Hypercortisolism

Nomenclature

Hypercortisolism (HC): Newer term

Hyperadrenocorticism: Older term

"Cushing's disease": Technically refers to PDH

"Cushing's syndrome": The clinical signs that arise from any of the three forms of HC

Three Forms

1. Pituitary-dependent HC (PDH) ~ 80-85% *majority of dogs!
2. Adrenal-dependent HC (ADH) ~ 15-20%
3. Iatrogenic
    a. Due to endogenous glucocorticoids
    b. Oral, injectable, topical, otic, ophthalmic

*Clinical signs are the same for all three forms, but the testing differs

Clinical Signs (6 Ps)

- PU
- PD
- PP *not cats or people unless they have concurrent diabetes
- Panting (due to #5 and #8, pulm. Mineralization, PTE etc.)
- Pendulous Abdomen
- Poor hair regrowth / alopecia
- Thin skin due to the glucocorticoid effect on fibroblasts and collagen
- Weakness (muscle atrophy from muscle catabolism)
- Weight "gain" (redistribution)
- *one of the few diseases that cause both PD (central effect) and PU (secondary nephrogenic DI)

Physical Exam

- Typically, BAR (unless macroadenoma)
- Weight redistribution
    - Appendicular fat/muscle atrophy
    - Truncal weight (fat) gain
- Pendulous abdomen due to:
    - Hepatomegaly
    - Distended bladder

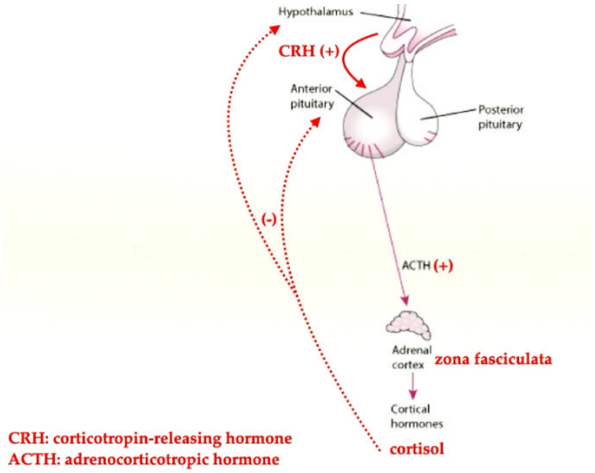
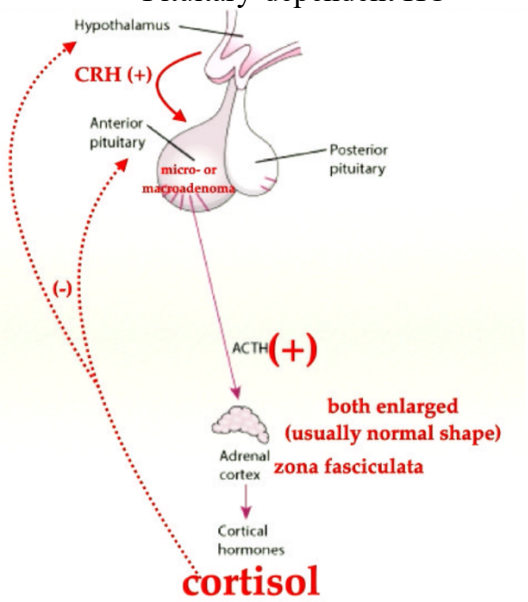
    - Abdominal fat deposition (unclear why) *people get fat deposition over their shoulders
    - Abdominal muscle atrophy
- Dermatologic changes
    - Bilaterally symmetric alopecia (endocrine alopecia) from hair follicle atrophy, thin skin
    - +/- hyperpigmentation
    - +/- calcinosis cutis

*This is an exam room diagnosis because there is not a single definitive test for diagnosing hypercortisolism, unlike Addison's disease

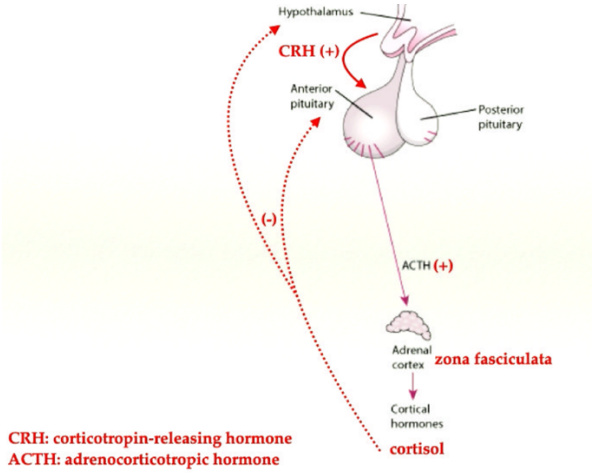
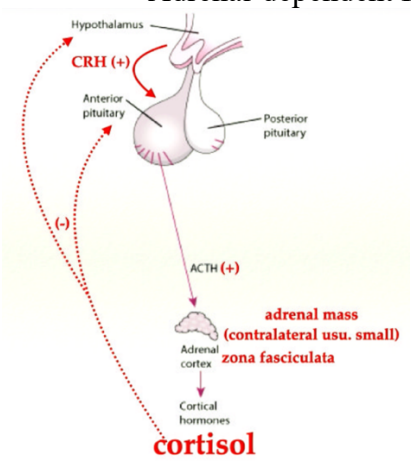
Hormone Classes of Interest in HC

- Protein/peptide hormones (most common)
    - All pituitary (ACTH, hypothalamus, pancreatic, PTH, EPO)
    - Short $T_{1/2}$, rapid acting, water soluble
- Steroid hormones
    - Adrenal corticosteroids, estrogen, progesterone, testosterone, calcitriol
    - Variable $T_{1/2}$, lipid soluble, from cholesterol
- Amino acid (tyrosine) hormones
    - Catecholamines, dopamine, T3, T4
    - Short $T_{1/2}$, (fT4) unless protein bound (tT4). Water soluble

Hypothalamus-Pituitary-Adrenal Gland Axis Review

In Health	Pituitary-dependent HC
	
	*usually a benign tumor

When trying to differentiate between pituitary and adrenal forms of HC you can measure ACTH. If it is PDH the ACTH should be high (but it is often normal) NOT zero which it should be with the negative feedback, but the tumor is causing an increased release of ACTH

In Health	Adrenal-dependent HC
	
	*50/50 adenoma vs carcinoma

If it is ADH the ACTH and CRH should be low due to the negative feedback on the hypothalamus and anterior pituitary

Overview on differentiating between PDH and ADH: measure ACTH, if it is high, it is PDH, if it is normal, it is probably PDH, if it is low it is likely ADH

Glucocorticoid Physiology

- Glucocorticoids work on virtually all tissues in the body
    - Anti-inflammatory and immunosuppressive effects
    - Increases blood glucose (especially during fasting) *glucose homeostasis
        - Enhances protein and fat catabolism
        - Enhance hepatic gluconeogenesis
        - Enhances glucagon secretion
        - Cause insulin resistance (diverts glucose to essential tissues)
    - Promote vascular integrity (reason Addisonians are hypotensive)
    - Promotes GI mucosal integrity (why Addisonians may have GI signs)
    - Decreases bone formation *people get osteoporosis
    - Involved in RBC production (reason there may be anemia with Addison's and mild primary polycythemia with HC)
    - Cortisol plasma $T_{1/2}$ is ~1-2 hours and peaks in the morning
    - Lymphopenia is the most common component of the stress leukogram!

FYI: Dexamathasome is 30x stronger than cortisol, prednisone is 4x stronger than cortisol

PDH vs ADH

Signalment: middle-aged to geriatric dogs (mean age ~10 years)

PDH **Pituitary-dependent hypercortisolism**	**ADH** **Adrenal-dependent hypercortisolism**
80-85%	15-20%
Anterior pituitary tumor Generally microadenoma Rarely macroadenomas Extremely rare: adenocarcinoma	Adrenal tumor 50/50 adrenocortical adenoma vs carcinoma Criteria of malignancy: >2cm, local invasion, hemorrhage, necrosis, mineralization
Generally small dogs	Generally large dogs
Both adrenals plump to enlarged but usually still normal shape	Unilateral tumor, contralateral adrenal gland atrophy *not always Compensatory atrophy due to the lack of ACTH
Technically, Cushing's disease = PDH	
When measuring ACTH it should be high to normal	When measuring ACTH it should be low (as well as CRH)

Pituitary Macroadenoma

- Rare form of PDH
- Definition: Pituitary tumor > 1cm or growing out of the Sella Turcica
- Signs: inappetence (different because dogs with Cushing's should be PP, mental dullness, disorientation, vision deficits (pituitary lives near the optic chiasm)
- Treatment options: radiation therapy (good for controlling the neuro signs, not great for controlling the Cushing's signs) or sx (hypophysectomy)
- Important differential for PDH dog with inappetence *not a differential for an ADH dog

Diagnostics "Exam Room Diagnosis"

Clinical Pathology

All of these changes are due to excess cortisol

CBC	**Chemistry**	**Urinalysis**
Stress leukogram (especially lymphopenia) Possible mild polycythemia Mild thrombocytosis (Cushing's and Pred are a ddx for a reactive thrombocytosis)	Mild-severe increase in ALP *Cats do not have an ALP steroid isoenzyme Mildly increased ALT Mild hyperglycemia (glucocorticoid) severe in cats Hyperlipidemia (mild to severe hypercholesterolemia and mild to moderate hypertriglyceridemia) Mildly decreased BUN – washout due to PUPD	Typically < 1.020, often isosthenuric (1.008-1.012) or hyposthenuric (<1.008) Mild proteinuria (increased BP and glomerulosclerosis) Possible lack of pyuria if bacteriuria

UCCR (Urine Cortisol Creatinine Ratio)

*Almost all animals with Cushing's will have an elevated UCCR (very sensitive but not specific)

- Urine cortisol creatinine ratio
- Sample from home; non-stressed
- Good screening test to rule-out
    - Extremely sensitive (95-99%)
    - Rare false positives
- NOT specific
    - All sick/stressed dogs test +
    - Many false positives

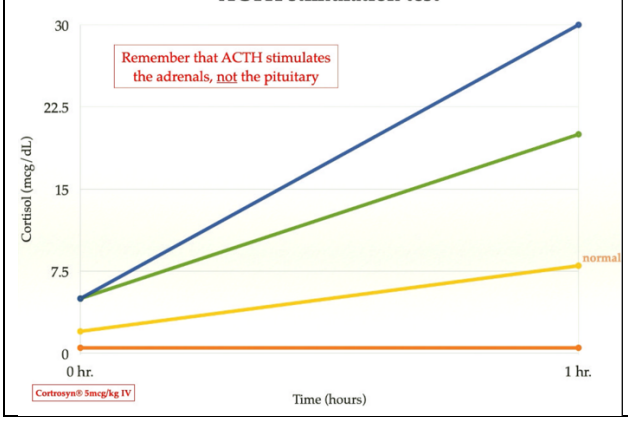
Endocrine Testing Overview

- Hormone concentrations
    - Often tested with their stimulus (ex: insulin with glucose)
- Stimulation tests
    - For hormone deficiencies
    - Ex: ACTH stim for Addison's, TSH stim for hypoT4
- Suppression tests
    - For hormone excess
    - Ex: LDDS test for Cushing's, T3 suppression test for hyperT4

*You always need to assess your patient, not just the assay to avoid misdiagnosis!

ACTH Stimulation Test (screening test)

- Gold standard for Addison's Disease
- Fair sensitivity and specificity (~60-90%) for Cushing's – better with PDH
- Evaluates 2 serum cortisol samples
    - Baseline/resting
    - 1 hour post Cortrosyn (synthetic ACTH) at 5 mcg/kg IV
- Interpretation
    - If 1 hour <2 mcg/dL: consistent with Addison's or iatrogenic HC
    - If 1 hour ~2-18 mcg/dL: inconsistent with HC
    - If 1 hour >20 mcg/dL: Consistent with HC



Orange: Addisonian or iatrogenic Cushing's syndrome

Yellow: Normal

Green: Adrenal-dependent (one adrenal gland stims)

Blue: Pituitary-dependent

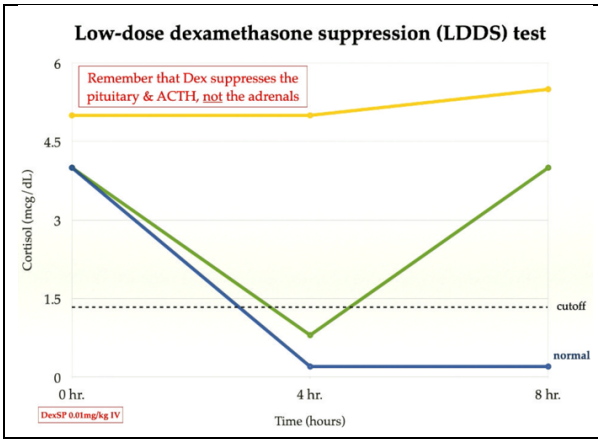
*Better test for PDH because you are stimulating two hyperplastic adrenal glands

Low-dose Dexamethasone Suppression Test (screening +/- differentiating test)

- Gold standard: good sensitivity (90-~95%) and so-so specificity (50-75%)
- Evaluates three serum cortisol samples
    - 0, 4, 8 hours after injections of DexSP (0.01 mg/kg IV)
- In normal dogs, exogenous dexamethasone will "suppress" cortisol for 24-48 hours
- Interpretation of LDDS test
    - If 8 hours < 1.4 mcg/dL: inconsistent with HC
    - If 8 hours > 1.4 mcg/dL: consistent with PDH
        - If 4 hour suppressed below 1.4 mcg/dL: consistent with PDH
        - If 4 or 8 hour <50% of baseline: consistent with PDH
        - If neither happen it could be either ADH or PDH
    - ~2/3 of PDH dogs will suppress at 4 or 8 hours (hence, differentiating)

*You can't suppress an adrenal tumor, but you can temporarily suppress a pituitary tumor

Adrenal tumors don't suppress because the ACTH is already 0. The excessive cortisol production has already initiated the negative feedback loop (which is what DexSP would have done) so ACTH is not being produced.



Blue: Normal

Yellow: Adrenal-dependent (did not suppress) *or PDH since it they may not always suppress

Green: Pituitary-dependent (suppressed and then increased) transiently responds

Brain dump: The PDH graph has a temporary dip because for a brief moment in time, the DexSp (which acts like cortisol) initiates negative feedback on the pituitary gland (which is producing a ton of ACTH). When ACTH is not being produced the cortisol levels in the blood temporarily decrease until the pituitary gland begins to overproduce ACTH again causing the graph to increase.

Endogenous ACTH Concentration (differentiating test)

- [eACTH]
- Short T1/2 ~ 10 min, labile hormone
- Trophic hormone leading to adrenomegaly
- Episodic release (even with PDH) therefore, results may be inconsistent
- **Usually suppressed (often unmeasurable) with ADH**
    - Their ACTH should be zero!

Imaging

- Ultrasound: probably best, most cost-effective test to differentiate ADH from PDH
- CT Scan: pre-adrenalectomy planning
    - Also assesses for pituitary macroadenoma
- MRI? Not cost-effective for adrenals but best for macroadenoma
- Normal dog adrenal < ~7-8 mm depth (depending on weight)
- PDH: bilateral enlargement (or high normal)
- ADH: unilateral adrenal gland mass with *contralateral adrenal gland atrophy* (classically, but not always)
- Iatrogenic HC: bilaterally small adrenal due to eACTH suppression

Treatment Overview

Medical

Trilostane *Vetoryl	**Mitotane *Lysodren**
Enzyme inhibitor (blocks 3B-hydroxysteroid dehydrogenase) converts cholesterol to cortisol Reversible (usually) Starting dose 0.5-1 mg/kg po BID with food (may be used TID, super short acting) FDA approved for dogs Comes in multiple sizes (5, 10, 30, 60mg capsules) Side effects: v/d, inappetence, lethargy	Causes selective adrenal necrosis of the zona fasiculata and reticularis (“lyse-adrenal”) Works well on hyperplastic adrenal glands but not normal adrenal glands or tumors!! Can cause irreversible necrosis – at risk for Addison’s Can occasionally impact other layers of the adrenal gland (glomerulosa) and cause electrolyte derangements Induction/loading dose 40-50 mg/kg/day x 5-10 days then maintenance at 40-50 mg/kg/week Only available in 500mg tablets

Monitor therapy with clinical signs, USG, water intake Treatment of choice for ADH pre-op *ACTH stims are not helpful for monitoring this drug therapy	Not FDA approved More predictable results with PDH, ADH is more resistant so higher doses may be needed Monitor therapy with clinical signs and ACTH stim tests! Treatment of choice for PDH with the right VCPR (More predictable)

Surgical Treatment

- Adrenalectomy
  - Laparoscopic for non-invasive adrenal tumors
  - Open laparotomy for invasive adrenal tumors
    - Worse prognosis due to intra-op hemorrhage and greater post-op complications
  - Complication for both include poor healing, risk of pancreatitis, post-op PTE
  - In rare cases, bilateral sx to treat refractory PDH leading to Addison's disease
- Hypophysctomy
  - For PDH
  - Transoral approach
  - Common surgery in people
  - Common in vet med in Europe and WSU
  - Will require lifelong glucocorticoids and L-thyroxine +/- DDAVP for Central DI
- Radiation therapy
  - For non-resectable adrenal mass (palliative)
  - For pituitary macroadenomas
    - Mainly to control neurologic signs
    - Variable results with improving PDH control

Rule outs for HC dog with poor appetite?

1. Drug reactions (GI side effects from Rx)
2. Over-controlled medically (ie, hypocortisolemic)
3. Prior disease has been unmasked by controlling HC (IBD)
4. Pituitary macroadenoma (PDH)
5. Metastatic disease (ADH)
6. New comorbidity has arisen
7. It wasn't Cushing's after all…

What about cats?

- Extremely rare
- Similar PDH/ADH distribution (~80/20%)
- Similar presentation except…

    - Eleveated ALP? Nope
    - Calcinosis cutis? Nope
    - PU/PD/PP? only if DM
    - Diabetes mellitus: 36/45 in 2 studies (80%) **diabetes and heart failure are the concerns for cats on steroids*
    - "Feline skin fragility syndrome": 25/45 (55%)
- Much worse prognosis and harder to treat than dogs

Why does a normal ACTH stimulation test rule out ADH?

ACTH stim test directly tests the ability of the adrenal glands to produce cortisol when stimulated, bypassing the pituitary. If the adrenal glands were impacted/atrophied etc. they would not respond appropriately to ACTH and would have little to no increase in cortisol

Monitoring Medical Treatment

- Monitoring clinical signs; have clients measure water intake
- Serial USGs – inexpensive monitoring tool
- ACTH stim
    - Unhelpful for monitoring trilostane Tx (except if concern for Addison's disease)
    - Excellent/imperative for monitoring mitotane Tx
    - "I'm back on the mitotane train" – Dr. Hulsebosch
- Pre- and post-pill cortisol levels for trilostante?
- UCCRs for trilostane

Possible Complications

- Hypertenstion – due to mineralocorticoid effects of cortisol
- Gallbladder mucocele – due to hyperlipidemia
- Calcinosis cutis (dorsum, inguinal, head) - due to altered calcium regulation
- Hypercoagulability and thromboembolic disease
    - Excess cortisol (leads to increased procoagulant factors and fibrinogen)
    - Obesity, recumbency, increased PCV
- Diabetes mellitus – due to insulin antagonism (especially cats!)
- Feline skin fragility syndrome (cats)
- Brusing (due to fragile vessels)
- Macroadenoma (if PDH)
- Hemoabdomen, ascites, metastasis (if adrenal mass)
- Cushing's myotonia (still muscles and gait) very rare complication

Summary

- HC is an "exam room diagnosis"

    - PU/PD/PP/Pot-bellied/Partial alopecia
- Baseline labs will r/o other diseases (DM, hyperT4) and confirm your suspicion
- Endocrine tests to confirm the Dx and to differentiate
- Understanding HPA physiology helps you understand HC
- Mainly medical Tx for PDH; medical Tx or Sx for ADH
- All dogs with HC have a tumor (only ~10% are malignant)