Canine Hyperadrenocorticism (HAC; Cushing’s Syndrome)

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Pathophysiology

- Syndrome characterized by chronic excess of systemic cortisol
  - Pituitary tumor making excess ACTH (most common)*
  - Pituitary hyperplasia due to excess CRH (not dogs and cats)
  - Autonomous adrenocortical tumor*
  - Iatrogenic
    - Excess ACTH (rare)
    - Excess glucocorticoids (common)*
  - (ACTH from non-pituitary sources – very rare in dogs and cats)

*3 most clinically important causes in dogs and cats

- Pituitary-Dependent Hyperadrenocorticism (PDH)
  - 80-85% dogs with HAC
  - Most have pituitary adenoma in pars distalis
  - Most microadenomas (< 1 cm)
  - 10-20% macroadenomas (> 1 cm)
  - Frequency and amplitude of ACTH “bursts” are chronically excessive
  - Chronic excess cortisol secretion
  - Adrenocortical hyperplasia
  - Relatively ineffective feedback on pituitary adenoma
  - Suppression of hypothalamic function and CRH
    - Loss of hypothalamic control of ACTH
  - ACTH and cortisol levels usually within reference ranges on single blood samples
    - Have to look at “area under the curve”

- Adrenal Tumor (AT)
  - Adenoma or carcinoma (carcinomas larger) (50:50 distribution)
  - Cortisol secretion independent of pituitary control
  - Suppression of CRH and ACTH
  - Atrophy of contralateral adrenal and normal cells in affected adrenal
  - Episodic random cortisol secretion
  - Can respond to ACTH

  (Non-Cortisol Secreting Adrenal Tumors
   - Carcinomas
   - Secrete adrenal steroids other than cortisol
   - Mutation in neoplastic tissue)
• Typical Cushing’s signs
• Low cortisol levels
• High levels of other steroid hormones)

• Iatrogenic Hyperadrenocorticism
  o Good medical history is essential!
  o Excessive administration of glucocorticoids
    ▪ Allergic or immune-mediated disease
    ▪ Oral, eye, ear, or skin medications
    ▪ Suppression of endogenous ACTH
    ▪ Bilateral adrenocortical atrophy

Signalment

Middle-aged and older dogs
• PDH: 55-60% female
  o 75% > 9 yrs
  o Median 11.4 yr
• AT: 60-65% female
  o 90% > 9yrs
  o Median 11.6 yr

Any breed can be affected
• PDH:
  o Poodles, dachshund, terriers, beagles, German shepherd dogs (GSD)
  o 75% < 20 kg
• AT:
  o Poodles, GSD, dachshund, labs, terriers
  o 50% > 20 kg

Clinical Signs, History, Physical Examination

• Polyphagia (> 90%)
• PUPD (80-85%)
• Abdominal enlargement (>80%) – “pot-bellied”
  o Hepatomegaly
  o Redistribution of fat
  o Abdominal muscle weakness
• Muscle weakness (75-85%)
• Panting
• Lethargy
• Obesity
• Heat intolerance
• Alopecia
  o Truncal
  o Bilaterally symmetrical
• Calcinosis cutis
• Thin skin, bruising, striae
• Seborrhea, pyoderma
• Comedones
• Hyperpigmentation
• Anestrus
• Testicular atrophy
• Facial paralysis
• Pseudomyotonia

Neurological Signs Associated with Pituitary Macroadenoma
  o Dull, listless
  o Decreased appetite
  o Aimless wandering
  o Pacing, circling
  o Behavioral changes
    ▪ Seizures rare

NOT Clinical Signs of Hyperadrenocorticism

• Anorexia/hyporexia
• Vomiting
• Diarrhea
• Sneezing
• Coughing
• Icterus
• Pruritus
• Pain
• Lameness due to inflammation
• Seizures
• Bleeding
• Renal failure
• Pancreatitis
• Liver failure
• Immune-mediated diseases

Hyperadrenocorticism

• Most patients are not critically ill
• Rarely an emergency
• Slowly progressing illness
• Not all dogs have all the signs
• Most dogs have one or a few signs
• This is a CLINICAL syndrome:
  • DON’T TRY TO DIAGNOSE IT WITHOUT THE CLINICAL SIGNS!!
Clinicopathological Findings

CBC
- “Stress leukogram”
  - Neutrophilia
  - Monocytosis
  - Lymphopenia
  - Eosinopenia
- Thrombocytosis
- nRBCS
- Mild erythrocytosis (females - androgens)

Serum Biochemistry
- ↑↑ AP (90-95%) (can be > 1000)
  - (SIAP is of little value - sensitive, but not specific)
- ↑ ALT (< 400)
- Mildly ↑ fasting BG
- Normal to ↓ BUN
- ↑ cholesterol and triglycerides
- Mildly ↑ bile acids
- Mild ↑ Na
- Mild ↓ K

Urinalysis
- SG < 1.015, often < 1.008
- Mild increase in UP:C (less than 5)
- Urinary Tract Infection (UTI) in 40-50%
- UTI often “silent”
  - Inactive sediment
  - No clinical signs
  - Low USG
  - Cystocentesis sample and culture is MANDATORY!

Diagnostic Imaging

Abdominal Radiographs
- Excellent detail
- Hepatomegaly
- Distended urinary bladder
- Urolithiasis
- Dystrophic calcification of soft tissues
- Osteoporosis of vertebrae
- Calcified adrenal gland
  - Rare
  - Consistent with adrenal adenoma or carcinoma
Thoracic Radiographs
- Calcification of airways
- Osteoporosis of vertebrae
- Pulmonary metastases
  - Rare
- Evidence of pulmonary thromboembolism

Abdominal Ultrasound Examination
- Adrenomegaly (PDH)
- Adrenal mass with small contralateral adrenal (AT)
- Calcified adrenal gland (AT)
- Tumor thrombus or metastasis
- Hepatomegaly
- Hyperechoic liver
- Distended urinary bladder
- Urolithiasis
- Dystrophic calcification of soft tissues

Advanced Imaging
- Brain CT or MRI may reveal pituitary tumor
  - Recommended to confirm cause of neurological signs
  - Recommended if considering radiation therapy or surgery
- Abdominal CT recommended prior to adrenalectomy

Complications of Hyperadrenocorticism
- Hypertension (> 50%)
- Urinary tract infection (UTI)
  - Pyelonephritis
  - Cystitis (clinically silent)
- Urolithiasis
  - Calcium-containing
  - Struvite, related to UTI
- Congestive heart failure
- Pancreatitis???
- Diabetes mellitus
- Poor wound healing
- Recurrent infections
- Joint laxity
- Hypercoagulability
  - Pulmonary thromboembolism
  - Aortic thromboembolism

Diagnosis of Canine Hyperadrenocorticism
• Screening tests
• Differentiation tests
• Need to understand sensitivity and specificity
  o False positives and false negatives
• Can improve predictive value of tests by only testing the appropriate population
  o Consistent clinical signs
  o No concurrent illnesses

**Screening Test: Basal Cortisol**

Just say NO for Cushing’s diagnosis
• Wide fluctuations throughout the day
• Normal dogs can be out of the reference range
• Basal levels higher with stress or other illnesses
• Cushing’s dogs usually in reference range
• Typical reference range: 1-5 ug/dl

*NOTE: Can be used to RULE OUT hypoadrenocorticism*

**Screening Test: Urine Cortisol: Creatinine Ratio**

UCCR: screening test
• High sensitivity
  o But not 100%
• Few false negatives - but how few?
  o Depends on study:
  o one study: 75% sensitive
  o earlier study: 99% sensitive
  o May have 1/100 - 25/100 false negatives
• Low specificity
  o Many false positives
  o ✆UCCR in 75 - 85% dogs with NON-adrenal disease

Good screening test for the “healthy” Cushing’s suspect
Quick, easy, outpatient test

**Screening Test: ACTH Stimulation Test**

Screening test – measures maximum secretory capacity of the adrenal cortex.

➢ *How to do it:*

Obtain baseline cortisol sample
• Inject Cortrosyn IV
  o 5 ug/kg (up to 250 ug max)
  o 1 vial if >25 kg
Wise Use of Cortrosyn
- If Cortrosyn in limited supply
- Reserve Cortrosyn for hypoadrenocorticism diagnosis and Cushing’s monitoring
- Use the 5 µg/kg dose
  - Reconstitute one vial (250 µg)
  - Store in freezer in aliquots in syringes
  - e.g. 5 x 50 µg doses - one per 10 kg
  - Will dry out in a frost-free freezer

➤ ACTH Stimulation Test and Steroids:

Two Separate Problems:
1. Cross-Reaction with the Cortisol Assay
2. Suppression of pituitary-adrenal axis

1. Cross-Reaction with Cortisol Assay:
   - Prednisone
   - Prednisolone
   - Hydrocortisone
     - Should be off prednisone for 12-24 hours
2. All glucocorticoids can suppress pituitary-adrenal axis
   - Depends on dose
   - Depends on duration of therapy
   - Depends on route
   - Depends on type of glucocorticoid

➤ How to interpret it:

ACTH Stimulation Test Results
- Pre-ACTH cortisol: normal: 0.5 - 6.0 µg/dl
- Post-ACTH cortisol:
  - Normal: <18 µg/dl
  - Exaggerated: >22 µg/dl
  - Grey zone: 18 - 22 µg/dl
- Hypoadrenocorticism: both values < 2 µg/dl
- Usually < 0.2 µg/dl

➤ Pros and Cons of the ACTH Stimulation Test
- More false negatives than LDDST
  - Lower sensitivity
- Fewer false positives than LDDST
  - Higher specificity
- Does not distinguish between PDH and AT
- One hour test
- Can combine with other procedures (e.g. ultrasound)
- Useful in a referral setting
- Only test for:
  - Iatrogenic Cushing’s
  - Hypoadrenocorticism
  - Monitoring mitotane or trilostane therapy
  - Monitoring post-adrenalectomy

**Screening Test: Low-Dose Dexamethasone Suppression Test (LDDST)**

- More sensitive (95%) than ACTH stimulation test
- Less specific (more false positives)
- CAN distinguish between PDH and AT
- Not useful for iatrogenic Cushing’s or hypoadrenocorticism

➢ *How to do it*

- Blood sample at 0 (pre), 4, and 8 hours
- Give 0.01 mg/kg dexamethasone IV (0.015?)
- Less expensive than ACTH stimulation test (at current price of Cortrosyn)
- Takes 8 hours
- Avoid stress, excitement, handling, other tests

➢ *How to interpret it*

**LDDST Results**

Normal patient:
- 0 hr: Cortisol = 1 - 5 mg/dl
- 4 hr: Cortisol < 1.4 mg/dl
- 8 hr: Cortisol < 1.4 mg/dl

Cushing’s patient:
- 8 hr: Cortisol > 1.5 mg/dl

**Discrimination Test: LDDST**

- Discriminatory test in some cases
  - Cannot confirm AT
- “Decrease” occurs in 60 - 65% of dogs with PDH:
  - 4 hr: Cortisol < 1.4 μg/dl, or
• BUT - 35-40% of PDH do NOT suppress
  o 4 hr cortisol > 1.5 μg/dl
  o and both > 50% baseline:
    ▪ Adrenal tumor
    ▪ PDH (35 - 40%)
• High Dose Dexamethasone Suppression Test (HDDST)
• Endogenous ACTH
• Abdominal Ultrasound
  o Not a good discriminating test in all cases
  o Results can be misleading
  o Is indicated if you suspect adrenal tumor

**Discrimination Test: High Dose Dexamethasone Suppression test (HDDST)**

➢ *How to do it*

• Give 0.1 mg/kg dexamethasone iv
• Blood sample at 0 (pre), 4, and 8 hours
• AT: no suppression at 4 or 8 hours
• PDH:
  o Cortisol < 1.4 mg/dl at 4 or 8 hours
  o Cortisol < 50% baseline at 4 or 8 hours
  o 25% PDH cases do NOT suppress

• Pituitary-Dependent Hyperadrenocorticism:
  o 35-40% do not suppress on LDDST
  o 25% do not suppress on HDDST
  o If no suppression on LDDST, will only pick up another 10-15% on the HDDST, so probably better to choose another test
  o Can NEVER DIAGNOSE adrenal tumor on LDDST or HDDST

**Discrimination Test: Endogenous ACTH**

• Specific for discrimination of PDH vs. AT

• Important to remember:
  o Must have diagnosis of Cushing’s
  o ACTH very labile
  o Special handling precautions (plastic, freezing)
  o Repeat measurement may be necessary
• Hospitalize dog overnight and sample at 8-9 am?

Normal range: 10 - 80 pg/ml
Adrenal tumor: < 20 pg/ml
PDH: > 45 pg/ml

20 < ACTH < 45
• Non-diagnostic
• Repeat test

**Discrimination Test: Abdominal Ultrasound Examination**

• Not a good discriminating test in all cases
• Results can be misleading
• Is indicated if you suspect adrenal tumor

➤ **Sources of ultrasound confusion**

• Adrenocortical nodular hyperplasia
  o 5-10% of HAC
  o Form of PDH
• Bilateral adrenocortical tumors
• Adrenocortical tumor AND pheochromocytoma
• Simultaneous PDH and AT

*Treatment of Hyperadrenocorticism*

Before commencing treatment
• Be confident of the diagnosis
• Patient must have consistent clinical signs, clinicopathological findings, and positive diagnostic testing

➤ **What to do if HAC strongly suspected but tests do not confirm?**

• Wait and retest
• Consider ACTH stimulation with sex hormone panel (controversial)

➤ **What to do if tests confirm HAC but patient has minimal signs?**

• Ensure that test results are not false positive
  o Stress
  o Concurrent non-adrenal illness
• No evidence that early treatment is beneficial
• Treat when
  o Signs affecting quality of life of dog, or
  o Signs affecting quality of life of owner, or
  o Signs concerning to veterinarian
    ▪ Monitor for occult complications of HAC
      • Hypertension
- UTI
- Proteinuria

Client Education

Medical therapy is indicated for PDH and for adrenal tumors in which surgery is not an option. Medical therapy for HAC is lifelong, requires diligent monitoring and follow-up, and is potentially expensive. Serious side effects are possible with all forms of medical therapy.

Surgical Therapy

- Surgery is indicated for functional adrenocortical tumors
  - Adenoma – good prognosis
  - Carcinoma with no metastases
    - Ultrasound
    - CT
    - Radiographs
- Recommend referral to specialists
  - Experienced surgeon
  - Good anesthetic support
  - Internist for management pre- and post-surgery
    - Hypertension
    - Hypercoagulability
    - Post-operative hypoadrenocorticism
- Surgery for pituitary tumors
  - Hypophysectomy
  - Routinely performed in Europe
  - Not currently widely available in the US

Medical Therapy: Mitotane

- o,p’-DDD
- Derived from DDT
- Lysodren®
- Adrenocortico-lytic
  - Fasciculata
  - Reticularis
  - Glomerulosa?
    - Zona glomerulosa makes NEW adrenocortical cells
- Previous treatment of choice for PDH – replaced by trilostane?
- Occasionally used for AT:
  - Pre-surgical stabilization
  - Surgery not an option
- Effective
• Safe, if used carefully

• Normal dogs are relatively resistant
  o Reduced GI absorption in normal dogs compared to dogs with hyperadrenocorticism
  o Cortex is damaged but dogs not clinically affected
  o (HAC dogs more sensitive to loss of cortical function)

• Some Cushing’s dogs appear “resistant”
  o Not getting drug
  o Drug not absorbed (give with food, crush or make suspension)
  o Bad batch of medication
  o Other medications interfering
  o Adrenal tumor
  o Resistant form of PDH (need a higher dose)
  o Incorrect diagnosis

• 2 phases of therapy:
  o Loading/induction
  o Maintenance
• Monitoring is key:
  o ACTH stimulation test
    ▪ Determine end-point of induction
    ▪ Confirm ongoing successful maintenance

*Mitotane Induction:*
• Dose: 50 mg/kg (500 mg tablets)
  o Divide daily dose
  o Give with food
• Talk to owner daily
• YOU (or nurse) call the owner
  o Pick up subtle signs of induction
  o Reinforces importance of close monitoring

• Stop therapy and do ACTH stimulation test when see:
  o Subtle decrease in appetite (usually happens first), or
  o Decrease in PUPD, or
  o Vomiting, anorexia, diarrhea, or
• ACTH stimulation test at 7 days even if no change in signs

• Concurrent prednisone: NO
• Owner has prednisone on hand - call first

• Successful induction is achieved when basal and post-ACTH cortisol:
  o both < 4 (5) mg/dl (40 ng/ml) and > 1 mg/dl
• Most cases take 5 - 15 days

_Mitotane Maintenance:_
• Give daily induction dose weekly (divided)

• Example:
  o 10 kg dog required 250 mg BID for induction (7 days)
  o Maintenance dose would be 250 mg twice weekly
  o Divide dose (125 mg BID)

• Continue to monitor with ACTH stimulation tests

_Mitotane Monitoring:_
• ACTH stimulation test:
  o At end of induction
  o 1 month later
  o 3 months later
  o every 6 months
  o 1 - 2 months after every dosage change
  o If problems arise
• POST ACTH cortisol is the most important
• CANNOT monitor with basal cortisol!

<table>
<thead>
<tr>
<th>Pre and Post ACTH Cortisol (µg/dl)</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 and 0.2 (goal is both values 1- 4 µg/dl)</td>
<td>Stop mitotane, give prednisone, check electrolytes, monitor ACTH stimulation tests</td>
</tr>
<tr>
<td>1 and 3</td>
<td>Continue maintenance dose</td>
</tr>
<tr>
<td>0.2 and 2</td>
<td>Continue maintenance dose</td>
</tr>
<tr>
<td>1 and 6</td>
<td>Increase weekly maintenance dose</td>
</tr>
<tr>
<td>3 and 9</td>
<td>Re-induce</td>
</tr>
</tbody>
</table>

_Mitotane Side Effects_
• Vomiting, diarrhea, loss of appetite
  o Not uncommon, often transient
• Lethargy
Iatrogenic Hypoadrenocorticism

- Cortisol deficiency alone:
  - Pre- and post-ACTH cortisols both < 0.2 mg/dl
  - Supplement with prednisone (0.1 - 0.2 mg/kg)
  - Follow ACTH stimulation tests
  - Usually recover (may take days, weeks, or months)

- Cortisol and aldosterone deficiency (< 5%):
  - Pre- and post-ACTH cortisols both < 0.2 mg/dl
  - Abnormal electrolytes
  - Usually do not usually recover
  - Manage as Addisonian
  - Damage to zona glomerulosa

Prognosis with Mitotane

- Dogs with PDH on mitotane:
  - Feldman and Nelson
  - 1500 dogs
  - Dogs that have died - mean survival 31.6 m
  - (range: few days to several years)
  - >35% relapse
  - 5% mildly overdosed during induction
  - Dogs that died:
    - 37% related to HAC
    - 20-30% due to pituitary tumor
    - <1% due to mitotane overdose

Planned Medical Adrenalectomy

- Induction of permanent addisonian state
- “not recommended” in literature
- Consider for selected cases?
  - Dogs that relapse frequently on maintenance mitotane
  - Dogs with diabetes and Cushing’s
  - Financial concerns
    - Expensive initially, then costs are fixed
“Utrecht Protocol”

- **Day 1:** start mitotane (usual dose - higher dose for smaller dog)
  - Continue for 25 days
- **Day 3:** start usual medications for Addison’s disease (DOCP or fludrocortisone, and prednisone)
  - Fludrocortisone 0.1 mg/5kg (divide BID)
  - Prednisone
    - 0.5 mg/kg initially
    - Gradually reduce to 0.1 mg/kg/day
- ACTH stimulation test at end of the 25 days
  - (Stop prednisone for at least 12 hours)
- Goal is pre and post cortisol < 1mg/dl
  - Continue Addison’s therapy as for other cases
- During induction:
  - Stop mitotane if dog is anorexic
  - Do NOT stop Addison’s therapy
  - Monitor electrolytes weekly

**Medical Therapy: Trilostane**

- Vetoryl® (Dechra)
  - Tested and licensed in Europe and USA for canine Cushing’s
  - Competitively inhibits steroid synthesis
    - Inhibits 3-β-hydroxysteroid dehydrogenase
    - Converts pregnenolone to progesterone
    - Converts 17-OH pregnenolone to 17-OH progesterone
  - Appears safe and effective
  - Monitor with ACTH stimulation tests
  - Adrenals keep getting bigger
  - Some reports of adrenal necrosis
- Reports of successful therapy of adrenal tumors (median survival 14 months)
- One case series of 3 dogs with adrenal metastasis (survived 11m, 16m, and 10 m)
- Has been used in cats

**Using Trilostane**

- Start with lower dose
  - 1 mg/kg BID (or less)
- ACTH stimulation tests
  - Start 3-4 hours post-pill
  - 10-14 days
    - Ensure not over-dosing
  - Monthly
  - Whenever clinical signs change
  - Aim for pre and post values between 2 and 6 ug/dl
  - ACTH response may decrease over time
  - Do not be too quick to increase dose

- SID or BID?
  - Use BID if ACTH stim results are good on SID, but clinical signs persist
    - Interpret ACTH stim results and clinical signs together
  - Use BID if significant co-morbidities or complications of HAC
    - Diabetes mellitus
    - Calcinosis cutis
    - Thromboembolic disease
    - Proteinuria?
    - Hypertension?

- Just use Vetoryl®!
  - Compounded trilostane?
    - No!
    - JAAHA study (Cook)
      - Marked variability within batches of medication
      - Marked variability between batches of medication
      - Several pharmacies evaluated

**Mitotane or Trilostane: Which to Use?**

- Effectiveness?
  - Similar
- Frequency of adverse effects?
  - Similar
- Cost comparison (assuming no dose increase):
  - Small dog
• Mitotane and trilostane equivalent in first month (mitotane induction is expensive)
  • Mitotane much less expensive in maintenance phase
  o Medium to large dog
    • Mitotane more expensive in first month
    • Differential is greater for larger dogs
    • Mitotane less expensive in maintenance phase

• Mitotane preferred for:
  o Adrenal tumor?
  o Require more consistent control of cortisol levels
    • Diabetic
    • Serious complications of HAC
    • Thromboembolic disease
    • Pseudomyotonia
    • Calcinosis cutis

• Transitioning between mitotane and trilostane
  o Stop first medication
    • Monitor clinical signs and ACTH stimulation tests
    • Start second medication when have clinical signs and exaggerated response to ACTH (high normal or above normal post-ACTH cortisol)
    • Probably happens more quickly with trilostane

STUDY!

Contact Dr. Lunn if you have a newly diagnosed (or strongly suspected) dog with pituitary-dependent Cushing’s NOT yet on therapy. We have a study that will provide about $300 of work-up, in return for allowing ophthalmology to perform some non-invasive tests on the patient. The purpose of the study is to compare a variety of endocrine and other tests in dogs with SARDS, dogs with advanced progressive retinal atrophy, and dogs with Cushing’s.

Contact Details for Study:

Dr. Freya Mowat (ophthalmologist and principal investigator): fmmowat@ncsu.edu
Dr. Kathy Lunn (internal medicine and co-investigator): kflunn@ncsu.edu
Melanie Foster (research associate): melanie_foster@ncsu.edu