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ISSUES IN ENDOCRINOLOGY

The Diagnosis of Canine Hyperadrenocorticism

Audrey Cook, *BVM&S, MSc VetEd, MRCVS, DACVIM-SAIM, DECVIM-CA, DABVP (Feline)*
Department of Small Animal Clinical Sciences,
Texas A&M College of Veterinary Medicine and Biomedical Sciences
College Station, Texas

Hyperadrenocorticism (HAC or Cushing's syndrome) describes the clinical manifestations of chronic exposure to excessive glucocorticoids. Spontaneous HAC is often caused by inappropriate secretion of adrenocorticotropic hormone (ACTH) by a pituitary tumor (i.e., pituitary-dependent HAC [PDH]) or may reflect the autonomous production of cortisol by an adrenal tumor (AT).[1]

There are occasional reports of dogs with HAC due to an aberrant response to a digestive hormone (i.e., food-dependent HAC) or from ectopic ACTH secretion, but these are extremely rare.

CLINICAL PRESENTATION

Spontaneous HAC is usually diagnosed in older dogs, particularly Boston terriers, dachshunds, miniature poodles, and beagles.[1] It is uncommon in dogs younger than 5 years of age. Onset is often insidious, and owners frequently attribute changes to aging. A strong understanding of the clinical manifestations of HAC is essential because it helps us identify suitable candidates for further testing. A dog with Cushing's syndrome must have some (usually many) of the classic signs (**BOX 1**).

More than 95% of dogs are polyuric/polydipsic; a normal water intake makes HAC less likely. Additionally, most manifest dermatologic changes;[2] in my experience, a good hair coat

BOX 1 Clinical Signs Commonly Associated With Canine HAC

- Polyuria and polydipsia
- Polyphagia
- Panting
- Abdominal distention
- Hepatomegaly
- Muscle weakness
- Dermatologic changes
  - Symmetric truncal alopecia
  - Hyperpigmentation
  - Comedones
  - Thin skin (**FIGURE 2**)
  - Poor hair regrowth

CLINICAL CHALLENGE
Diagnosis of canine hyperadrenocorticism is difficult in some cases due to factors such as the presence of nonadrenal illness and limitations in the tests.

BOX 2 Indications to Pursue Diagnostics for HAC

- Client concern (you ***hear*** something)
  - Increased thirst or urination
  - Hunger, food stealing
  - Panting
  - Difficulty jumping
- Physical examination (you ***see*** something)
  - Endocrine alopecia
  - Thin skin, comedones
  - Hepatomegaly/abdominal distention
- Comorbid condition (you are ***fighting*** something)
  - Recurrent urinary tract infection
  - Frequent otitis externa; pyoderma
  - Hypertension

(particularly if shaved hair grows back promptly) essentially rules out HAC. Although calcinosis cutis is pathognomonic for HAC, it is uncommon. A "pot-bellied" appearance with palpable hepatomegaly is expected, along with poor forelimb and hindlimb musculature (**FIGURE 1**). A small number of dogs with PDH will present with signs referable to a large pituitary tumor, such as personality change, vision loss, and poor appetite.[3] Retinal changes may be noted in dogs with concurrent hypertension.

A careful history is always important in a cushingoid patient because exogenous steroid administration may otherwise be overlooked.

FIGURE 1. Dog with PDH. Note the abdominal distention and hepatomegaly.

DIAGNOSTIC PROCESS

HAC can often be considered an "exam room" diagnosis, meaning that the owner's concern or the dog's physical appearance suggests HAC. Less frequently, a comorbid condition suggests the possibility (**BOX 2**). I do not advise pursuing a diagnostic workup for HAC without a strong clinical index of suspicion. Chasing a diagnosis based on biochemical changes alone often results in substantial frustration for both client and veterinarian. There are essentially 3 steps to the HAC diagnostic workup (**BOX 3**).

Step 1: Scrutinize Routine Laboratory Findings

Most dogs manifest many (or all) of the expected patterns on routine laboratory tests.[1]

Urine is usually dilute, with specific gravity less than 1.020. Hyposthenuria may be documented: In fact, HAC is one of the most common causes of a urine specific gravity less than 1.008. Proteinuria may be

FIGURE 2. Dog with PDH. Note the thin skin with alopecia and loss of elasticity.

noted and should be quantified with a urine protein-to-creatinine ratio. Urinary tract infection is also common and may not be accompanied by significant pyuria or overt clinical signs. A urine culture is often recommended in dogs with evidence of HAC.

On the biochemistry panel, the most consistent finding is increased alkaline phosphatase (ALP) activity. This is often substantially elevated (>1000 U/L; reference range, 24 to 147 U/L) and routinely accompanied by an increase in γ-glutamyl transferase activity. However, increased ALP activity is common in older and obese dogs, dogs with various physiologic stressors, and dogs with primary hepatobiliary disease. High ALP activity in the absence of clinical signs of Cushing's syndrome should not prompt a hunt for HAC. Cholesterol and triglyceride concentrations are consistently elevated; a normal value is unusual in a cushingoid dog. Other common biochemical changes are an increased phosphorus concentration (seen in <50% of cases but still a useful marker[4]), mild hyperglycemia, and (variably) a modest decrease in blood urea nitrogen. Some dogs have mild increases in alanine aminotransferase activity, but this is usually less than 3 times the upper limit of normal.

The complete blood count shows a stress leukogram (neutrophilia, lymphopenia, monocytosis, and eosinopenia). The hematocrit should be robustly normal or even mildly high (>50% is not uncommon); anemia is not consistent with HAC and should prompt further investigation. Platelets are often increased and may cause spurious hyperkalemia.

Step 2: Screen for HAC

There is limited consensus about the "best" screening test, although sensitivity and specificity data support the routine use of the low-dose dexamethsone suppression test (LDDST).[1] However, a clinician's confidence in a positive (or negative) result is determined by population characteristics, meaning that a result supporting HAC is inherently more believable in a geriatric dog with polydipsia and truncal alopecia than in an apparently normal juvenile (same test, different patient population).

Serum/plasma assays for "cortisol" cross-react with many synthetic glucocorticoids (apart from dexamethasone); exogenous steroids should therefore be withheld for at least 72 hours before adrenal function tests are performed. In addition, prolonged administration of exogenous steroids of any type will suppress adrenal gland function after 2 to 3 weeks.

BOX 3 Stepwise Diagnostic Approach for HAC

Step 1: Scrutinize routine laboratory findings for evidence of HAC

- Urinalysis
  - Specific gravity < 1.020
  - Proteinuria
- Chemistry panel
  - Increased ALP activity and cholesterol
  - +/- Increased phosphorus
  - +/- Hyperglycemia (mild; <150 mg/dL)
  - +/- Low BUN
  - +/- Increased alanine aminotransferase or γ-glutamyl transferase activity
- Complete blood count
  - Stress leukogram
  - Robust hematocrit
  - +/- Increased platelet count

Step 2: Screen for HAC (see text for details)

- LDDST
- ACTH stimulation test
- Urine cortisol-to-creatinine ratio (low specificity; a positive result is not adequate evidence to establish this diagnosis)

Step 3: Differentiate PDH from AT (necessary only if adrenalectomy is an option)

- Abdominal ultrasonography
- Endogenous ACTH measurement
- HDDST (limited reliability; failure to suppress does not differentiate PDH from AT)

LDDST

The LDDST is an elegant way to interrogate the pituitary-adrenal axis, with reported sensitivities of 85% to 100%.[1] In addition, it is more reliable in dogs with AT than the ACTH stimulation test.[5]

First, collect a baseline cortisol sample; serum is generally preferred, although some laboratories will accept heparinized plasma. Next, administer 0.01 mg/kg of dexamethasone IV. This dose is slightly

About 85% of dogs with HAC have PDH, particularly small dogs.

supraphysiologic and will suppress the release of ACTH (and therefore cortisol) in a normal dog for more than 12 hours. If the sodium phosphate formulation is used ("Dex SP"), the dose should be adjusted to reflect that 1.3 mg of this formulation contains 1.0 mg of dexamethasone.[1] The product used should be diluted for accurate dosing in small dogs (**BOX 4**). Subsequent blood samples are collected at 4 and 8 hours.

Cortisol concentrations indicating "suppression" vary, with some laboratories using a value of less than 0.7 mcg/dL and others defining suppression as anything less than 1.4 mcg/dL.[1] Lower values increase test sensitivity but may produce more false-positive results. Nonadrenal issues, such as fear and pain, affect cortisol release and cause false-positive results. Chronic illness may also affect results because long-term endogenous hypercortisolemia may shorten the half-life of exogenous glucocorticoids;[6] the suppressive effects of dexamethasone therefore abate within 8 hours.

One advantage of the LDDST over other screening tests is its ability to differentiate PDH from AT. PDH can be diagnosed with confidence if the 4-hour cortisol level is less than 50% of baseline or below the level established by the laboratory. The LDDST can cause confusion, so always look at the 8-hour result first and see if this value indicates HAC. If the answer is "yes," then look at the 4-hour result; suppression at this point indicates PDH. Failure to suppress at the 4-hour mark is not diagnostically useful; it is seen in many dogs with PDH and all those with AT.

BOX 4 Protocols for the Dilution of Dexamethasone for LDDST

- **Dexamethasone 2 mg/mL:**
  0.5 mL + 9.5 mL of saline = dexamethasone 0.1 mg/mL
  Administer 0.1 mL/kg (=0.01 mg/kg of dexamethasone)
- **Dexamethasone sodium phosphate 4 mg/mL:**
  0.32 mL + 9.68 mL of saline = dexamethasone 0.1 mg/mL
  Administer 0.1 mL/kg (=0.01 mg/kg of dexamethasone)

ACTH Stimulation Test

This test is convenient—it takes just over an hour. First, collect a baseline cortisol sample. Then inject cosyntropin (5 mcg/kg IM or IV; maximum, 250 mcg per dog) and collect a second serum sample 1 hour later. Compounded ACTH gel products are best avoided because their biological effect is uncertain. To save costs, reconstituted cosyntropin can be divided into aliquots in plastic syringes and kept frozen for up to 6 months.[7]

This test is based on the premise that the response to exogenous ACTH is proportional to functional adrenocortical tissue; this is increased in dogs with PDH or AT. Most labs use a cutoff serum concentration of 17 to 20 mcg/dL; a serum concentration above this level supports HAC.[1] The disadvantages to this test include poor specificity in dogs with chronic disease, meaning that false-positive results are likely. It also has poor sensitivity in dogs with AT; many dogs with this condition have normal results or findings suggesting hypoadrenocorticism,[8] likely due to limited ACTH receptor expression by neoplastic cortical cells. A "flat-line" or addisonian response is also seen in dogs with iatrogenic HAC; chronic exposure to exogenous glucocorticoids results in adrenocortical atrophy and a blunted response to exogenous ACTH.

Urine Cortisol-to-Creatinine Ratio

This test is overly sensitive and not very specific, meaning that false-positive results are common, particularly in dogs with other polyuric disorders.[9] However, a negative result is highly reliable and can be used to exclude HAC when there is a low index of suspicion. Test reliability is optimized by having the owner collect morning urine at home. Stress or fear can quickly increase cortisol concentrations in normal dogs, so it is unwise to collect this sample in the clinic environment.

Step 3: Differentiate PDH From AT

About 85% of dogs with HAC have PDH, particularly small dogs. HAC due to AT is most often reported in dogs that weigh more than 20 kg.

Differentiating the 2 forms is important because the diagnosis affects therapy and prognosis, but it is not necessary if the dog is a poor candidate for surgery or the owner is unwilling to consider adrenalectomy (the treatment of choice for AT).

Abdominal ultrasonography can readily differentiate PHD from AT but is operator and machine dependent. Normal adrenal gland width (at the caudal pole) is 3 to 5 mm, although it is not unusual to find 7-mm adrenals in large dogs with nonadrenal illness.[10] Bilateral, symmetric adrenomegaly indicates PDH in a dog with a positive result on a confirmatory test for HAC. A solitary mass in 1 gland suggests AT; contralateral atrophy (<4 to 5 mm) is expected. Dogs can develop PDH and have a concurrent pheochromocytoma or adrenal tumor.[11]

Abdominal radiography is a backup option if ultrasonography is not available. About 50% of ATs become calcified and can be seen on a plain lateral abdominal study. Calcification does not indicate malignancy.

Many reference laboratories offer highly sensitive assays for endogenous ACTH concentrations, which can be used to reliably differentiate the 2 forms of HAC. Dogs with AT have essentially undetectable levels, whereas those with PDH have normal or increased levels.[12] Endogenous ACTH is a fragile hormone, so careful sample handling is essential. Contact your laboratory to clarify requirements for sample submission.

The high-dose dexamethasone suppression test (which uses 0.1 mg/kg IV of dexamethasone) is rarely performed these days because its role has been supplanted by ultrasonography and measurement of endogenous ACTH. Suppression of cortisol production for the 8-hour test period is diagnostic for PDH, but a lack of suppression is inconclusive.[1]

SUMMARY

- The clinical recognition of dogs with HAC is a key part of the diagnostic process.
- Do not chase this diagnosis without overt clinical manifestations of HAC.
- The confirmatory tests have limitations; more than 1 may be needed to establish a diagnosis.
- If adrenalectomy is not an option, client resources may be directed toward treatment rather than differentiating PDH from AT. However, life expectancy for dogs with AT will be affected by the biological behavior of the tumor (benign vs malignant). TVP

Audrey K. Cook

Audrey K. Cook is a Diplomate of both ACVIM and ECVIM and is Board Certified in Feline Practice (ABVP). She is currently an associate professor of small animal internal medicine at Texas A&M, with particular interests in endocrinology, gastroenterology, feline medicine and endoscopy. Dr. Cook routinely speaks at national meetings and is a recipient of the Texas A&M University Distinguished Achievement Award in Teaching.

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