in is caused from either unilateral or bilateral neoplasia or bilateral nodular hyperplasia of the adrenal zona glomerulosa.

SIGNALMENT

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- 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.

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Feline Hyperthyroidism: update on pathogenesis and treatment

Hyperthyroidism is the most common endocrinopathy of cats. Hyperthyroidism in cats most often is caused by autonomously hyperfunctioning nodules of the thyroid gland. These nodules secrete thyroxine (T4) and triiodothyronine (T3), uncontrolled by normal physiologic influences (e.g., pituitary thyrotropin (TSH) secretion). One or both lobes of the thyroid gland can be affected. Rare cases of feline hyperthyroidism (1-2%) are caused by hyperfunctioning thyroid carcinoma.

Pathogenesis

Feline hyperthyroidism was first described in 1979 and 1980 by investigators in NYC and Boston. During a 14 year period from 1970-1984, an average of 1.9 cats per year were diagnosed with hyperthyroidism; however, it is now estimated that the incidence is as high as 2% of the feline population seen in tertiary care veterinary facilities. Since then, hyperthyroidism has become the most frequently diagnosed endocrinopathy in the cat with reports stemming from North America, Europe (esp UK), New Zealand and Australia.

Canned cat food has been implicated as a cause of feline hyperthyroidism in multiple epidemiological studies. (Kass 1999, Martin 2000, Edinboro 2004) The suspected goitrogen is bisphenol-A-diglycidyl ether (BADGE), a substance used in making the liner of easy-open “pop-top” cans. It is suspected that this compound can leach into the foods and be consumed by cats. While this BADGE-based lining is generally considered safe and is used for foods for human consumption, cats may be more susceptible to toxic effects of this compound because they have a greatly reduced ability to detoxify it via hepatic glucuronidation. Bisphenol A also reduces triiodothyronine binding and causes increased TSH secretion resulting in hyperthyroidism and goiter in rats and some humans. While cat studies may not be available, rodent studies show a very high safety margin. (Poole 2004) It should be noted that epidemiological studies showing associations are not the same as cause and effect. Over 90% of cats in the US consume commercial pet foods as their primary nutritional source, and relatively few develop hyperthyroidism.

More recently, investigators have honed in on the molecular aspects of feline hyperthyroidism. The disease in cats is more similar to toxic nodular goiter in humans and is characterized by autonomous growth of thyroid follicles. The pathogenesis of toxic nodular goiter is an abnormality in the signal transduction of the thyroid cell. The TSH receptor on the thyroid cells activated receptor-coupled guanosine triphosphate-binding proteins (G proteins). Uniquely, the thyroid cell proliferation and hormone production are both controlled by the TSH receptor- G-protein-cAMP signaling. Overexpression of stimulatory G proteins and underexpression of inhibitory G proteins have been demonstrated in

some humans with toxic nodular goiter. (Derwalht 1995, Delmer 1992) Mutations of the TSH receptor that result in the receptor remaining activated without ligand (ie, TSH) have also been reported in humans with toxic nodular goiter. (Parma 1997, Fuhrer 1997, Holzapfel 1997, Russo 1996) In hyperthyroid cats, the same abnormalities have been investigated and it appears that activation mutation of the TSH receptor may be part of the pathogenesis of feline hyperthyroidism in some cats. (Peeters 2002) Furthermore, abnormalities of G proteins, specifically significantly decreased G inhibitory protein expression has been described in tissues from hyperthyroid cats. (Hammer 2000)

In one study, the use of cat litter was associated with an increased risk of hyperthyroidism (Kass 1999); however, there was no significant difference between different litter brands suggesting that the use of litter is simply a marker of cats that are kept indoors. (Peterson and Ward 2007) Indoor cats are likely to live longer and hence have a higher risk of developing hyperthyroidism. Exposure to pesticides and herbicides has been associated with thyroid abnormalities in other species. (Gaitan 1990) In particular, the use of flea control products was associated with an increased risk of developing hyperthyroidism; however, no specific product or ingredient could be identified. (Scarlett 1988, Olkzak 2005)

One recent report implicated brominated flame retardants (BFRs) as carcinogens/goitrogens possibly associated with feline hyperthyroidism.(Dye 20007) Coincidently BFRs were introduced 30 years ago at the same time that feline hyperthyroidism emerged. Bromide, a halide, is an intriguing agent to implicate in feline hyperthyroidism because of the unique composition of thyroid hormones which contain the halide iodide. In this recent abstract, serum levels of lipid adjusted serum polybrominated diphenylethers (PBDE) levels were 10-400- fold higher than those found in human exposure The authors theorized that these findings of high PBDE serum levels is in accord with the most consistently identified risk factor which is “indoor living”. The authors also propose that cats are at increased risk because of meticulous grooming behavior and increased exposure to furniture and carpets. The small size of cats is also a possible risk factor for increased serum levels of PBDEs. Recent publications point to PBDEs as the most likely environmental contaminant that may contribute to feline hyperthyroidism. (Peterson 2012)

Signalment and Clinical Signs

Middle-aged to older cats are typically affected, and there is no breed or sex predilection. Hyperthyroidism is characterized by hypermetabolism; therefore, polyphagia, weight loss, polydipsia and polyuria are the most prominent features of the disease. Gastrointestinal signs of hyperthyroidism include vomiting caused by stimulation of the CRTZ and overeating and diarrhea caused by malabsorption. Activation of the sympathetic nervous system is also seen with hyperactivity, tachycardia, pupillary dilatation and behavioral changes also characteristic of the disease in cats. Long-standing hyperthyroidism leads to hypertrophic cardiomyopathy,

high-output heart failure and cachexia which may lead to death. Radiographic and echocardiographic evaluation of the hyperthyroid cat often reveals hypertrophic cardiomyopathy. Occasionally, pseudochylous thoracic effusions may be observed in severely hyperthyroid cats.

Clinicopathologic features of hyperthyroidism include erythrocytosis and an excitement leukogram (neutrophilia, lymphocytosis) caused by increased circulating catecholamine concentrations. Increased catabolism of muscle tissue in hyperthyroid cats may result in increased BUN, but not creatinine. In fact, GFR is increased in hyperthyroid cats, which may mask underlying renal insufficiency. Although hyperthyroidism increases GFR, the effect of thyroid hormone excess on the urinalysis is variable. Most cats, however, will have decreased urine specific gravity particularly if they are exhibiting polyuria as a clinical sign. Increased metabolic rate results in liver hypermetabolism; therefore, serum activities of liver enzymes increase (ALT, AST) in 80-90% of hyperthyroid cats. Serum cholesterol decreases, not as a result of decreased synthesis, but rather as a result of increased hepatic clearance mediated by thyroid hormone excess.

Diagnosis

Diagnosis of feline hyperthyroidism is achieved by measurement of total serum concentrations of thyroxine (TT4); total serum triiodothyronine (TT3) is generally non-contributory to a diagnosis. Because the disease has become more common and recognized in its early stages, serum free thyroxine concentrations (FT4) have recently been shown to be more diagnostic of early or “occult” hyperthyroidism. However, FT4 concentrations should be interpreted in light of the TT4 as nonthyroidal illness (CRF) can result in spurious elevations of FT4 as well. Free triiodothyronine (FT3) concentrations do not provide any further advantage over FT4. Diagnosis may be challenging in cats with occult hyperthyroidism who demonstrate clinical signs suggestive of hyperthyroidism (polyphagia, polydypsia, polyuria, weight loss, goiter) but who have normal (usually high-normal) TT4 concentrations. In cases of suspected occult hyperthyroidism, the T3 suppression test or the TRH stimulation test may be indicated.

Associated Conditions

Increased GFR and reduced muscle mass induced by hyperthyroidism can mask underlying CKD. Because it is not always possible to predict which hyperthyroid cats have underlying CKD, a treatment trial with methimazole or carbimazole should be considered. Serum T4 and renal parameters should be rechecked after 30 days of methimazole/carbimazole administration. If renal parameters remain normal after euthyroidism is restored, it is safe to proceed with permanent therapy such as thyroidectomy or radioactive iodine. Hyperthyroidism may contribute to the development or progression of renal disease in cats, suggesting that leaving a hyperthyroid cat untreated (or poorly regulated with methimazole) may be detrimental to long-term kidney function.

Cardiac disease associated with hyperthyroidism is mild and reversible in most cats with hyperthyroidism. Murmurs and tachycardia are common but often do not result in clinical signs. On the occasions when cats show more severe cardiac changes such as congestive heart failure or aortic thromboembolism, these should be stabilized before a cat undergoes thyroidectomy or radioiodine therapy. High blood pressure develops in

approximately 10% to 15% of untreated hyperthyroid cats. However, hypertension is generally mild to moderate in severity and reversible upon induction of euthyroidism

Liver disease may be suspected in cats with untreated hyperthyroidism because of their high liver enzymes (serum ALT and alkaline phosphatase). At the time of diagnosis, it is not always possible to know if increased liver enzymes are due to hepatic disease unrelated to hyperthyroidism or merely a manifestation of hyperthyroidism. If underlying primary liver disease is expected, especially if the cat is showing signs of apathetic hyperthyroidism (e.g., anorexia, depression, etc.), a treatment trial with methimazole or carbimazole should be considered.

Medical Therapy

Medical management requires no special facilities and is readily available. Anesthesia is avoided, as are the surgical complications associated with thyroidectomy. However, this form of treatment is not curative and requires regular biochemical monitoring to ensure the efficacy of treatment. The thyroid tumor continues to grow and, after many months, may transform from adenoma to thyroid carcinoma in approximately 10% of chronically treated cats. (Peterson 2012)

Long-term medical management best reserved for cats of advanced age or for those with concurrent diseases, and for when owners refuse either surgery or radioactive iodine. In addition to long-term treatment, medical management is also necessary prior to surgical thyroidectomy to decrease the metabolic and cardiac complications associated with hyperthyroidism.

Short-term medical management is often recommended as trial therapy prior to 131-I therapy to determine the effect of restoring euthyroidism on renal function.

Methimazole is specifically licensed for treatment of feline hyperthyroidism both in Europe and USA as 2.5-mg and 5-mg tablets (Felimazole, Dechra Veterinary Products). For most hyperthyroid cats, a starting dose of 1.25 to 2.5 mg methimazole administered once to twice daily is recommended. Methimazole can be reformulated in a organogel for transdermal administration and is effective in cats when administered at a dose of 2.5 mg twice daily transdermally. The gel is applied in a thin layer to the non-haired portion of the pinnae. Transdermal administration is associated with fewer gastrointestinal side effects than the oral route, but some cats resent manipulation of their ears and crusting can occur between doses leading to erythema.

Monitoring of cats on antithyroid drugs is extremely important. Initially, cats should be reassessed after 2 to 3 weeks and a serum total T4 concentration measured. If euthyroidism has not been achieved the dose of methimazole or carbimazole can be altered in 2.5 to 5-mg increments, reassessing the cat again in 2 to 3 weeks. Lack of owner or cat compliance should first be eliminated as a reason for a failure of therapy. When monitoring, time of serum T4 sampling in relation to the administration of the antithyroid drug is not important. The goal of medical therapy is to maintain total T4 concentrations within the middle third of the reference range.

Once the dosage has stabilized, the cat should be monitored every 3 to 6 months and as needed clinically. Because antithyroid medications have no effect on the underlying

lesion, the thyroid nodules continue to grow larger and larger over time. This may necessitate an increased daily dose with time.

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Self trauma in the form of excoriations of the head and neck occasionally develop, usually within the first 6 weeks of therapy. Hepatopathy characterized by marked increases in liver enzymes and bilirubin concentration occurs in less than 2% of cats. Withdrawal of the medication and symptomatic therapy is required. Other rarely reported side effects include a bleeding tendency without thrombocytopenia, prolongation of clotting times, and acquired myasthenia gravis.

Nutritional therapy (Hill y/d)

This is an iodine-deficient diet, containing levels below the minimum daily requirement for adult cats. By 12 weeks, almost all cats should have normal T4 values.
This therapy appears to be more effective in cats with only moderate elevations of T4 than cats with severe hyperthyroidism.

A major indication for the use of this y/d diet for management of feline hyperthyroidism is in cats that are not candidates for definitive treatment of the underlying thyroid tumor(s) with surgery or radioiodine, which remains the treatments of choice. Nutritional management with y/d food (canned rather than the dry y/d) could be considered in cats whose owners are not able to give oral medication or in cats that develop side effects from methimazole/carbimazole.

The thyroid tumor remains and will continue to grow larger. In cats with long-standing hyperthyroidism, transformation of adenoma to thyroid carcinoma can occur unless definitive treatment (surgery or radioiodine treatment) is used to cure the disease.
The cats fed this diet must not eat any other cat diet, table food, or treats because even tiny amounts of iodine may lead to failure of this diet to effectively control hyperthyroidism. The composition (protein/fat/carbohydrate breakdown) of y/d reveals that it is a high-carbohydrate, relatively low-protein diet. Feeding y/d for long periods is less than an “ideal” diet for an obligate carnivore, especially in an older hyperthyroid cat with severe muscle wasting (Table 1).

Surgical therapy

Surgical therapy entails either unilateral or bilateral thyroidectomy. Because most cats have involvement of both thyroid lobes, bilateral thyroidectomy is indicated in most cats. The two major techniques for bilateral thyroidectomy include the intracapsular and extracapsular methods. The aim of both techniques is to remove the adenomatous thyroid tissue while preserving parathyroid function. The major problem with the intracapsular technique for thyroidectomy is that it can be difficult to remove the entire thyroid capsule (and, therefore, all abnormal thyroid tissue) while concurrently preserving parathyroid function.

The most serious complication is hypocalcemia, which develops after the parathyroid glands are injured or inadvertently removed. Since only one parathyroid gland is required for maintenance of normocalcemia, hypoparathyroidism develops only in cats treated with bilateral thyroidectomy. After bilateral thyroidectomy, it is important to monitor serum calcium concentration daily until it has stabilized within the normal range. In most cats with iatrogenic hypoparathyroidism, clinical signs associated with hypocalcemia will develop within 2 to 5 days of surgery. Temporary hypothyroidism develops in most cats after unilateral or bilateral thyroidectomy, with serum T4 concentrations falling to subnormal levels for 2 to 3 months. However, clinical signs of hypothyroidism are rare. Because of the potential for recurrence of hyperthyroidism, all cats should have serum T4 concentration monitored once or twice a year (Table 1).

Radioactive iodine therapy

I-131 treatment avoids inconvenience of daily oral administration of antithyroid drugs as well as the side effects commonly associated with these drugs. Eliminates the risks and perioperative complications associated with anesthesia and surgical thyroidectomy
Its use requires special radioactive licensing and hospitalization facilities, and extensive compliance with local and state radiation safety laws.

Major drawback for most owners is that their cat must be kept hospitalized for a period (3 to 10 days in most treatment centers; but up to a month in some places) and visiting is not allowed. More precision can be gained with thyroid imaging (scintigraphy) since it can also be used to estimate thyroid tumor volume and identify ectopic (intrathoracic) thyroid tissue.

A proportion of cats treated with radioiodine will develop permanent hypothyroidism, with clinical signs developing 3 to 6 months after treatment. Clinical signs associated with iatrogenic hypothyroidism are generally very mild but may include lethargy, non-pruritic seborrhea sicca, matting of hair, and marked weight gain; bilateral symmetric alopecia does not develop. Diagnosis of hypothyroidism is based upon clinical signs, subnormal serum total T4 and free T4 concentrations, high serum cTSH values, and the response to replacement L-T4 therapy).Life-long L-T4 supplementation is needed (i.e., 0.1-0.2 mg L-thyroxine per day).

In cats with thyroid carcinoma (incidence <2-4% of all hyperthyroid cats), radioiodine offers the best chance for successful cure of the tumor because it concentrates in all hyperactive thyroid cells, i.e., carcinomatous tissue, as well as metastasis.

MONITORING

Methimazole -- physical examination, CBC (with platelet count), serum biochemical analysis, and serum T4 determination every 2-3 weeks for the initial 3 months of treatment. Adjust the dosage of methimazole to maintain serum T4 concentration in the low-normal range.

Surgical thyroidectomy – monitor for the development of hypocalcemia and/or laryngeal paralysis during the initial post-operative period. Serum T4 concentrations should be measured within the first week of surgery, and every 3 – 6 months thereafter to monitor for recurrence.

Radioiodine – Serum T4 concentrations should be measured 2 weeks after treatment and every 3 – 6 months subsequently.

The prognosis for uncomplicated disease is excellent. Recurrence is possible and is most commonly associated with poor owner compliance with medical management. Regrowth of hyperthyroid tissue is possible but uncommon after surgical thyroidectomy or radioiodine treatment.
In dogs or cats with thyroid carcinoma, the prognosis is poor. Treatment with radioiodine, surgery, or both usually is followed by recurrence of disease. Adjuvant chemotherapy is of questionable benefit.

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Association of Iatrogenic Hypothyroidism with Azotemia and Reduced Survival Time in Cats Treated for Hyperthyroidism

T.L. Williams, J. Elliott, and H.M. Syme

Background: Iatrogenic hypothyroidism can occur after treatment of hyperthyroidism, and is correlated with a reduced glomerular filtration rate in humans and dogs.

Hypothesis: Cats with iatrogenic hypothyroidism after treatment for hyperthyroidism will have a greater incidence of azotemia than euthyroid cats.

Animals: Eighty client owned cats with hyperthyroidism.

Methods: Two retrospective studies. (1) Longitudinal study of 12 hyperthyroid cats treated with radioiodine (documented as euthyroid after treatment), to assess changes in plasma thyroid stimulating hormone (TSH) concentration over a 6-month follow-up period, (2) Cross-sectional study of 75 hyperthyroid cats (documented as euthyroid) 6 months after commencement of treatment for hyperthyroidism to identify the relationship between thyroid status and the development of azotemia. Kaplan- Meier survival analysis was performed to identify relationships between thyroid and renal status and survival.

Results: Plasma TSH concentrations were not suppressed in 7 of 8 cats with hypothyroidism 3 months after radioiodine treatment. The proportion of cats with azotemia was significantly (P 5 .028) greater in the hypothyroid (16 of 28) than the euthyroid group (14 of 47). Twenty-eight of 41 cats (68%) with plasma TT4 concentration below the laboratory reference range had an increased plasma TSH concentration. Hypothyroid cats that developed azotemia within the follow-up period had sig- nificantly (P 5 .018) shorter survival times (median survival time 456 days, range 231–1589 days) than those that remained nonazotemic (median survival time 905 days, range 316–1869 days).

ConclusionsandClinicalImportance:
Iatrogenichypothyroidismappearstocontributetothedevelopmentofazotemiaafter treatment of hyperthyroidism, and reduced survival time in azotemic cats.

Key words: Euthyroid-sick syndrome; Subclinical hypothyroidism; Thyroid stimulating hormone.

Update: Thyroid disorders

Pathogenesis of hyperthyroidism

Feline hyperthyroidism was first described in 1979 and 1980 by investigators in NYC and Boston. During a 14 year period from 1970-1984, an average of 1.9 cats per year were diagnosed with hyperthyroidism; however, it is now estimated that the incidence is as high as 2% of the feline population seen in tertiary care veterinary facilities. Since then, hyperthyroidism has become the most frequently diagnosed endocrinopathy in the cat with reports stemming from North America, Europe (esp UK), New Zealand and Australia.

Canned cat food has been implicated as a cause of feline hyperthyroidism in multiple epidemiological studies. (Kass 1999, Martin 2000, Edinboro 2004) The suspected goitrogen is bisphenol-A-diglycidyl ether (BADGE), a substance used in making the liner of easy-open "pop-top" cans. It is suspected that this compound can leach into the foods and be consumed by cats. While this BADGE-based lining is generally considered safe and is used for foods for human consumption, cats may be more susceptible to toxic effects of this compound because they have a greatly reduced ability to detoxify it via hepatic glucuronidation. Bisphenol A also reduces triiodothyronine binding and causes increased TSH secretion resulting in hyperthyroidism and goiter in rats and some humans. While cat studies may not be available, rodent studies show a very high safety margin. (Poole 2004) It should be noted that epidemiological studies showing associations are not the same as cause and effect. Over 90% of cats in the US consume commercial pet foods as their primary nutritional source, and relatively few develop hyperthyroidism.

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Long-term medical management best reserved for cats of advanced age or for those with concurrent diseases, and for when owners refuse either surgery or radioactive iodine. In addition to long-term treatment, medical management is also necessary prior to surgical thyroidectomy to decrease the metabolic and cardiac complications associated with hyperthyroidism.

Short-term medical management is often recommended as trial therapy prior to 131-I therapy to determine the effect of restoring euthyroidism on renal function.

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Most clinical adverse reactions occur within the first 3 months of therapy. Mild clinical side effects of vomiting, anorexia, or depression occur in approximately 10-15% of cats, usually within the first 3 weeks of therapy. Mild and transient hematological abnormalities, including lymphocytosis, eosinophilia or leucopenia, develop in up to 15% of cats without any apparent clinical effect. More serious hematological complications occur in less than 5% of cats and include agranulocytosis and thrombocytopenia.

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This therapy appears to be more effective in cats with only moderate elevations of T4 than cats with severe hyperthyroidism.

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Its use requires special radioactive licensing and hospitalization facilities, and extensive compliance with local and state radiation safety laws.

Major drawback for most owners is that their cat must be kept hospitalized for a period (3 to 10 days in most treatment centers; but up to a month in some places) and visiting is not allowed. More precision can be gained with thyroid imaging (scintigraphy) since it can also be used to estimate thyroid tumor volume and identify ectopic (intrathoracic) thyroid tissue.

A proportion of cats treated with radioiodine will develop permanent hypothyroidism, with clinical signs developing 3 to 6 months after treatment. Clinical signs associated with iatrogenic hypothyroidism are generally very mild but may include lethargy, non-pruritic seborrhea sicca, matting of hair, and marked weight gain; bilateral symmetric alopecia does not develop. Diagnosis of hypothyroidism is based upon clinical signs, subnormal serum total T4 and free T4 concentrations, high serum cTSH values, and the response to replacement L-T4 therapy).Life-long L-T4 supplementation is needed (i.e., 0.1-0.2 mg L-thyroxine per day).

In cats with thyroid carcinoma (incidence <2-4% of all hyperthyroid cats), radioiodine offers the best chance for successful cure of the tumor because it concentrates in all hyperactive thyroid cells, i.e., carcinomatous tissue, as well as metastasis.

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Association of Iatrogenic Hypothyroidism with Azotemia and Reduced Survival Time in Cats Treated for Hyperthyroidism

T.L. Williams, J. Elliott, and H.M. Syme

Background: Iatrogenic hypothyroidism can occur after treatment of hyperthyroidism, and is correlated with a reduced glomerular filtration rate in humans and dogs.

Hypothesis: Cats with iatrogenic hypothyroidism after treatment for hyperthyroidism will have a greater incidence of azotemia than euthyroid cats.

Animals: Eighty client owned cats with hyperthyroidism.

Methods: Two retrospective studies. (1) Longitudinal study of 12 hyperthyroid cats treated with radioiodine (documented as euthyroid after treatment), to assess changes in plasma thyroid stimulating hormone (TSH) concentration over a 6-month follow-up period, (2) Cross-sectional study of 75 hyperthyroid cats (documented as euthyroid) 6 months after commencement of treatment for hyperthyroidism to identify the relationship between thyroid status and the development of azotemia. Kaplan- Meier survival analysis was performed to identify relationships between thyroid and renal status and survival.

Results: Plasma TSH concentrations were not suppressed in 7 of 8 cats with hypothyroidism 3 months after radioiodine treatment. The proportion of cats with azotemia was significantly (P 5 .028) greater in the hypothyroid (16 of 28) than the euthyroid group (14 of 47). Twenty-eight of 41 cats (68%) with plasma TT4 concentration below the laboratory reference range had an increased plasma TSH concentration. Hypothyroid cats that developed azotemia within the follow-up period had sig- nificantly (P 5 .018) shorter survival times (median survival time 456 days, range 231–1589 days) than those that remained nonazotemic (median survival time 905 days, range 316–1869 days).

ConclusionsandClinicalImportance: Iatrogenichypothyroidismappearstocontributetothedevelopmentofazotemiaafter treatment of hyperthyroidism, and reduced survival time in azotemic cats.

Key words: Euthyroid-sick syndrome; Subclinical hypothyroidism; Thyroid stimulating hormone.

UNUSUAL THYROID DISORDERS (FELINE HYPOTHYROIDISM, CANINE HYPERTHYROIDISM)

Deborah S. Greco DVM, PhD

DEFINITION/OVERVIEW

- Feline hypothyroidism - Low to non-existent circulating levels of serum thyroxine caused by failure of the thyroid gland to secrete hormone or failure of the pituitary gland to secrete thyroid stimulating hormone.
- Canine hyperthyroidism - High circulating levels of serum thyroxine caused by a thyroid tumor (usually adenoma) or by feeding of exogenous thyroid tissue (treats, food)

ETIOLOGY/PATHOPHYSIOLOGY

Feline Hypothyroidism

- Acquired hypothyroidism is most commonly associated with radioactive iodine therapy, surgery or medical treatment for hyperthyroidism. Rarely, lymphocytic (autoimmune) thyroiditis similar to that seen in dogs with hypothyroidism is observed.
- Congenital hypothyroidism in cats is more common than acquired and may be caused by aplasia or hypoplasia of the thyroid gland, thyroid ectopia, dyshormonogenesis, maternal goitrogen ingestion, maternal radoactive iodine treatment, iodine deficiency (endemic goiter), hypopituitarism, isolated thyrotropin deficiency, hypothalamic disease, or isolated TRH deficiency

Canine Hyperthyroidism

- Thyroid tumor (rare, usually adenoma)
- Exogenous thyroid tissue in food or treats (usually raw)

SIGNALMENT/HISTORY

- Congenital feline hypothyroidism is seen in young animals usually less than 1 year of age.
- Acquired feline hypothyroidism is seen in older cats (more than 8 years of age) treated for hyperthyroidism
- Immune mediated hypothyroidism is seen in young to middle age cats.

Risk factors

- *Feline hypothyroidism* - Radioactive or surgical treatment for hyperthyroidism
- *Canine hyperthyroidism*- Feeding of treats or pet foods containing thyroid tissue

CLINICAL FEATURES

Feline

- Disproportionate dwarfism,
- Large birth weight
- Weakness
- Mental dullness
- Hypotonia
- Delayed dental eruption
- Lethargy
- Inappetence,
- Constipation
- Dermatopathy

Canine

- Polydipsia/polyuria
- Hyper excitability
- Polyphagia
- Behavior changes

Physical examination findings

Feline

Hypothermia
Abdominal distension
Macroglossia,
Midface hypoplasia, broad nose, and a large protruding tongue
Effusions of the body cavities (myxedematous fluid accumulation)
Retained puppy haircoat
Thinning of the haircoat
Ataxia

Canine

Hyperactivity
Tachycardia
Seizures

DIFFERENTIAL DIAGNOSIS

Feline

Congenital hypothyroidism
- Pituitary dwarfism
- PSS
- Congenital renal disease
- FIP

Acquired hypothyroidism

Canine

Other causes of PU/PD (Cushings, DI, etc)
Other causes of liver enzyme elevation (Hepatopathy, etc)
Other causes of hyper excitability (Pheochromocytoma)

DIAGNOSTICS

Minimum data base

Feline

- Mild normocytic normochromic anemia
- Hypercholesterolemia, hypercalcemia

Canine

- Polycythemia (increased PCV)
- Increased liver enzymes (ALT, AST)

Radiographs

Feline congenital hypothyroidism - Epiphyseal dysgenesis

Thyroid hormone measurement

Feline hypothyroidism

- Low normal or low TT4 and or FT4 for the age of the kitten
  - Normal kittens aged 5-6 weeks, have serum total thyroxine (TT4) 2-3 times higher than normal adults.
- Low FT4 in a cat
- Endogenous cTSH - High

Canine hyperthyroidism

- High TT4 and FT4

- Low endogenous cTSH

Pathological Findings

Feline

- Goiter—enlarged thyroid gland filled with colloid
- Lymphocytic thyroiditis
- Congenital aplasia

Canine

- Thyroid adenoma

THERAPEUTICS

Drug(s) of Choice
Levothyroxine 0.1 mg per cat once or twice (kittens) daily

Precautions / Interactions
Avoid generic levothyroxine

Alternative Drugs- NA

Diet
Canine - discontinue diet or treats containing thyroid tissue

Surgical Considerations
Not applicable

COMMENTS

Client Education
Feline

- Life long therapy will be required in congenital and autoimmune hypothyroidism
- 50% of cats with acquired hypothyroidism will revert to normal within 6 mo to a year

Canine

- Feed commercial pet food and treats from major manufacturers

Patient Monitoring

- Growth should normalize in congenital cases
- Every month initially and then every 6 months

Prevention / Avoidance

- *Feline*
- Avoid goitrogens
- Adjust radioactive iodine dosage and tailor to individual patient

- *Canine*
- Avoid raw or homemade treats and pet food

AUTOIMMUNE POLYGLANDULAR SYNDROME
Deborah S. Greco

DEFINITION

- Autoimmune polyglandular syndromes (APS) include: APS Type 1 (diabetes, ectodermal mucositis, etc), APS Type 2 (hypoadrenocorticism, hypothyroidism, type 1 diabetes mellitus, premature ovarian failure), and APS Type 3 (liver cirrhosis plus endocrinopathies).
- Autoimmune polyglandular syndrome type II is defined as the occurrence of two or more of the following disorders in the same individual; adrenal insufficiency, primary hypothyroidism, insulin dependent diabetes mellitus (IDDM), primary hypogonadism (premature ovarian failure, immune mediated orchitis), myasthenia gravis, IMHA, ITP, hypoparathyroidism, hypopituitarism, and celiac disease.

ETIOLOGY/PATHOGENESIS

- Circulating organ specific autoantibodies are commonly present in APS type 2.[16] Environmental factors combined with an HLA-associated genetic predisposition are thought to trigger the process. Cell-mediated immune abnormalities in the Type II syndrome include defects and alterations of cell surface markers, but the most consistent abnormality is a functional defect leading to a decrease in suppressor T cell activity.
- Approximately 45% of all patients with idiopathic (autoimmune) adrenal insufficiency will develop one or more additional endocrinopathies (usually hypothyroidism). APS II is inherited as an autosomal dominant trait in humans associated with the presence of human leukocyte antigens (HLA).
- Hypothyroidism is the most common initial endocrinopathy in the dog.
- Hypoadrenocorticism is usually followed by the development of hypothyroidism, but some dogs will develop hypoadrenocorticism instead. All three endocrinopathies in a single dog is rare.

- Type 1 diabetes combined with immune mediated thyroid disease (Hashimoto's thyroiditis) is the most common initial endocrinopathy in humans and dogs.
- In a retrospective of 225 cases of canine hypoadrenocorticism, 4% of the dogs also suffered from hypothyroidism, 2 dogs had concurrent IDDM and hypoadrenocorticism, and one had concurrent hypoadrenocorticism, hypothyroidism, IDDM and hypoparathyroidism.
- Another retrospective of 45 dogs with adrenal insufficiency reported 4 dogs with concurrent hypothyroidism, one dog with concurent IDDM and one dog with concurrent primary gonadal hypoplasia.
- A single case of Type II APS has been described in a middle-age female dog presenting in a hypothyroid crisis; treatment of the hypothyroid state resulted in precipitation of the hypoadrenocorticism. The presence of serum autoantibodies to thyroid and adrenal tissue was observed in this dog as evidence of autoimmune polyglandular syndrome Type II.

SIGNALMENT/HISTORY

- Hypoadrenocorticism and hypothyroidism—mean age of onset of the disease was in young adulthood (5.4 years).
- Second endocrinopathy less than 1 year (hypoadrenal and hypothyroidism) or 18 months (IDDM and hypothyroidism) after the first endocrinopathy.
- Slight female predilection

CLINICAL FEATURES

- Dogs diagnosed with hypoadrenocorticism, most common clinical signs include:
  - Lethargy

- Collapse
- Vomiting
- Weight loss
- Weakness
- Ataxia
- Anorexia
- Bradycardia
- Megaesophagus
- Diarrhea

- A decreasing insulin requirement is often the earliest sign of adrenal insufficiency
- Concurrent hypothyroidism and IDDM often have increasing insulin requirements as hypothyroidism may cause insulin resistance.
- In dogs diagnosed with hypopadrenocorticism as the initial endocrinopathy, thyroid evaluation was performed because of:
  - Continued lethargy despite adequate mineralocorticoid replacement therapy
  - Persistent hyponatremia and/or hypercholesterolemia
  - Dermatologic disease
  - Bradycardia
  - Obesity
  - Heat-seeking behavior.

DIFFERENTIAL DIAGNOSIS

- Inadequate glucocorticoid or mineralocorticoid supplementation in dogs with hypoadrenocorticism

- In dogs with diabetes mellitus, rule out other causes of insulin resistance
- In dogs with hypothyroidism, rule out other causes of weakness or electrolyte disturbances (e.g. hyperkalemia)

DIAGNOSTICS

- CBC/Chemistry profile/Urinalysis abnormalities
  - Hyponatremia
  - Hypercholesterolemia
  - Hyperkalemia
  - Hypochloremia
  - Azotemia
  - Hypocalcemia
  - Hypercalcemia
- ACTH response test
- Serum TT4 and endogenous canine TSH
- Acetycholine receptor antibody titer

THERAPEUTICS

Drug(s) of Choice
Levothyroxine 22-44 microgram/kg/day
Deoxycorticosterone pivilate 1 mg/kg IM q 25-30 days

COMMENTS

Client Education

- See hypoadrenocorticism client handout

Patient Monitoring

- Serum potassium and sodium
- Post pill TT4 or cTSH levels

SUGGESTED READING

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