Hyperadrenocorticism results from pituitary, adrenal, or iatrogenic causes. Pituitary dependent hyperadrenocorticism is the more common of the two causes (80-85%), and results in excessive secretion of adrenocorticotropic hormone (ACTH) which in turn causes excessive cortisol secretion. In this case, eventually both adrenal cortices become hyperplastic. The majority of these cases are a result of a pituitary tumor, either benign or neoplastic, but may also occur due to hyperplasia of the pituitary, or due to a loss of responsiveness to the negative feedback system on ACTH secretion.

The remaining 15-20% of cases occurs due to adrenal tumors (adenomas or carcinomas). These tumors are typically identified on ultrasound. In this case these adrenal tumors secrete cortisol without regard to the ACTH levels. Typically these tumors affect only one adrenal gland (unilateral).

Iatrogenic Cushing’s syndrome usually results from prolonged or excessive administration of glucocorticoids. These patients may demonstrate all classic signs of hyperadrenocorticism. Injectable, oral, topical, or even ophthalmic glucocorticoid sources can result in this syndrome.

**Signalment**

Cushing’s disease is generally found in dogs older than 6 years of age or older. Poodles, Dachshunds, terrier breeds, Beagles, Boston Terriers, Boxers, and German Shepherds are commonly found with pituitary dependent hyperadrenocorticism (PDH). German Shepherds, Dachshunds, Labrador retrievers, and Toy Poodles can be affected by adrenocortical tumors, which may be somewhat more common in females. Occasionally Cushings may be seen in cats.

**Clinical signs**

Presentation of Cushing’s generally includes signs that progress slowly over time, as the excessive glucocorticoid levels must be chronically elevated. Chronically elevated cortisol levels have deleterious effects on the entire body, including the brain, muscles, bone, skin, kidney, liver, and vascular systems. Signs and symptoms commonly include polydipsia, polyphagia, polyuria, weight gain/obesity, abdominal enlargement (weakening of abdominal muscles), thinning haircoat progressing to alopecia (not affecting the head and limbs), panting/increased respiratory rate, lethargy, and muscle weakness are commonly seen.

Other signs that may be less commonly noted are tendency to bruise easily, heat intolerance, calcinosis cutis, skin hyperpigmentation, neuropathies, and myopathies. Patients with hyperadrenocorticism have increased tendency to develop secondary diabetes mellitus due to increased insulin resistance from cortisol. Hepatomegaly with concurrent elevations in alkaline phosphatase, alanine aminotransferase, and cholesterol are common (with normal total bilirubin levels). Hypertension may be found in these patients as well.

**Laboratory abnormalities**

A CBC, chemistry panel, electrolyte analysis, acid/base assessment, and ACTH stimulation test are all necessary for all suspect hyperadrenal patients. The most important test to diagnose Cushing’s disease is the ACTH stimulation test. CBC may demonstrate a mature leukocytosis with neutrophilia, lymphopenia, eosinopenia, and mild polycythemia. Serum is commonly lipemic. Chemistry changes may include elevations in AlkPhos (serum alkaline phosphatase), hyperglycemia, and hypercholesterolemia. ALT (alanine aminotransferase) may be slightly elevated. Urinalysis may reveal a low specific gravity (<1.020) +/- glucosuria if diabetes is present, and often with proteinuria. Yet BUN and Creatinine may be normal to slightly decreased. The low USG is due to the effects of glucocorticoids on the glomerular filtration rate (GFR) and renal response to anti-diuretic hormone (ADH). Urinary tract infections are common in these patients. Decreased renal reabsorption of calcium may result in urinary calculi forming in these patients.

Radiographic changes include hepatomegaly, ranging from mild to severe. Visualization of an adrenal mass is a rare finding on radiographs, although thoracic radiographs should be evaluated for evidence of metastases. Ultrasound would be preferred to detect adrenal masses.

**ACTH stimulation**

ACTH stimulation testing assesses the adrenal reserve capacity of the patient. This is the only way to confirm the presence or absence of Cushing’s disease. This test should be run as soon as the disease is suspected. Cortisol levels are stable in plasma or serum for as long as 5 days at room temperature. In the past a full vial of synthetic ACTH has been administered regardless of patient size. Due to shortages and difficulties in obtaining this product, it has been found that dosing can be changed relative to the patients’ weight. To dilute this product use the following protocols:

1. Mix 1ml sterile saline into 1 vial of 250mcg (0.25mg) Cortrosyn
2. Using a 6ml syringe- draw up 4ml sterile saline
3. Withdraw the 1ml of Cortrosyn solution into this syringe and mix well.
4. Place 1ml of this mixture into sterile red top tubes (makes 5 tubes of 50mcg each)
5. Label the tubes as 50mcg/ml and date the vial. Vials are to be placed in the freezer. (Solution is good when frozen for up to 6 months)

Procedure

1. Draw baseline blood sample- be sure no synthetic glucocorticoids have been administered (exception of dexamethasone SP).
2. Weigh the patient (canine)- round up the number of vials to fit the dog’s size
3. Thaw and administer Cortrosyn- IV
   - 10kg or less = 1 - 50mcg vial
   - 20kg or less = 2 -50mcg vials
   - 30kg or less = 3 -50mcg vials
   - 40kg or less = 4 -50mcg vials
   - 50kg or less = 5 -50mcg vials
   - >50kg or less = use standard method with 250mcg vial
4. Wait one hour- draw post sample.
   - (Alternatively the standard method may be used as described above under hypoadrenocorticism testing.)
   - Post stimulation adrenal response will be increased, or exaggerated, in dogs with hyperadrenocorticism (>22ug/dl).

Treatments

If hyperadrenal disease is related to an adrenal tumor, then surgical removal is an option. This should only be done after confirmation via ultrasound and evaluation of thoracic radiographs for metastases. In these cases glucocorticoid supplementation post surgery would be required.

   Surgery for pituitary tumors is not currently performed. Typically treatment of PDH involves medical management, with mitotane being the drug of choice. Trilostane, Ketoconazole, and L-Deprenyl are other treatment options. Ketoconazole works by decreasing cortisol production, and is used primarily to stabilize patients prior to adrenalectomy. L-Deprenyl has questionable efficacy. Mitotane is a cytotoxic agent that causes progressive necrosis of the zona fasciculata and zona reticularis within 5-10 days of treatment. Induction with mitotane starts with doses of 30-50mg/kg/d PO divided BID for 7-10 days. The owner should be given a supply of prednisone for emergency use. Multiple adverse effects can be seen with mitotane therapy, especially initially. Owners should be advised to discontinue therapy immediately if any decrease in appetite, water consumption, vomiting, lethargy, anorexia, or diarrhea occurs. These are common side effects of mitotane therapy, especially initially. However discontinuation of mitotane with glucocorticoid supplementation is advised should these signs occur. Use of mitotane in patients with renal or hepatic disease should be done with caution.

   Trilostane works by inhibiting an enzyme necessary for synthesis of cortisol (3-beta hydroxysteroid dehydrogenase). Lethargy and mild electrolyte abnormalities may be seen during the first few days of therapy due to decrease in the body steroid levels. If vomiting and diarrhea occur, Trilostane should be stopped for a few days, and then given only every other day to minimize these induction symptoms. Caution should be used in patients with renal or hepatic disease. Both mitotane and Trilostane may result in iatrogenic hypoadrenocorticism.

Alternative therapies

In cases of atypical Cushing’s disease, a number of alternative therapies an be considered including melatonin and flaxseed hulls with lignans have both been shown to reduce production of cortisol. Melatonin by be given via oral routes (3mg bid <30lbs; 6mg bid >30lbs) or via implants that last 3-4 months. Flaxseed hulls with lignans should be given once daily on food (1/2 tsp. <30 lbs; 1 tsp. >30 lbs). Both melatonin and flaxseed hulls should be given simultaneously if estradiol is also elevated.

Maintenance therapy

ACTH testing should be done 8-9 days after induction of therapy. If levels are normal or still too high, then the induction dose should be continued for an additional 3-10 days. If any of the adverse signs mentioned above occur, treatment should be discontinued and glucocorticoid therapy initiated. If these signs are accompanied by electrolyte disturbances, then the patient must be treated for iatrogenic Addison’s, which can be permanent. When the ACTH levels are between 1-5 ug/dL, then maintenance doses of mitotane should be followed (30-50mg/kg divided between 2-3 doses per week) for life. Patients receiving an adrenalectomy will usually end up with hypoadrenocorticism, and need to be treated as such. ACTH stimulation tests should be monitored every 3-6 months after the pet has stabilized. If at any point clinical signs should re-occur, then the induction dosing should be repeated.

Patients with Cushing’s disease are at risk of a variety of complications such as pulmonary thromboembolism, hypertension, congestive heart failure, infection, and reoccurrence of clinical signs. Therefore there is a guarded prognosis for long-term survival in these patients, with an average life span being 2 years post diagnosis.
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