

Part I
Cushing's Disease Is Hard To Diagnose
(cushing's disease is easy to treat)



Thomas Schermerhorn, VMD, DACVIM(SAIM)
Kansas State University
Manhattan, Kansas, USA

Overview

- Why test?
- When to test?
- How to test?
- Will you treat?
- How to treat?



CLINICAL SIGNS

- Polyuria
- Polydipsia
- Alopecia
- Pendulous abdomen
- Hepatomegaly
- Polyphagia
- Muscle weakness/atrophy
- Panting
- Skin signs (comedones, hyperpigmentation, calcinosis cutis)
- Reproductive signs (anestrus, testicular atrophy)



CLINICAL SIGNS

- Polyuria
- Polydipsia

- Pendulous abdomen
- Hepatomegaly

- Panting
- Restlessness

- Suspicion based on incidental findings



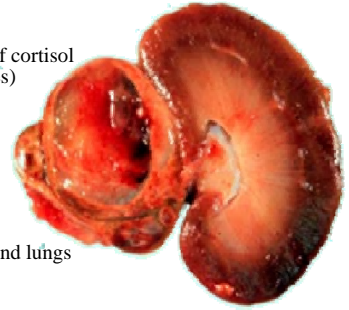
Pituitary Dependent Hyperadrenocorticism (PDH)

- *Most common form* - 85% of cases
- Pituitary tumor overproduces ACTH
- Excess ACTH causes bilateral adrenal hyperplasia



Adrenal Dependent Hyperadrenocorticism (ADH)

- ADH - 15% of cases
- Autonomous production of cortisol (+/- other steroid hormones)
- Adenoma~50%
 - Benign
- Carcinoma~50%
 - Malignant
 - local extension
 - metastasis to liver and lungs



Why test for Cushing's Disease

WHY

- Address a particular client complaint.
- Paraneoplastic syndrome.
- Prevent sequelae of hyperadrenocorticism.

WHY NOT

- No clinical signs/no client complaint
- Expensive to diagnose and treat.
- Undefined risk of complications - controversial

Diagnosis of HAC

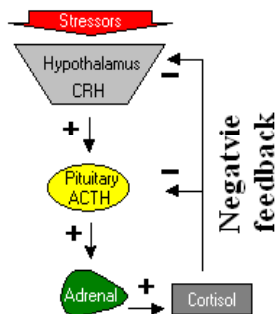


Definitive diagnosis is difficult

- No one test is perfect.
- Hypercortisolemia occurs during non-adrenal illness.
- Clinical signs may be present but diagnostics do not support the diagnosis of HAC (aka Atypical Cushings Disease)

Atypical Cushing's Syndrome in Dogs: Arguments For and Against
Behrend EN, *Vet Clin N Amer Small Anim Pract.* 2010 Mar;40(2):285-296.

Regulation of Cortisol Secretion



- ACTH secretion is pulsatile
- ACTH secretion influenced by:
 - Feeding
 - Physiologic/environmental stress
 - Pain
 - Trauma hypoxia
 - Pyrogens
 - Cold exposure
 - Surgery

When to test for Cushing's disease?

- Deciding when to begin a work-up for Cushing's disease is not always straightforward.
 - Could (should) you screen for Cushing's disease?
 - Laboratory abnormalities only?
 - Wait for clinical signs?
- Deciding NOT to do testing can be difficult also.

Suspect Cushing's

MDB

Adrenal testing to confirm

Characterize with appropriate function testing/diagnostic imaging

Treat appropriately

Streamlined diagnostic process
Confidence in the diagnosis

ADR/SICK/screen

MDB and Diagnostic imaging

Suspect Cushing's

Adrenal testing to confirm

Characterize with appropriate function testing/diagnostic imaging

Treat appropriately

Convoluted diagnostic process
Less certain diagnosis is correct

Testing and Prediction

Test Characteristics

Sensitivity = $a / (a+c)$ = true positive
Specificity = $d / (b+d)$ = true negative

	Dz+	Dz-	
Test +	a	b	PPV = $a/(a+b)$
Test -	c	d	NPV = $c/(c+d)$

100% Sensitivity – All affected have (+) test.
90% Sensitivity – 90% affected have (+) test; 10% affected will be misclassified.

100% Specificity – All unaffected have (-) test.
90% Specificity – 90% unaffected have (-) test; 10% unaffected will be misclassified.

Test Performance

Predictive value (+) = proportion of dogs with (+) tests that have disease
increases with increasing prevalence; decreases with decreasing prevalence

Predictive value (-) = proportion of dogs with (-) tests that do not have disease
decreases with increasing prevalence; increases with decreasing prevalence

2-Step Diagnostic Approach

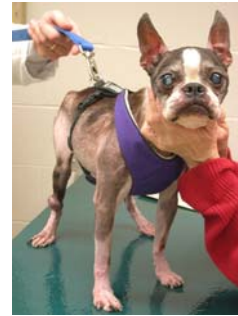
Screening Tests – confirm adrenal hypersecretion

- Urine cortisol:creatinine ratio (UCCR)
- Low dose dexamethasone suppression test (LDDST)
- ACTH stimulation test
- Combination of ACTH stim test + LDDS test
- Baseline cortisol concentration – **not recommended.**
- Determine GC-induced ALP isoform– **not recommended.**

Differentiating tests – distinguish PDH and ADH

- Adrenal US (other diagnostic imaging)
- Endogenous ACTH
- High dose dexamethasone suppression test (HDDST)

STEP 1 - Screening Tests



Screening Tests

Urine Cortisol:Creatinine Ratio (UCCR)

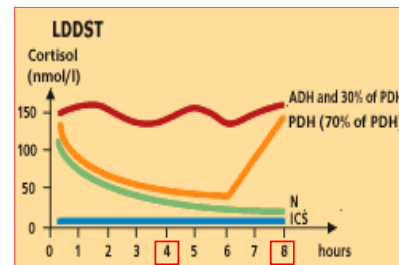
- Test principle – Excessive hormone secretion
- Useful for identifying affected dogs (sensitive test)
- Normal result virtually rules out HAC
- Abnormal result requires additional screening test (e.g. LDDS).



Screening Tests

Low Dose Dexamethasone Suppression Test

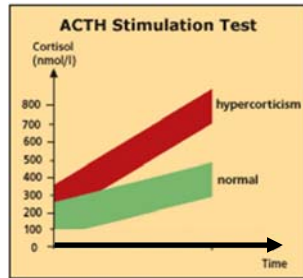
- Test principle – impaired negative feedback
- Effective screening test.
- Can be a differentiating test
- Stress/Nonadrenal illness = false + (less sensitive)



Screening Tests

ACTH Stimulation Test

- Test principle – Adrenal secretory capacity
- Good choice if non-adrenal illness is suspected
- Generally considered more Specific than LDDS
- Cannot distinguish between PDH and AT



STEP 2 - Differentiation Tests



Only after HAC has been confirmed using a screening test

Abdominal Ultrasound

Doesn't assess function – possible misdiagnosis

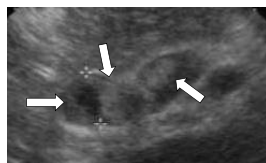
PDH

- Bilateral adrenal hypertrophy
- Normal and hypertrophied glands overlap in size



ADH

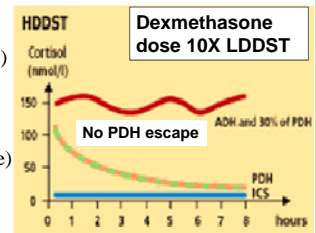
- Unilateral adrenal enlargement
- Nodular change
- Atrophy of contra-lateral gland



High Dose Dexamethasone Suppression Test (HDDST)

Misleading test if dog has not been properly screened
Only dogs with HAC should be tested.

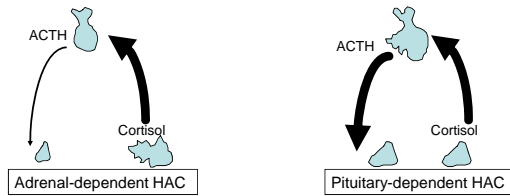
- Suppress – PDH
- No Suppression – AT
- Distinguishes PDH vs. ADH (70%)
- 30% PDH – no suppression
- Only rare AT suppress (incomplete)



ENDOGENOUS ACTH TEST

The use of eACTH as a screening test is limited

- Dogs with PDH can have normal ACTH values



eACTH test is **best** used to distinguish between PDH & AT

Diagnostic for PDH or AT in >80% of dogs (>95% when re-tested)

Other Imaging Tests

- **Computed tomography (CT scan)**
 - diagnosis of adrenal tumors
 - pituitary tumors when macroadenoma present
- **Magnetic resonance imaging (MRI)**
 - more accurate for visualization of small pituitary tumors but only 50% of dogs with PDH will have identifiable microadenoma

Summary

- Important to give careful consideration to advantages and risks of Cushing's disease testing for each patient.
- Diagnosis is challenging
 - Available tests are not perfect
 - Patient selection is important
 - Accurate diagnosis can be achieved

QUESTIONS

