PEER REVIEWED

# Canine Hyperadrenocorticism

## Challenges Establishing the Diagnosis

Ann Della Maggiore, DVM, Diplomate ACVIM, & Richard Nelson, DVM, Diplomate ACVIM
University of California–Davis

### TABLE 1. Clinical Signs & Examination Findings Indicative of HAC

- Polyuria and polydipsia
- Polyphagia
- Endocrine alopecia (thin skin, comedones, hyperpigmentation, failure of hair to regrow)
- Weakness
- Excessive panting
- Abdominal distension/hepatomegaly
- Calcinosis cutis

*Organized by prevalence of clinical signs*

Spontaneously occurring canine hyperadrenocorticism (HAC) is classified as:

- Pituitary-dependent caused by excess adrenocorticotropic hormone (ACTH) secretion (PDH)
- Pituitary-independent caused by a cortisol-secreting adrenocortical tumor (ATH).

PDH is the most common form of HAC, accounting for 80% to 85% of cases.

### CLINICAL SIGNS

Clinical signs for both forms of the disease primarily result from excessive circulating cortisol and include polyuria, polydipsia, polyphagia, and endocrine alopecia (**Table 1**).

- Some dogs with PDH develop a pituitary macrotumor that may cause anorexia, obtundation, pacing, and changes in behavior.

### TABLE 2. Clinicopathologic Findings That Increase Suspicion for Canine HAC

| COMPLETE BLOOD COUNT | SERUM BIOCHEMISTRY | URINALYSIS |
|---|---|---|
| Stress leukogram<br>Thrombocytosis<br>Mild erythrocytosis | Increased alkaline phosphatase<br>Increased alanine aminotransferase<br>Hypercholesterolemia<br>Hypertriglyceridemia<br>Hyperglycemia | Urine specific gravity ≤ 1.020 (often < 1.008)<br>Proteinuria<br>Urinary tract infection |

These results should be interpreted along with history and physical examination findings.
*Organized by prevalence of clinicopathologic findings.*

### TABLE 3. Diagnostic Tests That Differentiate PDH & ATH

| DIAGNOSTIC TEST | RESULTS INDICATING PDH | RESULTS INDICATING ATH |
|---|---|---|
| **LDDS Test** | 4-hour cortisol < 1 mcg/dL (varies with laboratory) or < 50% of basal cortisol concentration | Test does not identify ATH* |
| **HDDS Test** | 4-hour cortisol < 1 mcg/dL (varies with laboratory) or < 50% of basal cortisol concentration | Test does not identify ATH* |
| **ACTH Concentration** | Upper 50% or greater than reference range | Below reference range |
| **Ultrasound** | Bilateral adrenomegaly or normal adrenal size | Asymmetric adrenal glands (characterized by adrenal mass and small contralateral adrenal gland) |

* Lack of suppression does not confirm ATH because approximately 25% of dogs with PDH fail to exhibit suppression upon LDDS or HDDS testing.

### TABLE 4. Common Pitfalls to Avoid in Diagnosis of HAC

- **In dogs with no clinical signs**, pursuing:
  - » Endocrine testing based on abnormal laboratory values (ie, elevated ALP)
  - » Testing for "occult HAC"
- **Ruling out disease** because:
  - » Blood analysis is normal
  - » Adrenal glands are normal in size
- **Without considering clinical presentation**, diagnosis based on:
  - » ACTH stimulation test results
  - » LDDS test results
- **Reliance on ACTH stimulation test**
- **Failure to recognize** that false-positive and false-negative results occur with tests of the pituitary-adrenocortical axis

- Occasionally dogs with ATH develop retroperitoneal hemorrhage causing anemia, weakness, and abdominal pain.
- A tumor thrombus can develop from tumor growth into the phrenicoabdominal vein and caudal vena cava, causing vascular obstruction and ascites or edema.[1]

## DIAGNOSIS

Diagnosis of HAC is preceded by initial clinical suspicion for the disease after reviewing history and physical examination findings. Abnormalities identified on a complete blood count, serum biochemistry panel, and urinalysis provide additional support for HAC (**Table 2**). To establish a diagnosis of HAC, excess circulating cortisol must be documented by a urine cortisol:creatinine ratio (UCCR) and lack of appropriate negative feedback after glucocorticoid administration (low-dose dexamethasone suppression [LDDS] test).

## DIFFERENTIATION OF PDH FROM ATH

Once the diagnosis of HAC has been established, the following tests can be used to differentiate PDH from ATH (**Table 3**); sometimes more than 1 test is necessary.

- LDDS test
- High-dose dexamethasone suppression (HDDS) test[2]
- Measurement of endogenous ACTH concentration
- Imaging the adrenal glands with abdominal ultrasound.

## DIAGNOSTIC DIFFICULTIES

Suspicion for and diagnosis of HAC is relatively straightforward when all aspects of the evaluation are consistent with the disease. Unfortunately, discordant information is common and can create uncertainty about diagnosis (see **Diagnostic Algorithm**, page 22).

Problems with establishing a diagnosis of HAC usually result from one of several possibilities (**Table 4,** page 19). In our experience, the most common problems result from a combination of:

## CONSIDER THIS CASE: CASE PRESENTATION

A 9-year-old, castrated male Shih Tzu was referred to the University of California–Davis Veterinary Medical Teaching Hospital for further evaluation of cystic calculi.

### History

The dog had a history of persistent increased serum alkaline phosphatase (ALP) activity during the past year (526–1530 IU/L). The owner stated that, during the past 6 months, the dog seemed to have increased panting and appeared to be drinking "a lot of water."

### Physical Examination

Results of a physical examination were unremarkable; the hair coat and skin thickness were normal and hepatomegaly was not identified.

### Diagnostic Results

Pertinent results from diagnostic tests are listed in **Table 5**.

The case was then transferred to the Internal Medicine Service for evaluation and treatment recommendations for HAC.

## QUESTIONS

- Does this patient have spontaneous canine HAC?
- What supports the diagnosis of HAC?
- What does not support the diagnosis of HAC?

### TABLE 5. Pertinent Diagnostic Test Results

| DIAGNOSTIC TEST | RESULT | REFERENCE INTERVAL |
|---|---|---|
| **ACTH stimulation test** (mcg/dL) | | |
| Pre-ACTH serum cortisol concentration | 12 | 0–6 |
| Post-ACTH serum cortisol concentration | 37 | 6–15 |
| **Alkaline phosphatase** (IU/L) | 1500 | 14–91 |
| **LDDS test** (mcg/dL) | | |
| Baseline serum cortisol concentration | 9 | 0-6 |
| 4-hour post-dexamethasone | 1.1 | 0-0.8 |
| 8-hour post-dexamethasone | 12.9 | 0-0.6 |
| **UCCR test** | 16* | < 13.5 |
| **Ultrasound** (abdominal) | Normal-sized adrenal glands; irregular, enlarged nodule involving cranial pole (0.93 cm diameter) (**Figure 1**) | |
| **Urine specific gravity** | 1.027 | n/a |

** Measured using urine collected in hospital; ideally, the test should use urine collected at home in a stress-free environment.*

## CONSIDER THIS CASE: CASE DISCUSSION

This case demonstrates a dog with:

- Debatable clinical signs of HAC
- Increase in serum ALP activity, which may or may not be caused by HAC
- Endocrine test results supportive of PDH in a dog with normal-sized adrenal glands and a "nodule" on the cranial pole of one gland.

## ANSWERS

*Evidence against HAC* in this dog includes lack of supportive clinical signs and physical examination findings. *Evidence for HAC* includes endocrine test results used to establish the diagnosis of HAC. We are left with the questions:

- Does this dog have HAC?
- Do you initiate treatment for HAC?

All information should be critically examined whenever conflict exists in the diagnostic evaluation for canine HAC.

1. **History and physical examination are the most important parameters** when establishing the diagnosis of HAC.
2. **Results of other diagnostic tests, including the UCCR and LDDS tests, become disputed** if clinical signs and physical examination findings do not strongly support existence of HAC, as in this case.
3. **Treatment for HAC is NOT indicated** if the history and physical examination findings do not strongly support HAC.

### Serum Alkaline Phosphatase

Increased serum ALP activity is not pathognomonic for HAC and, by itself, should NOT be used as an indicator to pursue diagnosis of HAC. Increased ALP activity can be seen with a variety of other conditions, most notably hepatobiliary disease.

### Urine Cortisol:Creatinine Ratio

The UCCR was only slightly increased and measured using urine collected in the hospital.

- The current recommendation for measuring UCCR is to have the owner collect a urine sample first thing in the morning for 2 consecutive days—a protocol that maximizes the sensitivity and specificity of the test (99% and 77%, respectively).[2,3]
- A normal UCCR in 1 or both urine samples is strong evidence against HAC unless clinical signs and physical examination findings strongly support the disease.
- Positive test results in both urine samples support performance of the LDDS test in a dog with appropriate clinical signs and physical examination findings.

### Low-Dose Dexamethasone Suppression Test

The LDDS test is considered the best test for establishing a diagnosis of HAC, except in dogs with suspected iatrogenic HAC.

- The 8-hour post-dexamethasone cortisol concentration establishes the diagnosis:
  - » A concentration *less than 1 mcg/dL (varies with laboratory) is strong evidence against HAC* unless clinical signs and physical examination findings strongly support the disease.
  - » Concentrations *greater than 1 mcg/dL (varies with laboratory) support a diagnosis of HAC* assuming history and physical examination findings strongly support the diagnosis.
- Sensitivity and specificity of the LDDS test have been reported to be 85% to 100% and 44% to 73%, respectively.[2]
- False-negative and especially false-positive results occur with the LDDS test. A positive LDDS test does not, by itself, confirm a diagnosis of HAC, as illustrated by this case. LDDS may be falsely positive with stress, excitement, or nonadrenal illness, which should be considered when interpreting results.

### ACTH Stimulation Test

The ACTH stimulation test is the gold standard for diagnosis of hypoadrenocorticism and iatrogenic HAC, and for monitoring trilostane and mitotane treatment. In our experience, this test has not been reliable for establishing a diagnosis of spontaneous HAC.

- Reported sensitivity for PDH is 80% to 83% and, for ATH, 57% to 63%; specificity is 85% to 93%.[2] The decreased sensitivity of this test, especially with ATH, can lead to normal results in animals with HAC (being diagnosed as free of disease).
- Inconclusive test results are common and, clearly, abnormal test results with post-ACTH serum cortisol concentrations greater than 30 mcg/dL occur in dogs that do not

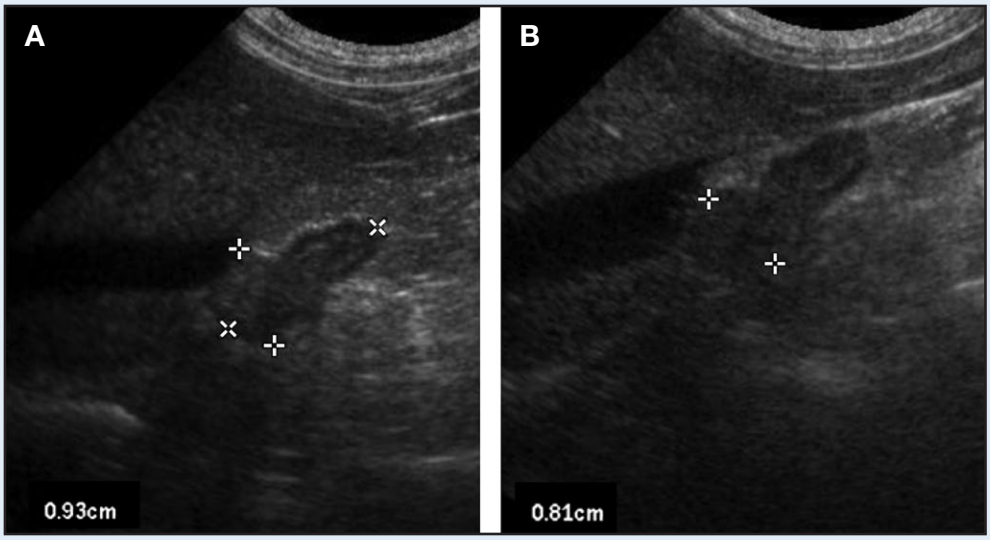



*Figure 1. Right adrenal mass upon initial evaluation (**A**, 0.93 cm) and repeat ultrasound evaluation 1 year later (**B**, 0.81 cm).*

have HAC, as illustrated in this case. Similar to the LDDS test, false-positive results occur with stress, excitement, or nonadrenal illness, which should be considered when interpreting results.
- We do not use the ACTH stimulation test when evaluating dogs for spontaneous HAC due to the test's decreased sensitivity.

## CASE OUTCOME

The decision was made not to initiate treatment for HAC for this patient due to the:
- Lack of history and physical examination findings to support diagnosis of HAC
- Discrepancy between results of endocrine tests (marginally positive UCCR despite suggestive findings on LDDS and ACTH stimulation tests).
- Findings on abdominal ultrasound.

### Initial Follow-Up

The dog was sent home, and recheck abdominal ultrasound was recommended in 1 to 2 months to assess if there were changes in the size of the adrenal "nodule." In addition, the owner was instructed to determine 24-hour water intake beginning a week after discharge. Water consumption was calculated to be approximately 65 mL/kg/24 H (normal, < 90 mL/kg/24 H[4]); this finding did not support a diagnosis of HAC.

### Long-Term Follow-Up

At the 6-week recheck, the dog's hair—where shaved for the abdominal ultrasound—had regrown, physical examination was unremarkable, and urine specific gravity on a free-catch urine sample was 1.034. The owner reported no clinical signs consistent with HAC.

The dog was followed for more than a year; adrenal measurement remained unchanged (**Figure 1**), and no clinical signs of HAC developed (**Figure 2**). Repeat hormonal testing was not done.

*Figure 2. Picture of Ben at his 1-year recheck; no clinical signs of HAC were evident at this time.*

- Testing for HAC in a dog with minimal to no clinical signs or
- Failure to recognize that false-positive and false-negative results occur with all tests used to assess the pituitary–adrenocortical axis, even when the dog manifests physical findings consistent with disease.

## IN SUMMARY

Many clients notice subtle changes in their dogs' health, and often seek veterinary care quickly. As a consequence, veterinarians often test for HAC early in the development of the disease, when, compared to testing performed in dogs with advanced disease:[5]
- Clinical signs are minimal and mild
- Endocrine tests are less reliable in differentiating between normal and HAC
- False-positive and, especially, false-negative test results are more common.

**Diagnosis of HAC is appropriate** when the following all support the diagnosis:
- Clinical signs
- Findings on physical examination
- Results of routine blood, urine, and hormonal tests.

**Diagnosis of HAC is NOT as evident** when the information used to establish the diagnosis conflicts, most notably when clinical signs and physical examination findings are supportive of the diagnosis but endocrine test results are not, and vice versa.

Clinicians must be prepared to critically evaluate all diagnostic information gathered to determine if additional testing or re-evaluation is indicated, taking into consideration the common pitfalls that complicate the diagnosis of HAC. When endocrine tests do not support the suspected diagnosis of HAC based on clinical signs and physical examination findings, re-evaluation in 2 to 3 months is indicated. ■

ACTH = adrenocorticotropic hormone; ALP = alkaline phosphatase; ATH = adrenocortical tumor hyperadrenocorticism; AUS = abdominal ultrasound; HAC = hyperadrenocorticism; HDDS = high-dose dexamethasone suppression; HPAA = hypothalamic-pituitary-adrenocorticol axis; LDDS = low-dose dexamethasone suppression; PDH = pituitary-dependent hyperadrenocorticism; UCCR = urine cortisol:creatinine ratio

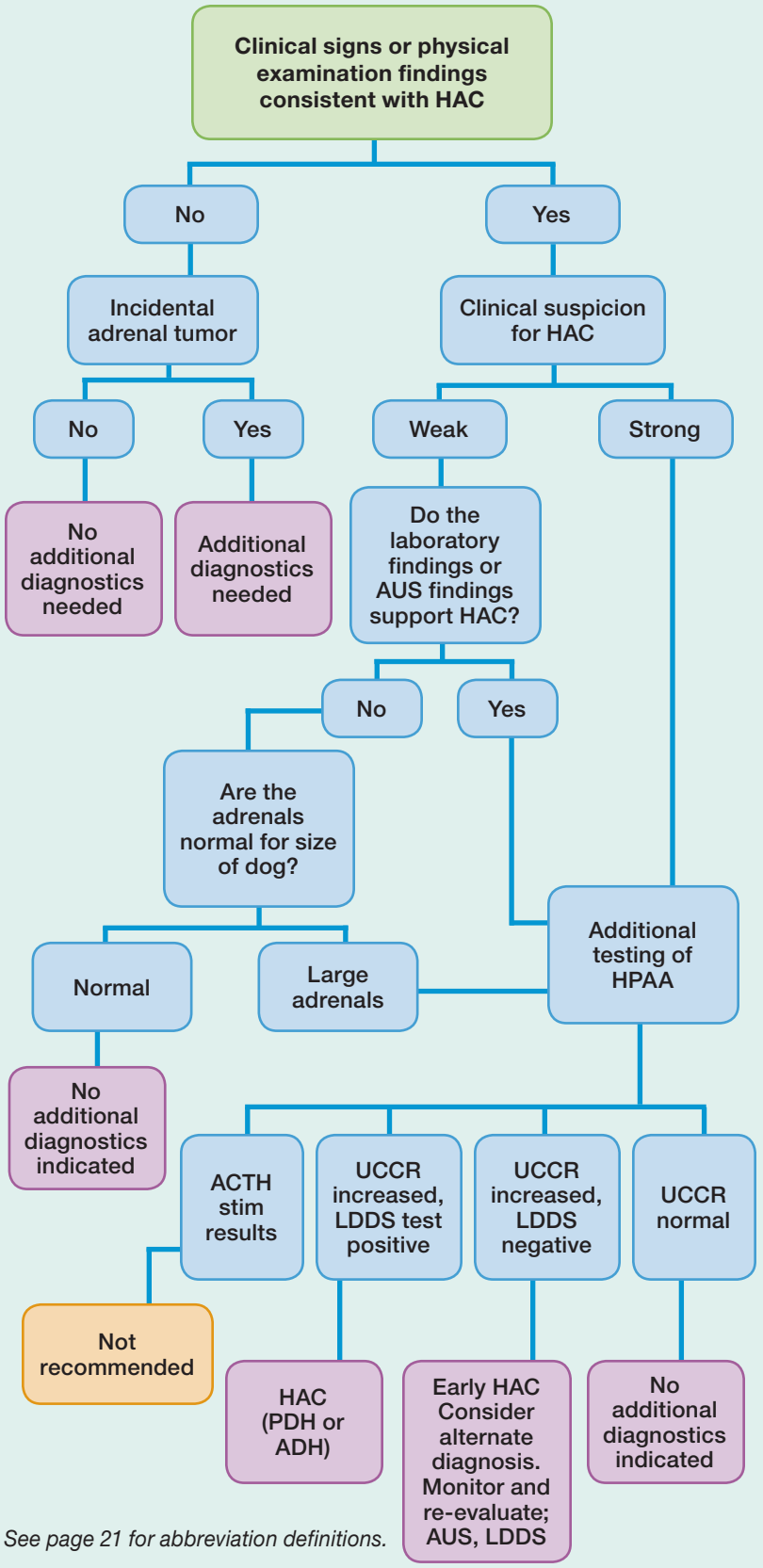
**References**

1. Lang JM, Schertel E, Kennedy S, et al. Elective and emergency surgical management of adrenal tumors: 60 cases (1999-2006). JAAHA 2011; 47:428-435.

***Ann Della Maggiore**, DVM, Diplomate ACVIM, is a staff internist at University of California–Davis School of Veterinary Medicine. She received her DVM from UCD, where she also completed a residency in small animal internal medicine.*

***Richard Nelson**, DVM, Diplomate ACVIM, is a professor at University of California–Davis School of Veterinary Medicine. He received his DVM from University of Minnesota and completed a small animal internal medicine residency at UCD.*

## HAC DIAGNOSTIC ALGORITHM




*See page 21 for abbreviation definitions.*

2. Rijnberk A, van Wess A, Mol JA. Assessment of the two tests for the diagnosis of canine hyperadrenocorticism. Vet Rec 1988; 122:178-180.
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