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VCA Clinical Consults

What's Your Diagnosis?

PATIENT HISTORY

SIGNALMENT: "Mia Sophia" is a 10 year old FS Shih Tzu. Weight 18.3 pounds/8.3 kg.

PERTINENT PAST HISTORY: "Mia Sophia" has been a relatively healthy dog. She visits her veterinarian annually and is current on recommended vaccinations and monthly heartworm and flea prevention. She eats a complete and balanced commercial dog food. She has a history of corneal ulceration and suspected atopy which is managed by a veterinary-prescribed omega 3 fatty acid supplement and Temaril-P during her pruritic season.

CURRENT HISTORY: At her annual wellness visit the owner expressed mild concern about a chronic skin condition characterized by thinning hair and a thick dark crusting layer of skin that easily peels off. The owner felt the skin condition had worsened over the previous 6 months and it was not pruritic like her previous flare-ups of atopy and pyoderma have been. Her owner also requested a few small skin masses be evaluated. When questioned further about systemic signs, "Mia Sophia's" owner reported that she did seem to be thirsty all the time and was urinating more than normal. ***Clinical Note: Owners often don't voluntarily report clinical signs as it pertains to signs of eating, drinking or urinating excessively. Since their pets don't seem to be sick and in fact, are eating and drinking exceptionally well, these signs often go unreported. A complete history must include questioning about these signs.***

FROM ANNUAL WELLNESS VISIT TO ADRENALECTOMY!

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CURRENT HISTORY

On examination, "Mia Sophia" was noted to have a moderately pendulous abdomen and marked hepatomegaly. She had gained 1.5 pounds from the previous year. She had a diffusely thinning hair coat and hyperpigmented lichenified skin on her back. There were numerous raised, irregular papillomatous wart-like growths on her dorsum. Thoracic auscultation was unremarkable as was the remainder of her exam. Her veterinarian suspected a possible endocrinopathy such as hyperadrenocorticism or hypothyroidism and recommended screening bloodwork as a starting point **(see Table 1).** A blood pressure was also performed and was within normal limits.

TABLE 1.
"MIA SOPHIA'S" ANNUAL WELLNESS BLOODWORK

WBC (ref. range: 5,500-17,000/uL)	**18,040**
Neutrophils (ref. range: 3,600-11,500/uL)	**15,334**
Platelets (ref. range: 170-500,000/uL)	**742,000**
Alk Phos (ref. range: 5-150 U/L)	**462**
ALT (ref. range: 15-115 U/L)	51 (normal)
Cholesterol (ref. range 150-325 mg/dL)	**425**
Total T4 (ref. range: 1.0-4.0 ug/dL)	1.7 (normal)
Urine specific gravity	1.008
Urine protein and sediment	Negative

"Mia Sophia" had several biochemical and hematologic findings which could be consistent with hyperadrenocorticism (HAC) and her thyroid hormone concentration was normal. ***Clinical Note: It must be confirmed that owners are not (or have not recently been) administering any form of glucocorticoid in oral, topical or ophthalmic preparations.*** **See Table 2** for the most common laboratory abnormalities associated with HAC. Most importantly, "Mia Sophia" had a suggestive clinical history, clinical signs and a physical examination which were all consistent with HAC so her veterinarian recommended a screening test for HAC. ***Clinical Note: Asymptomatic elevation of ALKP is common in older dogs and many of these dogs are unnecessarily tested for HAC. In concordance with ACVIM Consensus recommendations for HAC testing from 2012, it is important to test only dogs that have the CLINICAL SYNDROME of Cushing's in order to prevent erroneous test results.***

There are several screening tests for HAC including the Urine Cortisol:Creatinine Ratio (UCCR), the Low Dose Dexamethasone Suppression Test (LDDST) and the ACTH stimulation test.

The UCCR has very high sensitivity (approximately 100%) but very low specificity (approximately 20%) which means this test has excellent negative predictive value. ***Clinical Note: If the UCCR is negative the dog is extremely unlikely to have HAC, however, if the UCCR is positive another screening test MUST be done. The UCCR has limited clinical utility in patients showing clinical signs of HAC—these patients should have either a LDDST or ACTH stimulation test performed as the first line screening test.*** **Table 3** lists the two most commonly used tests for HAC and highlights the advantages and disadvantages of each.

"Mia Sophia" had a LDDST performed. **See Table 4** for the LDDST protocol and interpretation. Her cortisol results were consistent with HAC as follows:

TABLE 2.
COMMON CLINICAL SIGNS, BIOCHEMICAL, AND HEMATOLOGIC ABNORMALITIES IN HAC

CLINICAL SIGNS	BIOCHEMICAL ABNORMALITIES	HEMATOLOGIC ABNORMALITIES
Polyuria, polydipsia – Approximately 80-90% of patients with HAC exhibit pu/pd	Elevated ALKP – ***Clinical Note: Elevated ALKP is found in 85-95% of dogs with HAC. The degree of elevation does not correlate with the severity of HAC.***	Stress leukogram – most commonly characterized by neutrophilia without a left shift and lymphopenia
Polyphagia	Elevated ALT — ***Clinical Note: ALT is usually elevated to a significantly lesser degree than ALKP.***	Erythrocytosis
Panting	Hypercholesterolemia (+/- hypertriglyceridemia)	Thrombocytosis
Abdominal distention	Hyperglycemia – usually mild but 5-10% will have overt Diabetes Mellitus	
Muscle weakness / lethargy	Hypophosphatemia	
Dermatologic abnormalities – truncal, bilaterally symmetrical alopecia, thin skin, comedones, hyperpigmentation, failure to regrow hair, calcinosis cutis, etc.	Decreased BUN	

- Pre-dexamethasone cortisol concentration: 3.1 ug/dL (ref. range: 1.0-6.0 ug/dL)
- 4 hour post-dexamethasone cortisol concentration: 4.2 ug/dL
- 8 hour post-dexamethasone cortisol concentration: 3.7 ug/dL

These results confirmed a diagnosis of hyperadrenocorticism for "Mia Sophia" but did not differentiate between pituitary (PDH) or adrenal-dependent (ADH) disease. ***Clinical Note: The LDDST is the preferred screening test due to its high sensitivity and up to 65% of dogs with naturally occurring HAC can be differentiated as PDH vs ADH by the LDDST. Approximately 35-40% of patients with PDH and almost 100% of dogs with ADH will fail to be differentiated by the LDDST. Dogs who don't differentiate on a LDDST could have PDH or ADH and further differentiating testing is necessary.***

The tests available to differentiate between PDH and ADH are as follows:

- **High Dose Dexamethasone Suppression Test (HDDST)—**This test is performed in the same fashion as the LDDST but a higher dosage (0.1 mg/kg IV) of dexamethasone is used. If cortisol suppression occurs at 4 or 8 hours then the diagnosis of PDH is made. If cortisol suppression does not occur, the chance of PDH vs ADH is still 50:50 and further testing is required. ***Clinical Note: A lack of suppression is considered inconclusive; therefore many practitioners bypass the HDDST in lieu of a more definitive test such as ultrasound.***
- **Endogenous ACTH level—**Patients with PDH have normal to elevated levels of endogenous ACTH and patients with ADH have low to undetectable levels of ACTH. Although this test offers valuable information, it is expensive and requires special blood tubes and handling so is often not performed in general practice.

TABLE 3.

LDDST VS ACTH STIMULATION TEST AS SCREENING DIAGNOSTIC TESTS FOR HAC

LDDST: Advantages	ACTH: Advantages
• More reliable in confirming dogs with HAC as it is much more sensitive compared to ACTH stim (90-95% in dogs with PDH and close to 100% in dogs with adrenal-dependent HAC). • Fewer false negatives compared to ACTH stim. LDDST fails to confirm HAC in only about 5-10% of dogs with the disease. ***In other words, 5-10% of dogs with PDH will exhibit "normal" cortisol suppression with this test.*** • Less expensive than ACTH stim. • Can function as both screening and differentiating test in many cases of PDH (65%).	• Takes only 1 hour to perform. • Fewer false positives than with LDDST (specificity is 85%). • Can also detect hypoadrenocorticism. • Only test to detect iatrogenic hyperadrenocorticism. • Only test available to monitor mitotane or trilostane therapy. • Provides baseline on which to begin medical therapy.
LDDST: Disadvantages	**ACTH: Disadvantages**
• Specificity is low (40-50%). There can be many false positives—especially in dogs with non-adrenal illness. • Test can be dramatically affected (and give false positive) by stress—e.g. high anxiety patient in hospital environment, anesthesia, other diagnostic procedures (radiographs, ultrasound, etc.). • Takes 8 hours to complete. • No other diagnostics can be performed during the test day. • Cannot detect iatrogenic hyperadrenocorticism. • Does not provide pre-treatment information which can be used to monitor the effects of medical therapy.	• More expensive compared to LDDST. • More false negatives compared to LDDST for PDH (sensitivity is 80%). • More likely to miss an adrenal tumor (sensitivity is only 60%). • Only a screening test—it can never serve as a differentiating test like the LDDST.
General Recommendations: • **In dogs with clinical signs of HAC and no other illness—perform the LDDST.** ***The LDDST is considered the test of choice unless iatrogenic HAC is suspected.*** • **If clinical signs are mild or only laboratory abnormalities are present—perform the ACTH stimulation test.** • **In dogs with non-adrenal illness, exogenous steroids (including topicals) or for dogs receiving phenobarbital—perform the ACTH stimulation test** • ***Clinical Note: If the clinical syndrome of HAC is present and you obtain negative test results on your first screening test—perform the other screening test next!***	

- **Ultrasonography or advanced imaging (CT/MRI)—**Imaging the adrenal glands directly can identify bilaterally enlarged adrenals which are more consistent with PDH versus findings consistent with an adrenal mass. ***Clinical Note: A number of ultrasonographic findings are possible in patients with PDH and ADH and the reader is referred to the first listed reference for additional information if desired.***

An abdominal ultrasound was recommended for "Mia Sophia" as it has the benefit of differentiating for HAC as well as identifying concurrent abnormalities. The ultrasound revealed an enlarged hyperechoic liver and bilateral renal pelvic dilation considered to be consistent with HAC. The left adrenal was very small (0.1 cm in height). A large (4 cm) rounded heterogeneous mass was identified in the cranial pole of the right adrenal gland **(see Figure 1).** The caudal pole of the right

FIGURE 1

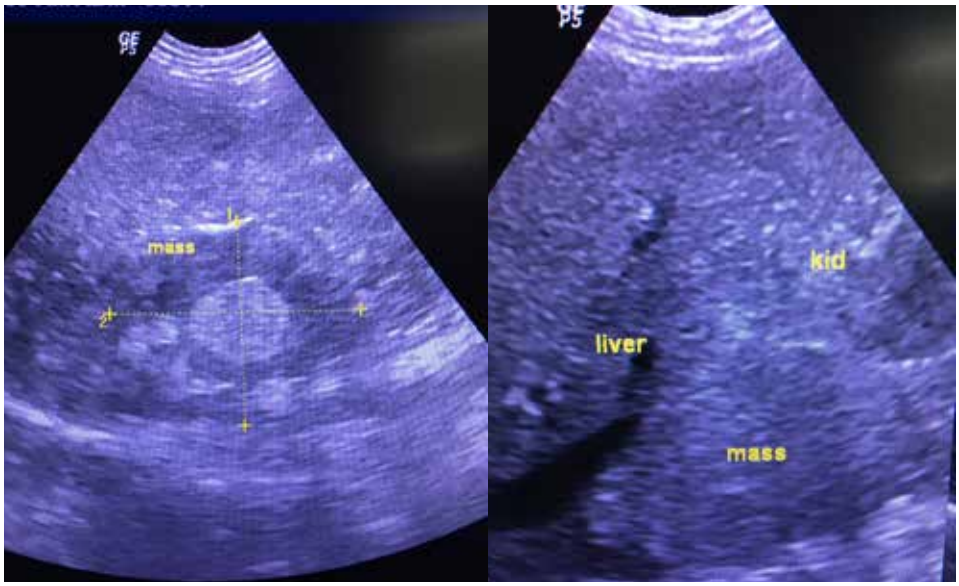

TABLE 4.
LOW DOSE DEXAMETHASONE SUPPRESSION TEST (LDDST) PROTOCOL AND INTERPRETATION

PROTOCOL:

- **STEP 1:** Draw serum for pre-dexamethasone cortisol measurement
- **STEP 2:** Administer 0.01 mg/kg dexamethasone IV
  - ***Clinical Note: Dexamethasone (2 mg/mL) or Dexamethasone Sodium Phosphate (4 mg/mL) can be used for the test but note DexSP is equivalent to only 3 mg/mL dexamethasone and should be calculated accordingly.***
  - ***Clinical Note: The volume of dexamethasone or dexamethasone SP for toy and small breed dogs is often VERY small. It is often easiest to measure the amount in a small U-100 insulin syringe and then dilute the volume in 0.9% NaCl for more accurate dosing. After injection of the small volume, reaspirate blood back into the syringe and re-inject to confirm the total dosage in the syringe is administered.***
- **STEP 3:** Draw serum for 4 hour post-dexamethasone cortisol measurement
- **STEP 4:** Draw serum for 8 hour post-dexamethasone cortisol measurement

It is critical to MINIMIZE any stress during this test. No other procedures (e.g., radiographs, ultrasound, cystocentesis, toenail trim, etc.) should be performed while a patient is undergoing a LDDST!

INTERPRETATION OF RESULTS:

- **STEP 1:** First, evaluate the 8 hour post-dexamethasone cortisol measurement. A normal result (one NOT consistent with HAC) is <1.0 ug/dL. HAC is confirmed if the 8 hour result is equal to or greater than 1.4 ug/dL. ***Clinical Note: Non-adrenal illness and drug therapy may be associated with elevated post results. A result between 1.0 and 1.4 ug/dL is inconclusive and if there is strong clinical suspicion for HAC, an ACTH stimulation test should be performed.***
- **STEP 2:** Second, evaluate the 4 hour post-dexamethasone cortisol measurement. If the result is <1.4 ug/dL OR is <50% of baseline, then pituitary dependent disease is confirmed. ***Clinical Note: It is in this manner—a suppressed 4 hour result—that the LDDST can function as a screening AND a differentiating test.***

adrenal gland was also small. The adrenal mass displaced and compressed the adjacent caudal vena cava although no specific invasion into the vena cava was noted. Although the mass appeared circumscribed, it was very closely associated with the large vessels, the right side of the liver and the right kidney. Given the small contralateral left adrenal gland, these findings were most consistent with a functional adrenal tumor causing HAC. ***Clinical Note: The right and left adrenal findings on "Mia Sophia's" ultrasound are considered "classic" for a unilateral functional adrenal tumor.***

DIAGNOSIS

Adrenal-dependent Hyperadrenocorticism (ADH)

Right adrenal gland mass

DISCUSSION

A detailed discussion of naturally occurring hyperadrenocorticism and adrenal neoplasia are beyond the scope of this article and the reader is referred to the listed references.

Adrenal-Dependent Hyperadrenocorticism (ADH)

Approximately 80-85% of dogs with HAC have pituitary-dependent disease with the remaining 15-20% of dogs having ADH with functional adrenal tumors—either adenomas or adenocarcinomas. Most affected dogs have a unilateral tumor although bilateral masses have been reported. Most dogs with ADH are >9 years old and females are more commonly affected. Approximately 50% of affected dogs weigh >20 kg in contrast to the small breed dogs who more commonly have pituitary-dependent HAC.

Functional adrenal tumors secrete cortisol which suppresses corticotrophin-releasing hormone from the hypothalamus and ACTH secretion from the pituitary gland. This negative feedback causes varying degrees of atrophy of the unaffected adrenal gland. While the unaffected adrenal gland should be atrophied as it was in "Mia Sophia," some patients do have contralateral glands that are normal in size. ***Clinical Note: Finding a normal-sized adrenal gland does not rule out the possibility of a functional adrenal tumor in the contralateral gland. Keep in mind that some dogs can be affected by both PDH and ADH simultaneously. Functional (i.e., cortisol-secreting) adrenal tumors also cannot be differentiated ultrasonographically from other adrenal tumors such as pheochromocytoma or non-functional tumors. If ultrasound results are not typical, further testing may be required to fully define the nature of the adrenal gland mass.***

Clinical Signs and Diagnosis

The clinical syndrome of Cushing's disease is the same for both ADH and PDH. Refer to **Table 2** for the most common clinical signs as well as biochemical and hematologic abnormalities expected in dogs affected by HAC. Additionally, dogs with ADH may have local signs associated with invasion of the caudal vena cava (e.g., thrombosis, pitting edema, weakness, etc.) or evidence of distant metastatic disease, however, in general the clinical signs are the same for both types of HAC. The available screening and differentiating tests for HAC have previously been described in this report.

Surgical Treatment

The treatment of choice for ADH is adrenalectomy. Many of these masses are malignant and removal of the mass prevents risk of local tumor growth with invasion into surrounding structures as well as minimizes metastasis. The removal of the functional adrenal mass also results in complete resolution of the clinical syndrome of HAC. The survival time for dogs treated with adrenalectomy ranges from 23-31.8 months which is twice as long as what is expected with medical management of ADH (approximately 14-16 months).

A number of factors must be considered prior to adrenalectomy including the presence of metastatic disease and the local invasiveness of the adrenal tumor. Thoracic radiographs (three view) must be completed as a metastasis evaluation prior to surgery. The metastatic rate for adrenocortical adenocarcinomas is between 14 and 50%. Advanced imaging using abdominal CT or MRI is highly recommended to assess for mass invasion into the surrounding abdominal tissues to determine the feasibility of surgical resection.

Adrenalectomy procedures should be performed by a highly skilled surgeon in a facility with excellent monitoring capabilities and an intensive care unit. Adrenalectomy procedures have a reported intraoperative complication rate of 15% and a postoperative complication rate of up to 50%. Common postoperative complications include the development of DIC, thromboembolic disease, pneumonia, sepsis, pancreatitis, renal failure and hypoadrenocorticism. Perioperative mortality rate is quite high and has been reported to be between 5 and 29% with some reports up to 60%.

Medical Management

When surgery is not feasible—as in the case of a non-resectable tumor or significant concurrent disease or an owner declines surgery—medical management with either an adrenocorticolytic drug (i.e., mitotane) or a competitive adrenal enzyme inhibitor (i.e.,trilostane) should be recommended.

Historically mitotane (Lyosodren®) has been considered the drug of choice because it is adrenocorticolytic. While it is known that mitotane significantly decreases the adrenal gland size of dogs with PDH, this has not been documented in dogs affected by adrenal tumors. Mitotane would clearly be the best medical option if it prevented additional tumor growth, decreased adrenal gland tumor size, or even induced complete necrosis of the tumor. Mitotane would be expected to give higher survival times; however, dogs with adrenal tumors treated with mitotane DO NOT have longer expected survival times (15.6 months) when compared to affected dogs treated with trilostane (14 months). In addition, mitotane treated dogs have been reported to experience more adverse effects.

TABLE 5.
"MIA SOPHIA'S" ABDOMINAL CT SCAN

Abdomen CT Findings: Pre and post contrast images show a large, heterogeneously contrast enhancing mass, measuring approximately 4.5 cm x 4.3 cm x 2.7 cm in the area of the cranial pole of the right adrenal gland and caudal and dorsal aspect of the right liver. The caudal pole of the right adrenal gland and the entire left adrenal gland are subjectively small. The mass compresses and displaces the caudal vena cava ventrally but does not invade into it. The remainder of the liver is normal. There is no lymphadenomegaly. No other abnormalities are seen.

Impressions:
The origin of the mass is difficult to determine definitively but is likely to be the right adrenal gland with invasion into the liver. Given its CT features, the mass likely represents malignant neoplasia. Histopathology is required for definitive diagnosis.

Approximately 60% of dogs treated with mitotane experience adverse side effects compared to only 23% of trilostane treated dogs. ***Clinical Note: Trilostane is not without its possible side effects. The most commonly reported adverse effects include anorexia, vomiting, diarrhea, lethargy and shaking. Acute adrenal necrosis—although uncommon—has been reported in dogs treated with trilostane and can be life-threatening.***

In general, trilostane is less toxic than mitotane and should be considered as a first option when medical treatment for dogs with adrenal tumors is selected. ***Clinical Note: The adrenal glands of dogs affected by PDH and treated with trilostane have a tendency to enlarge over time. It is unknown if the adrenal glands in dogs with ADH treated with trilostane experience this same growth. IF these glands continue to grow, as do the glands of dogs with PDH, it might contribute to the local complications such as compression of the vena cava. It may be reasonable in a patient with a very large adrenal tumor or with compression of the vena cava at the time of diagnosis to consider mitotane in preference to trilostane.***

ADDITIONAL DIAGNOSTICS AND TREATMENT

"Mia Sophia" was referred for further evaluation by a board certified surgeon for adrenalectomy. In order to fully evaluate for metastatic disease as well as the extent of local disease within the abdomen, "Mia Sophia" underwent additional imaging prior to surgery.

Three-view thoracic radiographs were performed and were unremarkable. Given the nature of the adrenal mass on ultrasonography and its proximity to and compression of the large vessels, liver and kidney, a CT scan was recommended for full staging and surgical planning **(see Table 5).** The owner was informed of the results and the

TABLE 6.
ADRENAL MASS HISTOPATHOLOGY

Microscopic Description: The specimen comprises nests and cords of adrenocortical secretory cells confined by a capsule. The cells are polygonal with distinct cellular borders and an abundant amount of deeply eosinophilic (outer layers) or lightly eosinophilic (inner layer), slightly vacuolated cytoplasm. Nuclei are round, central to eccentric and hyperchromatic with stippled chromatin and prominent nucleoli. There is mild anisocytosis, mild anisokaryosis and no mitotic figures.

Microscopic Diagnosis: Adrenocortical adenoma (presumptive), functional

Comments: The sample was very small and there was extensive crush artifact. Features of malignancy were not identified but this section may not be representative of the entire neoplasm and an adenocarcinoma remains a possibility.

likely invasive nature of the mass. The owner elected to proceed with an abdominal exploratory to determine resectability and remove if feasible without excessive risk. "Mia Sophia" went to surgery under the same anesthesia. The right adrenal mass was identified and was noted to extend into the caudate process of the caudate liver lobe and disappear into the hilus. The adrenal mass and liver lobe were determined to not be safely surgically resectable and a biopsy was obtained from the adrenal mass. Even the biopsy was difficult to obtain and only a very small sample could be obtained with electrocautery and was submitted for histopathology.

"Mia Sophia" recovered uneventfully from anesthesia. She was maintained on IV fluids and analgesics until she started eating and drinking well and was discharged from the hospital 2 days post-operatively. Histopathology reported the adrenal mass as a presumptive functional adrenocortical adenoma **(see Table 6).** However, given the invasive characteristics of the mass on CT and at surgery, malignancy was considered to be more likely and the owner was counselled accordingly.

LONG TERM TREATMENT

Two weeks post-operatively, "Mia Sophia" had an ACTH stimulation test performed in preparation for beginning medical management with trilostane. The pre-ACTH cortisol concentration was 7.2 ug/dL (ref. range: 2-6 ug/dL) and the post- ACTH cortisol concentration was significantly elevated at 27.9 (ref. range: 6-18 ug/dL). Trilostane (Vetoryl®) was started at 10 mg PO BID (2.4 mg/kg daily dose divided BID). ***Clinical Note: Dogs should be started on standard dosages of trilostane when beginning medical therapy. Dogs with ADH do not necessarily require higher dosages of trilostane to control their hypercortisolemia.***

A recheck ACTH stimulation test performed 14 days later revealed no evidence of trilostane over dosage with a pre-ACTH cortisol concentration of 4.7 ug/dL and a post-ACTH cortisol concentration of 17.9 ug/dL. ***Clinical Note: Although "Mia Sophia's" first post-ACTH cortisol measurement was higher than what is considered an ideal range (at 17.9 ug/dL), trilostane dosage adjustments are typically not recommended until the 30 day recheck in order to avoid issues with drug over dosage. In fact, "Mia Sophia" had quite a robust cortisol response during the first 14 days with her post-ACTH cortisol concentration dropping from 27.9 to 17.9 ug/dL.*** The dosage of trilostane was maintained and another ACTH stimulation test was performed one month later. This test revealed markedly improved control (pre-ACTH cortisol concentration 2.4 ug/dL and post-ACTH cortisol concentration 10.8 ug/dL). The owner reported improved clinical signs with markedly less pu/pd and polyphagia. "Mia Sophia" was monitored every 3 to 6 months with ACTH stimulation tests. **See Table 7** for additional information about minimizing the cost of repeated ACTH stimulation tests. Her post-ACTH cortisol concentrations varied

TABLE 7.
ACTH STIMULATION TESTING—NEWER DOSING PROTOCOL

The preferred form of ACTH for both diagnosis of and monitoring treatment success of HAC is cosyntropin. Cosyntropin is expensive and the repeat testing required for dosage adjustment and appropriate therapeutic monitoring can be cost-prohibitive for many owners. ***Clinical Note: Compounded ACTH is available but is not recommended!***

Use of a lower cosyntropin dosage can greatly reduce the cost of an ACTH stimulation test and allow more owners to diagnose and properly monitor HAC treatment. A study published in 2016 supports the use of lower ACTH dosages for the monitoring of treatment to help make Cushing's disease more affordable.

DIAGNOSIS:

- 5 ug/kg cosyntropin IV (or IM) is the lowest recommended dosage for ACTH stimulation testing for diagnosis of HAC.
- ***Clinical Note: The 5 ug/kg IV dosage has previously been proven to be pharmacodynamically equivalent to the 250 ug/dog IV dosage which has historically been recommended.***
- ***Clinical Note: In the current study, the 1 ug/kg dosage was NOT pharmacodynamically equivalent to the 5 ug/kg dosage for the DIAGNOSIS of HAC. When the 1 ug/kg dosage was used, the clinical interpretation of the ACTH stimulation test for diagnosis of HAC would have been different in 23% of dogs.***

MONITORING:

- Intended for dogs who have previously been diagnosed with Cushing's and are receiving mitotane or trilostane.
- 1 ug/kg cosyntropin IV can be used. ***Clinical Note: This dosage MUST be given IV. IM is not an option!***
- ***Clinical Note: The 1 ug/kg and 5 ug/kg dosage were pharmacodynamically equivalent for the accurate monitoring of HAC.***
- ***Clinical Note: It is imperative that the post sample be drawn at exactly 60 minutes as with this lower dosage of cosyntropin the peak ACTH-stimulated cortisol concentration is much shorter!***

DILUTION OF COSYNTROPIN

- When using the lower dosages for ACTH stimulation testing, small dogs will require significant dilution of consyntropin in order to achieve accurate dosing.
- Example of dilution protocol: Cosyntropin is supplied as 250 ug of lyophilized powder in 2 mL vials. Reconstitute according to manufacturer recommendations with 1 mL sterile saline. Add the original 1 mL of reconstituted cosyntropin to 24 mL of sterile saline to achieve a final volume of 25 mL. This is equivalent to 10 ug/mL and is appropriate for dosing small dogs.
- ***Clinical Note: When cosyntropin is diluted at 250 ug/mL (manufacturer's recommendation), the product is stable frozen for up to 6 months. With the dilution protocol outlined above, cosyntropin (in concentrations as low as 0.5 ug/mL) will remain fully stable when frozen for 4 months.***

between 4 and 10 ug/dL and the owner continued to report good clinical control of her HAC. Her dermatologic lesions improved and her haircoat began filling in as well. Recheck thoracic radiographs and abdominal ultrasound were performed one year after diagnosis with no evidence of metastatic disease and only mild growth of the right adrenal mass. This lent additional support to the mass being a functional adenoma as opposed to an adenocarcinoma. ***Clinical Note: It is interesting to note that despite the usage of trilostane, the left adrenal gland remained small.***

"Mia Sophia" presented 6 months later with complaints of hind limb weakness and unusual pain-like episodes which presented as flank biting on the right side and vocalization. On examination, "Mia Sophia" had mild pitting edema of her pelvic limbs. A recheck ultrasound revealed additional mild growth of the right adrenal mass but the compression of the vena cava was much more dramatic. The blood flow was very turbulent and venous distention was present. There was a small amount of ascites present. Recheck bloodwork revealed significant thrombocytosis (platelet count of 791,000/uL) but was otherwise fairly unremarkable. She was also documented to be hypertensive for the first time (she had been previously routinely monitored) and was started on amlodipine. Given the combination of thrombocytosis, turbulent vena cava blood flow and hypertension, "Mia Sophia" was considered a fairly high risk for thromboembolic disease and clopidogrel was started (18.75 mg q day; ¼ of a 75 mg tablet).

"Mia Sophia" was monitored very closely. Adequate control of her blood pressure was achieved and she continued to do fairly well for the next two months before declining dramatically with signs of veno-occlusive disease. She was euthanized at that time, almost exactly 2 years after her diagnosis.

CLINICAL MESSAGE

"Mia Sophia" started this journey with ADH as an annual wellness visit. Her owner had no major concerns about her health as she was eating and drinking well and had even gained weight. Certainly no clinical signs that would indicate illness to an owner! This highlights the important point that dogs with HAC—whether PDH or ADH—are not sick dogs. Owners usually don't present their dogs until signs of pu/pd become excessive and result in urinary accidents in the house or until a previously well-behaved dog starts stealing food off the counter or the incessant panting begins keeping an owner up all night! We must continue to include meaningful questioning in our examinations such as inquiry about increases or changes in water consumption, urination pattern, panting and appetite.

HAC presents as a classic clinical syndrome—with supportive history from the client, suggestive physical examination findings and typical laboratory changes. Many older dogs have asymptomatic elevations of ALKP and we should not jump to the conclusion of HAC without other clinical and laboratory support. Testing asymptomatic dogs—who may in fact have non-adrenal illness—will often result in false positive results and a dog being unnecessarily treated for Cushing's which is obviously dangerous. Patients with asymptomatic elevations of ALKP should first undergo pre and post-prandial bile acid testing and ultrasonography in order to identify underlying disease before HAC is considered.

Sometimes we are presented with a sick dog—one who has vomiting, diarrhea or other ailments—but they also appear to have a history (prior to the illness) and physical examination that supports HAC. These dogs should be treated for their non-adrenal illness BEFORE being tested for HAC. Screening tests (e.g., UCCR, ACTH stimulation test, or LDDST) for the evaluation of HAC should never be performed in sick dogs!

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CLINICAL ASSESSMENT

1 All dogs with asymptomatic elevations of ALKP or other liver enzymes should have an evaluation for hyperadrenocorticism. **True or False?**

2 Which of the following is the preferred screening test for hyperadrenocorticism in dogs who appear generally healthy other than clinical signs of HAC?

- **a.** Urine Cortisol:Creatinine Ratio
- **b.** ACTH Stimulation test
- **c.** Low Dose Dexamethasone Suppression Test
- **d.** Endogenous ACTH level

3 Which of the following is the preferred screening test for hyperadrenocorticism in dogs with concurrent diabetes or other chronic illnesses?

- **a.** Urine Cortisol:Creatinine Ratio
- **b.** ACTH Stimulation test
- **c.** Low Dose Dexamethasone Suppression Test
- **d.** High Dose Dexamethasone Suppression Test

4 Which of the following can serve as a DIFFERENTIATING test for hyperadrenocorticism in dogs?

- **a.** Low Dose Dexamethasone Suppression Test
- **b.** High Dose Dexamethasone Suppression Test
- **c.** Endogenous ACTH level
- **d.** Abdominal ultrasound
- **e.** All of the above

5 What is the only test available to detect iatrogenic hyperadrenocorticism?

- **a.** Low Dose Dexamethasone Suppression Test
- **b.** High Dose Dexamethasone Suppression Test
- **c.** Abdominal ultrasound
- **d.** ACTH stimulation test

6 Following is a LDDST result. **What are the two possible interpretations of this test?**

Pre: 5 ug/dL
4 hour Post: <1 ug/dL
8 hour Post: <1 ug/dL

7 Following is a LDDST result. **What are the two possible interpretations of this test?**

Pre: 10 ug/dL
4 hour Post: 4 ug/dL
8 hour Post: 14 ug/dL

8 Following is a LDDST result. **What are the three possible interpretations of this test?**

Pre: 4 ug/dL
4 hour Post: 3.8 ug/dL
8 hour Post: 6.3 ug/dL

9 The treatment of choice for ADH is medical management with mitotane or trilostane. **True or False?**

10 Mitotane and trilostane appear to be equally effective and give similar survival times for the medical management of ADH in dogs who do not undergo surgery. **True or False?**

11 Use of a lower Cosyntropin dosage greatly reduces the cost of the ACTH stimulation test and allows more owners to diagnose and properly monitor HAC treatment. The new "lose dose" ACTH stimulation protocol using 1 ug/kg IV is sufficient for BOTH the diagnosis and monitoring of patients with HAC. **True or False?**

CLINICAL ASSESSMENT ANSWERS:

1. **False.** Dogs with elevated ALKP or other liver enzymes should only be evaluated for hyperadrenocorticism if there is a clinical history (i.e.,pu/pd, polyphagia, panting, weight gain, hair coat or skin changes, etc.) and physical examination changes support the suspicion. Also evaluate the remainder of the bloodwork critically for other features supportive of Cushing's disease (i.e.,hypercholesterolemia, thrombocytosis, dilute urine, proteinuria, etc.) prior to performing screening testing for this endocrinopathy.

2. **C. Low Dose Dexamethasone Suppression Test.** The LDDST is the preferred screening test for HAC in dogs as it is much more sensitive when compared to the ACTH stimulation test and will more reliably identify dogs with HAC. If the UCCR is positive, another screening test must be performed. The Endogenous ACTH level is only useful as a differentiating test between PDH and ADH.

3. **B. ACTH Stimulation Test.** The ACTH stimulation test will result in fewer false positive results than the LDDST in dogs with concurrent illness. The LDDST can be dramatically affected (and give false positives) by stress or concurrent illness.

4. **E. All of the above.** The LDDST is technically a SCREENING test for HAC in dogs but it can function as both a screening and differentiating test in approximately 65% of dogs affected by PDH.

5. **D. ACTH Stimulation test.** Iatrogenic HAC involves excessive dosages or prolonged administration (even low dose) of glucocorticoids that leads to adrenal atrophy and suppressed ACTH levels with then resultant suppressed cortisol levels. Iatrogenic HAC is clinically indistinguishable from naturally occurring HAC—they generally have the same pu/pd, polyphagia, weight gain and hair coat changes. The only test which will identify iatrogenic HAC is the ACTH stimulation test and will result in low cortisol levels with very little stimulation from Cosyntropin.

6. Based on the 8 hour result, this is a normally suppressed LDDST. The first conclusion is that this patient is normal and does not have HAC. The second conclusion that could be drawn is that this patient is one of the 5-10% of dogs affected by PDH that suppresses normally. If the patient has clinical signs commonly associated with HAC an ACTH stimulation test should be performed as an additional screening test.

7. Based on the 8 hour result, this is a positive LDDST consistent with HAC. The fact that the 4 hour sample suppresses to >50% of baseline (baseline was 10 ug/dL) also serves to differentiate this patient as being affected by PDH. The second conclusion is that this is a false positive sample in a dog with non-adrenal illness or excess stress levels.

8. Based on the 8 hour result, this is a positive LDDST consistent with HAC. The fact that the 4 hour sample does not suppress to <1.4 ug/dL OR to >50% of baseline means that both PDH and ADH are both still differentials for this patient. 35-40% of dogs with PDH and 100% of dogs with ADH will not be differentiated by the LDDST. If the dog has appropriate clinical signs, a differentiating test (i.e.,ultrasound, HDDST, endogenous ACTH) should be performed. The third conclusion is that this is a false positive sample in a dog with non-adrenal illness or excess stress levels.

9. **False.** The treatment of choice for ADH is adrenalectomy. Many adrenal masses are malignant and removal of the mass prevents the risk of local tumor growth as well as minimizes chances of metastasis. Adrenalectomy also results in complete resolution of the clinical signs of HAC.

10. **True.** Neither drug is superior as far as delivery of longer survival times. 14-16 months is a reasonable expectation of survival for dogs affected by ADH undergoing medical management. Mitotane treated dogs are reported to experience more adverse side effects compared to dogs receiving trilostane and for this reason, trilostane may be the preferred medical therapy for ADH.

11. **False.** The new low dose (1 ug/kg IV) Cosyntropin protocol is sufficient ONLY for monitoring mitotane or trilostane therapy—NOT for the diagnosis of HAC.