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

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/atropy
- 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 Cushing Disease)

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.

Testing and Prediction

Test Characteristics

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test+</td>
<td>Sensitivity = a / (a+c) = true positive</td>
</tr>
<tr>
<td></td>
<td>Specificity = d / (b+d) = true negative</td>
</tr>
</tbody>
</table>

- 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**

1. **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).

**Low 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 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

ACTH → Cortisol

Adrenal-dependent HAC

ACTH → Cortisol

Pituitary-dependent HAC

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