Hyperadrenocorticism: Diagnosis and Management

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Overview

Hyperadrenocorticism is caused by excessive cortisol secretion by the adrenal glands either due to excessive ACTH production from a pituitary tumor or a functional adrenal tumor.

HAC is most commonly due to a pituitary tumor (85-90%). A microadenoma (tumor < 1cm) is present 90% of the time. Macroadenomas are present at the time of diagnosis in about 10% of dogs, however 10-25% of dogs with microadenomas will go on to develop a macroadenoma.

HAC secondary to an adrenal tumor occurs 10-15% of the time. The adrenal tumor can be either benign (functional adenoma) or malignant (functional carcinoma).

Signalment

- Middle aged to older dogs, vast majority > 6y/o with 75% > 9 y/o
- Rarely diagnosed in dogs young than 5 y/o
  - Growth retardation was noted along with the classic signs
- No sex predilection
- Larger breed dogs may be more likely to develop adrenal tumor than small breeds, but can happen to any breed.

Clinical Manifestations

- Most common: Polyuria, polydipsia, polyphagia, panting, abdominal distension, endocrine alopecia, hepatomegaly, and systemic hypertension
- Less common: lethargy, hyperpigmentation, comedones, thin skin, poor hair regrowth, insulin-resistant DM, thromboembolism, ligament rupture, and reproductive difficulty
• Pituitary macroadenoma syndrome: inappetence, anorexia, stupor, circling, pacing, ataxia, and behavior changes

Common Laboratory and Imaging Abnormalities

• CBC: stress leukogram, thrombocytosis

• Urinalysis: USG usually < 1.020, but they can concentrate higher than that at times. Proteinuria is common (~ 75%, especially if also hypertensive)

• Chemistry: Elevated ALP, elevated ALT (usually mild to moderate), elevated cholesterol, elevated triglycerides, hyperglycemia (mild – not enough to cause glucosuria)

• Abdominal Ultrasound: Hyperechoic, hepatomegaly and possible adrenal changes – bilaterally adrenomegaly or adrenal tumor

When to Test

Any combination of clinical signs and/or biochemical abnormalities that are consistent with Cushing’s disease could be a reason to test. An absence of common manifestations should strongly decrease the suspicion of HAC. Conversely, failure to identify common laboratory (such as a normal ALP) or imaging abnormalities does not rule out HAC. The presence of ultrasonographically normal-sized adrenal glands does not rule out HAC.

Testing is recommended after incidental identification of an adrenal mass on ultrasound. It is also recommended in poorly regulated diabetic dogs on high dosages of insulin when another cause for insulin resistance cannot be identified.

Testing

Testing should ideally be avoided if there is severe illness going on as this can create false positives. No screening test for Cushing’s disease is 100% sensitive or specific. Keep in mind that the following steroids cross-react with the cortisol assay: prednisolone, prednisone, methylprednisolone, fludrocortisone, cortisone, and hydrocortisone. It is recommended to wait 24 hours after these steroids to perform a screening test.

Additionally, keep in mind that all steroids have the potential to affect the hypothalamic-pituitary-adrenal axis (as does ketoconazole) so any steroid that has been used chronically can affect Cushing’s screening. The duration of suppression is depended on duration of use, dose, administration route, and whether the steroid is long or short acting.

The LDDST is more sensitive than the ACTH Stim but less specific and for this reason is considered the “screening test of choice” by many veterinary endocrinologists. It is
difficult to do without advanced planning since it takes the whole day but has the potential for determining if PDH or not; typically I offer owners the ACTH stimulation test first out of convenience since it can usually be done on the same day as an appointment. An inverse pattern (the 8hr cortisol concentration is within the reference range, but the 4hour cortisol is above the cutoff) on the LDDST is suspicious for Cushing’s disease and should prompt further testing.

It is possible to do endogenous ACTH and/or abdominal ultrasound as differentiating test. Any screening test may be negative in a patient with HAC. If a test is negative but suspicion for HAC remains, an alternate test should be performed. If more than 1 test is negative, the possibility that the patient does not have HAC should be considered. Alternatively, the patient may have mild HAC and the tests have not yet become positive. It may be worthwhile to retest in 3–6 months if clinical signs progress.

**ACTH Stimulation Test**

Performing an ACTH stimulation test:

- Draw pre cortisol sample
  - simultaneously, pull and hold endogenous ACTH sample if needed
- Then, give synthetic ACTH (synacthen, cortrosyn)
  - Synthetic ACTH dose: 5mcg/kg IV (max dose of 250mcg)
- Draw a post ACTH cortisol sample 1 hour later (up to 90 minutes is acceptable)

**Low Dose Dexamethasone Suppression Test (LDDS test)**

Performing a LDDS test:

- Draw pre sample (this measures cortisol at time zero)
- Then, give dexamethasone
  - Dexamethasone sodium phosphate (dex SP) dose – 0.01mg/kg IV
  - Dose based on concentration of active ingredient
- Draw post samples at 4 hours and at 8 hours post administration of dexamethasone

It is recommended that animal *not* be fed during a LDDST in order to limit excitement (does not matter for ACTH Stim).

**Interpretation of LDDS Test**

To determine if the patient has Cushing or not, ONLY need to look at 8 hour post.
Positive test:

- 8 hr post cortisol is > lab cut off
  - Suspicious for but not diagnostic of PDH
  - 4 hr > lab cut (inverse pattern)

**Differentiation Test**

A differentiation test can only say if it has PDH, never can say if it is an AT.

- 4 hour post cortisol value is < lab cut off
- 4 hour post cortisol value is < 50% baseline cortisol
- 8 hour post cortisol value is < 50% baseline cortisol

**Food-Induced HAC**

In humans with this condition, it is a congenital defect resulting in abnormal expression of glucagon inhibitory peptide (GIP) receptors on the adrenal glands. GIP is secreted by the stomach during every meal and normally binds to receptors on the pancreas to stimulate insulin production. In a patient with food-induced HAC, GIP released with each meal binds also to the GIP receptors on the adrenal gland and subsequently causes the release of cortisol. This is thought to also be the cause in dogs as well.

Most dogs with this disorder had an early onset of clinical signs, usually between 2-5 years of age. They have the same symptoms and laboratory abnormalities as classic HAC dogs.

If the basic diagnostic work-up for HAC has been performed but negative and you suspect food-induced HAC a diagnosis can be obtained using this testing: Have owners fast the dog for 12 hours and then obtain a first morning sample. Then have the owner feed the dog and then 4 hours later obtain another urine sample. Submit each labeled as pre- and post-meal urine samples for UCCR. There is not a known range at this time, but at least a 2-fold increase should be seen however a 100-fold increase is diagnostic.

**Treatment**

Lysodren/Mitotane: 25mg/kg PO q12 Loading dose for 5-10 days until owner notices the drug is working (whichever happens first). Perform ACTH stim and once adequate control is reached (for Lysodren, I prefer the Pre- and Post- stim to be between 2-3ug/dL), give 25-50mg/kg divided into 3 doses for the week. Until the ACTH Stim shows adequate control, continue with loading dose daily. Most dogs can tolerate Lysodren very well and over the long term it ends up being cheaper than Trilostane. Because the risk of Addisonian crisis is higher with Lysodren vs. Trilostane I try to reserve this for owners that are more compliant.
Trilostane seems to be more user-friendly and easier for owners to understand follow up monitoring so this has become my first line therapy. It only comes name brand as Vetoryl in 5mg, 10mg, 30mg, 60mg, 120mg. I generally prefer that may patients not receive a compounded formulation as it has been found that the concentration of the active ingredient in compounded formulations can vary widely. However, if not financially feasible, compounded trilostane is a reasonable option.

There are many studies that exist exploring different dosing options (once a day dosing, ultra low-dose, low dose). More evidence is being published that dogs tend to be better controlled on twice-daily therapy. I generally choose a starting dose of 1-2mg/kg PO BID and find that most dogs tolerate this well. If dogs cannot tolerate this initial starting dose (usually they develop inappetence, vomiting and/or diarrhea), I would recommend decreasing either the dose or frequency and slowly increasing in smaller increments.

Functional adrenal tumors are best treated with adrenalectomy. Surgery is technically challenging, especially on the right side due to the proximity with large blood vessels. Experienced surgeons should only perform this in a 24 hours facility ideally with a well-equipped ICU. There is a reportedly poorer prognosis if the mass is greater than 5 cm, if there is vascular invasion, if there is evidence of venous thrombosis, if metastatic disease is present, or if the mass is an adenocarcinoma. Therefore adrenalectomy may not be the best for these patients. While vascular invasion does increase the risk, it does not prevent performing an adrenalectomy. For patients that survive 2 weeks, the prognosis is excellent for fully excised functional adenomas. If surgery is not a good option for the patient or not financially feasible, medical management with either mitotane or trilostane can be used. Studies have shown that median survival time is not significantly different for trilostane and mitotane therapy.

Overall median survival for dogs with adrenal tumor (AT) treated with either trilostane or mitotane is 277 days. Presently, only hypophysectomy and radiation therapy address the site of the disease in pituitary-dependent HAC.

**Monitoring**

The current recommendation is to perform an ACTH stim 2 weeks after starting therapy. I personally, however, do not increase the dose based on the results at the 2-week mark since they are always higher than at the 4-week time point. If the owner feels the pet is doing well and tolerating Trilostane well, I often will wait until the 4-week mark for recheck. Ideally, the pre- and post- trilostane cortisol levels are <5ug/dL but I will accept up to 7 if the owners feel the pet has no signs of Cushing’s disease. I will increase the dose by ~50% with no maximum dose. Similarly, if the pre-and post-trilostane cortisol levels are >0.5ug/dL and the owners are very happy and the pet is not showing any signs of hypoadrenocorticism then I will not decrease the dose. I have managed many dogs that tolerated this seemingly Addisonian level of cortisol for years. Should the pet
show any sign that could be interpreted as related to hypoadrenocorticism, however, I do decrease the dose by 25-50%. An additional ACTH stimulation test can be done at trough (9-12 hours post dose) to prove that the cortisol levels to increase over the course of the day.

A recent study showed that for monitoring ACTH stims (NOT diagnostic stims) a dose of 1 ug/kg cosyntropin IV can be used rather than 5mcg/kg. If using the low dose, it is important that the cosyntropin only be used IV rather than IM as that was the only route studied. In addition, a post sample should strictly be obtained at 60 minutes post ACTH administration. This lower dose was not recommended for diagnostic ACTH stims as in 4 dog evaluated the result of the low-dose test was within the reference range while those of the high-dose test were consistent with a diagnosis of HAC, which is a significant different.

There have been 2 studies evaluating only baseline cortisol concentrations as a means to monitor patients receiving trilostane for HAC with conflicting results. Therefore at this time, an ACTH stim is still the only test reliably used for monitoring.

Most studies use an ACTH stimulation test that is done 4-6 hours after the dose of trilostane. Many recent studies and anecdotal experience have shown that there is large variability in cortisol results depending on when the stim is done (starting a stim at 3 hours could potentially yield cortisol levels that are significantly different than a stim started at 6 hours). Some studies show that it is best to strive for the same time post administration (ie if the first ACTH stmi was 4 hour post trilostane administration, continue to do 4 hour post stims). For this reason, I put more weight on the clinical signs of the patient rather than the results of the stim. Both are necessary, however, to monitor for hypoadrenocorticism as well as difficulty in assessing clinical signs in some patients. Once regulated, I recommend rechecking every 3-4 months with an ACTH stimulation test.

Non-invasive blood pressure and urine protein to creatinine ratio should also be rechecked throughout the course of disease, as hypertension and proteinuria may not resolve with treatment. A 2012 study documented that ~40% of dogs being treated for HAC had ongoing proteinuria. These animals may require amlodipine or an ACE inhibitor. Dogs with Cushing’s disease can have markedly high levels of proteinuria (UPCR up to 16 in some studies). Hypoalbuminemia is not observed in dogs with HAC and proteinuria.

**Owner Expectations with Treatment**

If therapy is successful, most of the clinical signs and complications resolve with time. PU, PD, PP should resolve when or shortly after cortisol secretion is adequately controlled. Cutaneous manifestations, non-healing wounds, muscle weakness, etc, can take up to 3-6 months to resolve. Calcinosis cutis may never fully clear. Liver enzymes
elevations may not normalize or improve much. There is no evidence right now that the risk of thromboembolisms decreases with therapy.