"Ellie Cole's Case"

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Introduction

Ellie Cole is an 11-year-old female spayed Labrador that presented for a second opinion for refractory diabetes mellitus. Her blood glucose was persistent in the 600+ mg/dL range on glucose curves and free style libre. She was polyuric (PU), polydipsic (PD) and had all the other hallmarks of diabetes. Otherwise, she was bright and alert. Upon regulating her diabetes, she was subsequently diagnosed with hyperadrenocorticism (HAC), also referred to as Cushing's disease. Cushing's disease has a myriad of presentations and clinical signs that may be manifested over the course of the disease(2). These often include muscle wasting, pot-belly, alopecia (commonly bilateral), polyuria/polydipsia, polyphagia, and fat depositions along the back, as well as elsewhere(2). Approximately 10% of dogs that develop HAC will also develop hyperglycemia due to insulin resistance and gluconeogenesis brought on by HAC.

This disease can manifest as primary, secondary, or iatrogenic forms of HAC. Primary HAC is caused by a benign adenoma of the adrenal cortex, which leads to excess production of cortisol. Secondary HAC, the most common form found in canines, is a benign adenoma of the pituitary gland. This results in an increase in ACTH release and the subsequent stimulation of the adrenal glands resulting in bilateral hypertrophy and excess cortisol production. Iatrogenic Cushing's disease can be induced by chronic and or excessive administration of exogenous steroids (2). In this case we will examine a case of Cushing's disease.

History and Presentation & Diagnostic Testing

Ellie Cole is an 11-year-old spayed Labrador that presented for refractory diabetes mellitus. The referring veterinarian had been treating her with minimal response. Her blood glucose never decreased below 600 mg/dL during multiple glucose curves. She was PU/PD and had symptoms associated with uncontrolled diabetes mellitus. Otherwise, she was bright alert and responsive.

Physical examination revealed a slight potbellied appearance, rough hair coat (bordering alopecic) and muscle wasting. The owner also reported polyphagia and frequent episodes of panting. The patient has a history of dermatitis and alopecia and a non-healing wound on the back right hock that was being treated.

Bloodwork revealed an increased ALP (1273 IU/L). HAC is often associated with an elevated ALP but is not pathognomonic for the disease. Other entities such as cholestasis, liver

injury, bone damage, or various drugs (phenobarbital) can elevate it. he CBC revealed a stress leukogram. The chemistry was otherwise unremarkable with all values within normal limits.

January 27 – BG 450 mg/dL to 600 mg/dL increased Vetsulin to 12 U BID

February 19th – BG 400 mg/dL increased vetsulin to 14 U BID

March 5th – BG 375 mg/dL Vetsulin increased to 18 U BID

March 15th – BG 400 mg/dL Vetsulin increased to 22 U BID – placed a Freestyle Libre

April 2nd – BG 325 mg/dL Vetsulin maintained

April 23rd – BG 350 mg/dL Vetsulin increased to 26 U BID

May 25th – BG down to 230 mg/dL Vetsulin left alone – ACTH stimulation test performed – post cortisol reading was 25 mcg/dL.

As shown above many modifications were made over the course of 5 months to the dosing amount of Vetsulin increasing well above the normal dosing range (up to 24 units BID) to reduce blood glucose levels into the range of 150 to 250 mg/dL. This allowed us to have a greater confidence in future ACTH stimulation test results as without some regulation of blood glucose levels false positives may be obtained [4,27]. The ACTH stimulation test was compatible with Cushing's disease. The normal cortisol range for post ACTH stimulation is up to 17 mcg/dL and anything greater than 22 mcg/dL is suggestive of Cushing's disease. Ranges within 17 mcg/dL to 22 mcg/dL being considered borderline. Ultrasonographic examination revealed bilaterally enlarged adrenal glands, which supported Cushing's disease. Ellie's post sample revealed 25 mcg/dL and was consistent with Cushing's disease.

Ellie began a treatment regimen of Vetoryl (trilostane) 40 milligrams (1.25 mg/lb) (once daily while maintaining her dose of Vetsulin (20 Units BID: 1.65 IU/lb). Over a two-month course she slowly began to improve. On subsequent ACTH stimulation tests, her cortisol began to normalize and blood glucose curves showed a decreased blood glucose into the 150 to 200 mg/dL range.

Since that time, multiple ACTH stimulation tests have been normal. Post ACTH stimulation cortisol levels varied from 7 to 9.2 mcg/dL. Clinical signs are minimal and acceptable for the owners. Ellie is currently being treated with 30 mg of Vetoryl once daily and 6 units of Vetsulin twice daily. Her glucose is well maintained and ranges from 130 – 160 mg/dL.

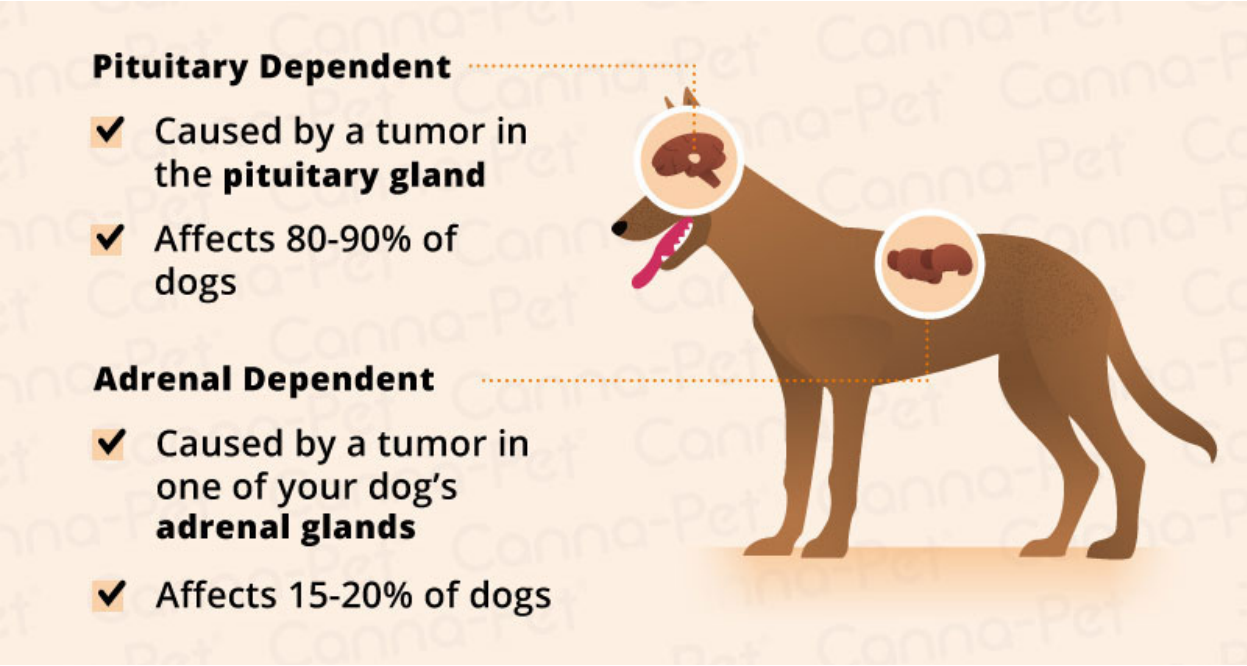
Anatomy and Pathology

There are two common forms of endogenous Cushing's disease involving a benign hypertrophy of either the pituitary or adrenal glands. Cushing's "syndrome", or iatrogenic Cushing's disease, can be induced with excess dosing of exogenous glucocorticoids [2]. Pituitary dependent Cushing's disease is the result of a benign tumor (adenoma) of the pituitary gland

which is attached to the hypothalamus at the base of the brain. The adenoma releases more ACTH than is physiologically normal, which stimulates the adrenal glands to produce excessive glucocorticoids. The excessive production of ACTH results in bilateral enlargement of adrenal glands which can be appreciated on ultrasonography or other form of advanced diagnostic imaging[15].

Cushing's disease caused by functional adrenocortical neoplasia generally result in a unilaterally enlarged adrenal gland. The ipsilateral adrenal gland will atrophy from lack of ACTH stimulation because of the negative feedback from excess cortisol production from the adrenal tumor. Treatment of choice is the surgical removal of the effected adrenal gland which is always dangerous and can be impossible should the tumor have invaded the surrounding structures [15].

10% of Cushing's disease cases can manifest as refractory diabetes mellitus due to increased secretion of glucocorticoids stimulating gluconeogenesis and impairment of insulin sensitivity. It does this by one or both of the following potential mechanisms. It can be either due to the breakdown of muscles or fat (proteolysis and lipolysis). This can increase insulin resistance due to an increase in the circulation of fats and protein [1]. Visceral and peripheral fat is laid down throughout the body in greater amounts which adds as well to insulin resistance and glucocorticoids. It also has an effect on the beta cells in the pancreas at several steps in their enzyme production pathway. This is thought to be the tipping point of a Cushingoid patient exhibiting clinical signs and symptoms consistent with diabetes mellitus [1].



(Fig. 1)

Diagnosis, Treatment and Prognosis

Diagnostic tests for this disease process include but at not limited to a urine cortisol/creatinine ratio, low and high dose dexamethasone suppression test, and an ACTH stimulation test. Urine cortisol/creatinine ratio is commonly a first line diagnostic test. It is fairly sensitive but is not specific for Cushing's disease. It is most generally used for its negative predictive value when evaluating for Cushing's disease, if the ratio is not elevated then Cushing's is unlikely [16]. ACTH stimulation testing is used to evaluate the maximal response of the adrenocortical reserve, but it cannot differentiate between pituitary dependent hyperadrenocorticism (PDH) and adrenal dependent hyperadrenocorticism (ADH). The sensitivity of this test is 60 to 80%. Additional testing is recommended to conclusively confirm hyperadrenocorticism (HAC) [13].

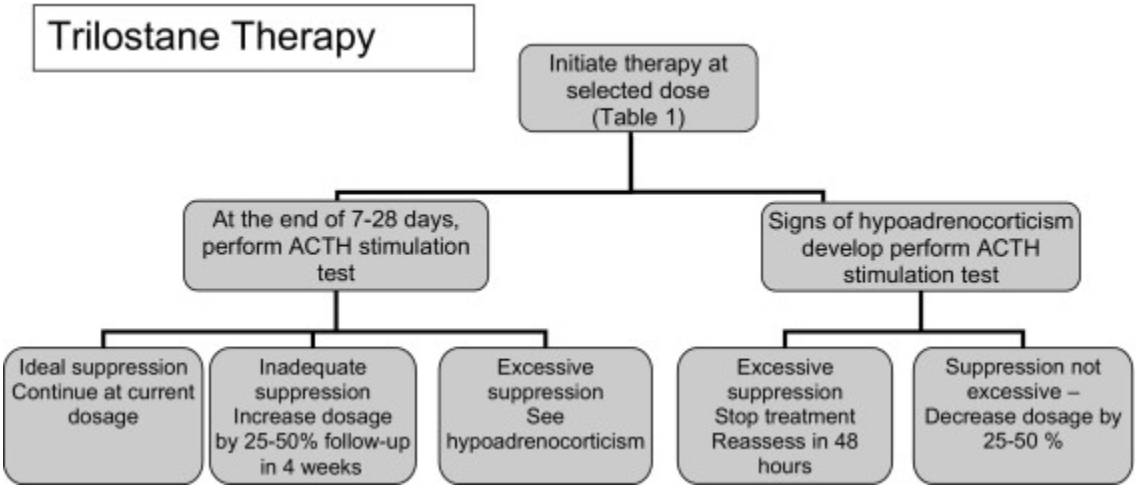
A low dose dexamethasone suppression test (LDDST) is a screening test used to detect HAC [14]. Administration of exogenous steroids (dexamethasone) temporarily suppresses the hypothalamic-pituitary axis which decreases cortisol production. This is the normal response. If the cortisol levels fail to suppress this is compatible with Cushing's disease. The sensitivity of this test is 90%. A high dose dexamethasone test is a discriminatory test. It would be indicated if the LDDST was negative, but a high degree of Cushing's disease remained [14]. It will suppress 75% of all pituitary dependent PDH cases and none of the ADH cases. Other diagnostics such as CT or ultrasonography could be utilized to support a diagnosis of ADH. For both the LDDST and HDDST dexamethasone is used because it can be differentiated from cortisol by the analyzer. Prednisone or hydrocortisone cannot be used for either of these tests as analyzers cannot discriminate between either drug or cortisol [14].

Treatment of canine Cushing's disease consists of reducing the amount of circulating cortisol being released by the adrenal glands under the influence of excess ACTH in the case of PDH [8]. Usually this is resolved with the use of Trilostane to suppress the production of cortisol from the adrenal glands at the level of 3 beta-hydroxysteroid dehydrogrenase, an essential enzyme for the production of cortisol [13]. By reducing the levels of cortisol, we can then recheck our ACTH stimulation test to see if there is a response from the adrenal glands when exogenous ACTH is administered.

Trilostane is our first line drug for HAC. As an enzyme inhibitor all effects are concentration dependent and reversible [12]. There can be severe side effects, although uncommon. Overdosing this drug can induce an Addisonian crisis through near complete suppression of cortisol release at the level of the adrenal gland [8]. The most common side effects noted with the initiation of Trilostane therapy has been lethargy and decreased appetite [17]. Monitoring of therapy with Cushing's disease centers around clinical signs and rechecking ACTH stimulation tests periodically. It is advisable to recheck an ACTH stimulation test 14 days

after the initiation of Trilostane therapy [8]. Generally, this drug requires 2 to 4 dose adjustments and has an 86 to 93% success rate in the treatment of Cushing's disease [8].

Trilostane is dosed at 2 to 3 mg/kg and has been dosed in intervals of 60 mg for 5 to 20 kilogram canines, 120 mg for dogs weighing 20 to 40 kilograms and 240 mg for dogs 40 to 60 kilograms[22]. Dosing of this drug is always rechecked 14 days after initiation of treatment by performing an ACTH stimulation test, along with a chemistry panel to evaluate a sodium potassium ratio to screen for Addison's disease. Dose modifications should be made at those times, and it may take multiple rechecks. Evaluation of treatment is primarily based on clinical signs and modifications are only made based on these criteria [22].



(fig 2)[24]

Mitotane is another option for the treatment of Cushing's disease. It also has adverse side effects, which cause a "selective necrosis" of the adrenal glands [9]. This is a treatment for adrenal tumors (ADH) and or PDH [11]. There is the potential to induce an Addisonian crisis due to the selective necrosis of the adrenal glands. This results in a severe lack of cortisol and all the clinical manifestations of Addison's disease which can be life threatening [10]. Most patients become refractory to the drug within 1 year and relapse. For these reasons this drug is not a first line drug for the treatment of HAC. There are other treatment modalities such as L-deprenyl and ketoconazole that are of questionable efficacy whose use is not recommended [19].

Mitotane has been dosed bimodally, with an initial loading dose proceeding a maintenance dose [22]. A loading dose of 40 to 50 mg/kg is administered, and maintenance doses are instituted after a reduction in clinical signs are noted by the owners [22]. A Dose of 25 mg/kg can be used and then modified based on clinical signs [22].

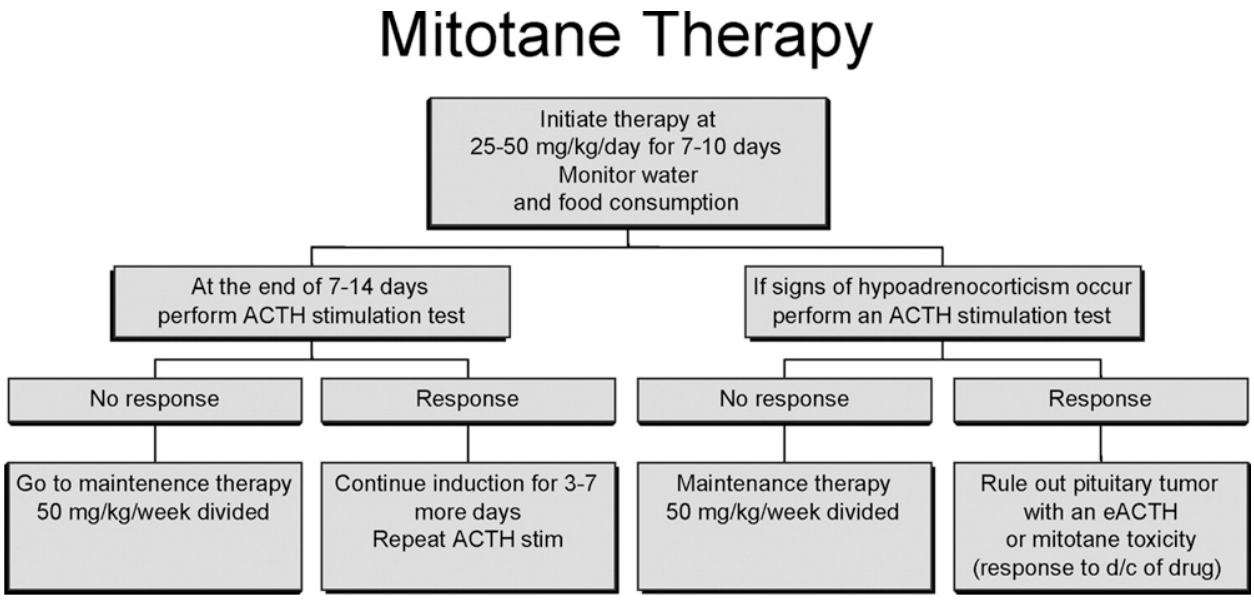


Fig. 1. Algorithm for the use of mitotane for the treatment of PDH.

(fig – 3)[23]

By providing appropriate medical management and close monitoring, a dog with PDH can live a long normal life with little to no side effects. If the disease is caught before there are deficits, such as insulin resistance or renal disease the prognosis is especially good [8]. Comorbidities such as hypercoagulable states (PTE or other thromboembolic events can be life threatening), hypertension or other associated diseases, can have a negative prognostic impact [20]. While HAC is associated with these comorbidities it has yet to be more directly correlated to morbidity in itself [21].

Outcome

Since the modification of Ellie's insulin dosing and use of Trilostane, she has been steadily improving. Her clinical signs have returned to acceptable levels, and her owners feel she is enjoying a good quality of life. She has also been placed on Glycobalance by Royal Canine to further assist with glucose regulation. Her glucose levels are being monitored via a freestyle libre at home and no further modifications have been required for either of her medications. Insulin resistance in patients with HAC varies as to whether or not they will require insulin for management long term [6]. Without other comorbidities Ellie's HAC should be comfortably manageable for the rest of her life with proper monitoring and owner compliance [7].

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