HYPERADRENOCORTICISM:
CUSHING’S SYNDROME IN THE CANINE AND FELINE

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Hyperadrenocorticism, more commonly referred to as Cushing’s syndrome is the overproduction of cortisol in the body. It is much more common in the dog, but it can be diagnosed in the cat as well.

Cushing’s can be caused by three different ways - pituitary gland tumor, adrenal gland tumor or iatrogenic.

The pituitary gland controls adrenal function and produces a hormone called ACTH (Adrenocorticotropic Hormone), a hormone that stimulates the adrenal glands. If there is a pituitary tumor present, there is an over production of ACTH, which in turn causes an overproduction of cortisol. This is a naturally acquired form of Cushing’s and is the most popular. 80-85% of Cushing’s Disease patients have Pituitary Dependent Cushing Syndrome (PDCH) or PDH – Pituitary Dependent Hyperadrenocorticism.

Adrenal Gland Tumors make up for the remaining 15-20% of the Cushing’s Disease patients. The Adrenocortical tumors secrete an excessive amount of cortisol independent of pituitary control. Most of these tumors are diagnosed as adenomas or carcinomas. It typically affects one adrenal gland rather than both (less than 20% of these patients), whereas only 5-10% of these 15-20% of adrenal gland patients will have bilaterally enlarged adrenals. This form develops autonomously which then gives it the freedom to act on its own independently.

The last form is an iatrogenic form – which is induced medically with oral or injectable medications. It can even be caused by long term topical/ocular medications. Examples of medications that can cause this are steroids such as depo-medrol, prednisone/prednisolone, topical steroids, ocular meds, aural meds, ophthalmic medications and even transdermal medications.
It is important to remember that these patients typically do not present with major illness, but just symptoms and side effects. These are not typically lethargic, sick patients. The most common side effects and symptoms that they may exhibit are polyphagia, polydipsia, polyuria, panting, alopecia, pruritis, potbellied appearance, thin skin/bruising, muscle weakness. Other symptoms they can exhibit but that are not quite as common are calcinosis cutis, lameness, mild lethargy, testicular atrophy (intact males), failure to cycle (intact females), myotonia (muscle contractions). Many patients will have a failure to regrow hair due to the atrophy of hair follicles. Many patients will have hepatomegaly noted on physical exam which can be easily palpable due to the weakened abdominal muscles. This can also be seen on abdominal radiographs and/or abdominal ultrasound. Often times hyperpigmentation of the skin is noted and exophthalmos is commonly noted as well. On occasion a patient can have bilateral or unilateral nerve paralysis, but this is not very common.

Cushing’s is known to affect middle aged to older patients – usually greater than 6 years of age for both PDH and Adrenocortical Tumors. 50-60% of canines with PDH are female and 60-65% of canines with functioning adrenocortical tumors are also female. It tends to be a 50:50 ratio in feline patient between males and females.

Poodles, Dachshunds, terriers, German Shepherds, Boston terriers, Boxers and Labradors and the most common canine breeds (for both forms – PDH and Adrenocortical tumors). In felines – most commonly found in domestic felines. 75% of dogs with PDH are small breeds weighing less than 20kg. Approximately 50% of dogs with adrenocortical tumors weigh more than 20kg.

Again, most patients are mostly stable overall and not ill, but they can have secondary illnesses due to prolonged disease and/or side effects. These can be but are not limited to hypertension, pyelonephritis/urinary tract infections, pancreatitis, congestive heart failure, diabetes mellitus, and pulmonary thromboembolisms.

Hypertension is usually higher in dogs that are poorly controlled or untreated. This is due to an increase in protein loss in the urine secondary to glomerular damage. Urine protein loss is common; however, serum protein and serum albumin loss are uncommon. There is a concern for retinal or renal vascular damage, however vision loss is rare. Need to get the Hyperadrenocorticism controlled first, then hypertension will usually resolve as the Cushing’s Syndrome becomes more controlled.

Urinary tract infections and pyelonephritis are common side effects due to a lack of urine concentration secondary to the PU/PD. Chronic UTI’s can eventually lead to chronic kidney injuries and or failure in many cases. Sterile urine culture and sensitivities are necessary to choose an appropriate antibiotic choice. Failure to control Cushing’s can predispose a patient to repeat UTI’s and lead to pyelonephritis. It is uncommon to have urinary calculi in Cushing’s patients.
Patients with Cushing’s disease are often diagnosed with Pancreatitis. However, patients with Cushing’s disease typically have hyperlipidemia, hypercholesterolemia, and signs of infection on blood work which can lead you to believe that a patient has pancreatitis. It is in fact RARE that a dog gets pancreatitis as a secondary problem with Cushing’s Syndrome. They are more likely to have “Garbage Can Gastritis” from having voracious appetites rather than pancreatitis as a secondary problem.

Patients with Cushing’s disease can have secondary congestive heart failure. Glucocorticoid excesses can cause hypertension secondary to hypervolemia which causes an increase in the workload of the myocardium and results in myocardial hypertrophy, causing CHF as hypertension and fluid retention become more severe. Since this is a disease that affects older patients already, they may have chronic mitral valve and tricuspid valve disease. This is an uncommon phenomenon, but it is not unheard of and makes treatment more difficult. The combined effect of valvular insufficiency, hypertension and hyperadrenocorticism is what can cause CHF. Controlling Cushing’s disease is, lowering the blood pressure is most important in this case.

Diabetes Mellitus and Cushing’s Syndrome patients present with much of the same symptoms, so it is important to diagnose them individually, and the carefully monitor each disease carefully. Insulin levels may need to be greatly reduced as Cushing’s is initially being treated; however patients that have Cushing’s are known to be insulin resistant, making management difficult. It is reported that approximately 10% of dogs and 80% of cats will become diabetic after being diagnosed with Cushing’s due to the glucocorticoids circulating in the body.

Patients with Cushing’s become hypercoagulable due to the protein loss that they have. Antithrombin III is a protein that is found in the vessels, and when there is protein loss, it leads to Pulmonary Thromboembolisms (PTE’s). This can lead to the formation of thrombi in the veins of the legs and pelvis and dislodge and embolize to the pulmonary arteries. The concern is that this can be a secondary problem of multiple disease processes (PTE’s caused by Neoplasia, Protein Losing Nephropathies, CRF, Pancreatitis, Sepsis, DM, IMHA, Cardiac Dz, HW Dz, Trauma, Sx, Etc.) – so carefully examination of your patient again is necessary. Predisposing factors include obesity, hypertension, increased HCT (resulting in vascular stasis), sepsis, prolonged periods of recumbency. More common in dogs that have undergone surgical removal of an adrenocortical tumor.

Diagnosing Cushing’s Syndrome can sometimes be challenging. It is being found now that some if not many patient’s symptoms and other diagnostics precede what their bloodwork results tell us. First and foremost, a complete physical exam, basic CBC, complete chemistry panel, urinalysis +/- culture and sensitivity to rule out infection, and basic thyroid function is needed. Some clinicians may also recommend abdominal radiographs and/or abdominal ultrasound as a first diagnostic step.
The initial diagnostics are not always normal and often contain many changes. The CBC changes may include a mature leukocytosis, neutrophilia, monocytosis, lymphopenia, eosinopenia (usually stress related). The RBC morphology is usually normal; however occasionally nucleated RBC’s (immature) or mild erythrocytosis (females) is noted. The Chemistry profile may have elevated liver enzymes, decreased BUN, elevated amylase/lipase/triglycerides/cholesterol, decreased phosphate, increased fasting BG, abnormal electrolytes. The blood is usually lipemic. Liver function test, bile acids, may be mildly increased. Insulin levels may be normal or increased. Low T3/T4 concentrations are noted at times as a response to TSH that parallels normal, but pre and post values may be decreased. The urine is often dilute with a concentration often times <1.008 (85% of patients <1.020). Glucosuria in noted in approximately 10% of cases. Abdominal Ultrasound +/- Radiographs often find hepatomegaly, potbelly, distended bladder, osteoporosis, calcinosis cutis, excellent abdominal contrast, adrenal calcification if adrenal tumor, CHF (rare), PTE (rare), calcified trachea and main stem bronchi.

The next step in diagnosing Cushing’s is to perform an ACTH stimulation test. This is a 1-2 hour test and can diagnose traditional Cushing’s Syndrome approximately 80-80% of the time. There should not be any additional stress added to the patient if doing this test during a hospital stay, such as radiographs, ultrasound, other diagnostic testing, because the bodies stress response can falsify the results. When interpreting the results – a decreased result supports Iatrogenic Cushing’s or Addison’s Disease. If the results are less than 2 (reference laboratory reference ranges will differ), then the patient is an Addisonian. An elevated result supports Cushing’s. And if there is a normal result, and Cushing’s is still suspected, a Low Dose Dexamethasone Suppression test (LDDST) is recommended.

If the ACTH stimulation test is inconclusive, a LDDST is the next diagnostic test performed. This is an 8 hour test. The results are compared with the baseline result to differentiate between Adrenal or PDH.

A cortisol creatinine ratio can also be done to help rule in or out Cushings. If it is elevated, it is supportive of Cushings, and normal results can help to rule out Cushings. This test is not always helpful, especially in atypical cushings cases or early diagnosis.

A High Dose Dexamethsone test (HDDST) is only done to differentiate between adrenal dependent and pituitary dependent cushings as adrenal glands do not suppress cortisol levels at all. This is also an 8 hour test. Typically a HDDST is not performed because we have such advanced diagnostics that we can determine these results without an additional 8 hour test.

Lastly if all of the above are not as helpful in diagnosing Cushings Disease, an Adrenal Panel can be sent out to the University of Tennessee. This tests all the hormones in the body. This is performed as an ACTH Stim test, but gives us a bit more informatin about the different hormones being released by the pituitary and adrenal glands and other medicinal options.
If a patient is having difficulties neurologically, and a client wants to pursue further diagnostics, a CT scan or MRI can be performed to diagnose the pituitary tumor and determine if radiation therapy would be needed. A CT scan would like be needed to help with RT planning in this situation.

Treatment

The simplest form of Cushing’s to treat is iatrogenic Cushing’s Syndrome. First and foremost, the medication causing the condition must be weaned off from slowly. Unfortunately, there will be a recurrence of the original disease that was being treated to begin with and other treatment options for that condition may need to be considered. The only patients that have iatrogenic Cushing’s that should remain on their steroid therapy are those that are on chemotherapy protocols and those that are being treated for an immune mediated process.

The best form of treatment for an adrenal gland tumor is surgical resection. An abdominal ultrasound +/- is necessary first to help determine if the tumor is resectable. If tumor is benign (adenoma), prognosis is better and if surgery was successful, there is a good chance the patient may go back to normal health. If the tumor is malignant (carcinoma), chances of regrowth are greater and patient may not return to normal. Chemotherapy is an option for longer survival. Some medications used to treat PDH can help these patients as well. Occasionally, removal of an adrenal gland may require glucocorticoid or mineralcorticoid therapy, especially if the other adrenal gland is atrophied due to the presence of the tumor. Some clinicians may try to shrink a tumor first with mitotane therapy or in the event that a client elects to not go to surgery. A concern for the opposite condition, Hypoadrenocorticism or Addison’s is then a possibility.

PDH treatment is often times clinician dependent and training dependent. The most common medication reached for is Trilostane or Vetoryl. Other therapies can include mitotane, ketoconozole, and anipryl but are less common. Radiation therapy can also be considered in some cases when a patient is showing neurologic concerns, but also not very common.

It is important to not just treat symptoms or numbers. A patient that has just an elevated alkaline phosphatase that is otherwise healthy is not a Cushing’s patient unless diagnosed appropriately. Or a patient that is showing symptoms such as PU/PD, polyphagia without a diagnosis may not be cushingoid. It is important to do all necessary diagnostics before starting medication and discussing long term complications with the client. It is a long term commitment and long term follow-up is needed on behalf of the client, patient and clinician, so medications cannot just be started with-out strict guidelines.

Overall, the prognosis is good if the owner is compliant with recheck bloodwork and keeps a close eye on clinical signs. Approximately 50% of adrenal tumors are benign and 50% are malignant. If treated early enough, even malignant adrenal tumors can be cured with surgery. Some patients may have symptoms of arthritis or allergies that were masked by the cortisol. They may surface after therapy has been started and now need to be treated.