

Hyperadrenocorticism (Cushing's Disease)

What is it?

Hyperadrenocorticism a condition wherein the adrenal glands (small glands which live next to the kidneys) overproduce cortisol and other hormones. This is due to either too much stimulation from the brain's pituitary gland (Pituitary dependent hyperadrenocorticism/ "PDH"), or due to a tumor on one of the adrenal glands (Adrenal dependent hyperadrenocorticism/ "AT"). About 85-90% of cases are pituitary dependent, and most of those are due to a small hyperactive nodule in the pituitary, known as a microadenoma. However, some cases are due to a macroadenoma, which is a mass in the pituitary large enough to cause neurologic signs such as confusion, seeming "lost", unsteadiness on the feet, even seizures. Over time, a microadenoma can grow to become a macroadenoma, but overall, neurologic signs from Cushing's disease are not a frequent occurrence. Of those 10-15% of cases caused by an adrenal tumor, about half those tumors are invasive and malignant, meaning they can metastasize (spread throughout the body).

Signs of Cushing's disease are many- they include inability to concentrate the urine, which leads to excessive urination and thirst, a ravenous appetite, hair loss, enlarged liver, liver enzyme elevations, persistent skin and urinary infections, poor wound healing, thinning of the skin, pigmentation of the skin, panting, a "potbellied" appearance (wasting of limb muscles with truncal obesity), agitation or lethargy, muscle weakness, high blood pressure, protein losses in the urine, and increased propensity to become diabetic. Some dogs with Cushing's only show one of these signs and otherwise seem to be a normal pet.

The effects of Cushing's syndrome on the body are also similar to what might happen if the dog received a dose of cortisone every day. Cortisone is an anti-inflammatory substance, so underlying inflammatory conditions such as arthritis, inflammatory bowel disease, inflammatory liver conditions, or even severe urinary infections might progress silently and insidiously without the dog showing signs of the problems until the Cushing's disease is controlled.

Cushing's disease is typically seen in middle aged to older female spayed dogs but it can happen in dogs as young as about 4 years old, of any breed and any sex. Some breeds have higher incidence, including miniature Schnauzers and Dachshunds.

Diagnosis

If your pet has shown any of the above signs of Cushing's, there are a number of tests to try to determine if the dog has the disease or not. No test is 100% perfect; so sometimes more than one test has to be done to be sure. Screening tests include urine cortisol:creatinine ratio, Low Dose Dexamethasone Suppression Test (LDDST), or

ACTH stimulation Test. Each test has its merits and drawbacks. The LDDST can also sometimes tell if the problem is pituitary or adrenal dependent in origin.

If the dog is confirmed to have Cushing's disease, differentiating tests are done to further determine pituitary vs adrenal origin. These include the LDDST mentioned above, the High Dose Dexamethasone Suppression Test and Abdominal Ultrasound. We often recommend ultrasound to screen for other disease conditions that could mimic or be concurrent with Cushing's disease, especially certain liver conditions. In cases where neurologic signs are present, a CT scan or MRI might be recommended to look for a large pituitary tumor in the brain. The veterinarian will likely perform a combination of these tests to determine the nature of the dog's problem.

It is important to know for sure that the dog does or does not have Cushing's disease because treatment is often life-long and requires careful monitoring. Also, it is important to know whether it is due to an overactive pituitary or an adrenal tumor, because the treatment for each is different.

Treatment

Pituitary dependent hyperadrenocorticism (PDH)

Treatment for PDH involves medical therapy to suppress cortisol production from the adrenal glands, even though it is the pituitary in the brain that is over-secreting a master hormone that tells the adrenals to make too much cortisol. There are two main medical options, Lysodren and Trilostane, although some have used Anipryl (Selegiline/ L-Deprenyl) or ketoconazole with some success.

- **Lysodren:** This drug actually destroys the cells of the layer of the adrenal gland that secretes cortisol. Since the adrenal glands can regenerate those cells, Lysodren is usually given on an ongoing basis. It is chemically related to DDT, so it is a strong medication that needs to be monitored carefully. It is the standard medical treatment for Cushing's disease in the United States. Initially, a "loading dose" is given, which usually involves giving the drug twice daily at a specified dose, usually for no longer than a week at first. The dog's water intake and food intake are carefully monitored, and if at any time during the induction phase, the dog starts to drink much less water, has any vomiting or diarrhea, or even slows down its appetite, the drug is stopped, and an ACTH stimulation blood test is performed within 24 hours to see if control of cortisol levels has been achieved. If it has not yet been controlled, the Lysodren is given for another few days, under specific instructions from the veterinarian, until control occurs. Otherwise, even if thirst and food habits remain the same at day 8, we still stop the drug and run an ACTH stimulation test, to be sure we do not risk over-treatment. It is impossible to know how much Lysodren each dog will take to achieve "induction" but most of the time control of cortisol levels occurs within 7-14 days. The next phase then begins, called "maintenance". In this phase, the veterinarian chooses a dose of Lysodren to be given 1-3 times per week, which they believe will maintain

control of cortisol levels. An ACTH stimulation test is then done 1 month or so into maintenance, and then perhaps every 3 months thereafter, along with a CBC/Chemistry panel and urinalysis to look for side effects and monitor concurrent conditions.

- We also typically check electrolytes along with the ACTH stimulation test, because Lysodren can occasionally also affect the layer of the adrenal gland that controls electrolytes.
- **Trilostane:** This medication is the standard of care in Europe, but is not yet FDA approved in the US. It is chemically related to RU486, (the “morning after” abortion pill), so any women who are pregnant or are trying to become pregnant should not handle the pills directly. This drug inhibits an enzyme involved in production of several adrenal hormones, including cortisone and aldosterone, so all the same possible effects as seen with Lysodren may occur. The benefit is that it seems to cause less upset stomach due to the drug itself than Lysodren, and its effects usually last < 24 hours with few cases of permanent adrenal suppression occurring. Cost may be an issue for large dogs. Dose is often compounded according to the size of the dog. It is given once to twice daily, and the same signs are watched for as with Lysodren therapy. We usually have the ACTH stimulation test and electrolytes checked about 7-10 days into Trilostane therapy to see if the dose is appropriate. ***It is important to actually *TIME* the ACTH stimulation test to be run 2-4 hours after the Trilostane is given. This standardizes the results for the most accurate interpretation. The dose is highly variable, and over time, a dog may require increasing amounts to maintain control. We usually perform ACTH stimulation test in another month, then every 3-4 months, along with general CBC/Chemistry panel/Urinalysis to monitor for side effects and concurrent illnesses.
- **Deprenyl/ Selegiline/Anipryl®:** This medication works for less than 15% of dogs with PDH. Its action is to alter the brain chemicals that lead to an overactive pituitary. It also has effects that improve “cognitive dysfunction” (senility) in older dogs. It does not improve cortisol levels however, so in advanced cases of Cushing’s disease, it is not an advisable treatment. We use very little of this drug since it is so incomplete in its benefits. It can still be used to manage cognitive dysfunction but would not be expected to effectively treat most cases of Cushing’s syndrome.
- **Ketoconazole:** This is an anti-fungal medication that also inhibits the enzymes that produce cortisol. However, it is much weaker in this effect than Trilostane and over time, more and more of it is needed, and can lead to liver toxicity at higher doses. We do not typically use it to definitively treat Cushing’s, although it has been used in Asia for this purpose.

Addisonian Crisis

It is important to watch for signs of too little cortisol, whenever a dog is on ANY of the medications to control Cushing's. If cortisol levels drop too low, the dog may be weak, lethargic, shaky, anorectic, or experience GI upset. If any of these signs occur at ANY time in a treated Cushing's patient, the veterinarian should be notified. Some veterinarians will provide an emergency supply of prednisone tablets to have at home in case the dog experiences such an event and cannot be taken immediately to a veterinarian. Prednisone will counteract some of the effects of over-treatment for Cushing's, but some dogs actually need to be hospitalized for complications if they get too sick. Also, some dogs are extremely sensitive to the medications and may have other layers of the adrenal gland affected, which might lead to severe electrolyte disturbances or even permanent adrenal gland suppression. The dog then would potentially become reliant on external hormones in the form of a daily prednisone pill and monthly DOCP injections. These complications are usually avoidable if close monitoring of the dog is employed. DO NOT begin an induction regimen when the pet sitter is caring for the dog/primary owner is on vacation, or when it would be impossible to take the dog to a veterinarian that week.

Adrenal Tumors- Treatment

Treatment of adrenal tumors centers around surgical excision of the tumor, if possible. That is because about 50% of these are malignant. Radiation or chemotherapy is not an option for this type of tumor. Sometimes, a CT or MRI scan is advised by the surgeon to try to determine how invasive the tumor is. These tumors can sometimes invade large blood vessels and adjacent organs, so are not always amenable to surgery. The surgery is not a routine surgery, so it is advisable to have a surgical specialist perform the surgery. Dogs with Cushing's are at risk for poor healing, infection, and blood clot formation, so careful monitoring is required postoperatively, and sometimes we put the dog on Lysodren or Trilostane prior to surgery to make the dog stronger. Also, in the few months after surgery, the unaffected adrenal that had been suppressed by the effects of the adrenal tumor must "grow back" and provide enough cortisol to live on. This process may take a month or so, so often prednisone is prescribed at low doses to replace cortisol until the normal tissue recovers function.

In cases where it is determined that the patient is too high of a risk to undergo surgery, or if the tumor is inoperable, it might still be possible to treat medically with Lysodren or Trilostane, but not all tumors will respond to these medications, and the dose might be much higher than the dose used to treat the pituitary dependent form. Doses must be individualized to fit the patient's needs.

Concurrent issues/sequelae:

For either form of the condition, pituitary or adrenal dependent, concurrent management of the ensuing high blood pressure, concurrent infections, proteinuria, urinary incontinence, etc will be required. As the Cushing's disease is controlled, these issues should improve but will likely always require concurrent management, even though they are secondary sequelae.

Prognosis

Cushing's disease is a "quality of life" disease. If left uncontrolled, it is slowly debilitating. Even well controlled dogs with Cushing's still retain some abnormalities that are not 100% controlled, but the pet's quality of life should be much better. There should be improvement in thirst and urination habits, appetite should normalize, panting should improve, and muscle strength should improve. Recurrent infections should be better controlled. Some owners also note that they thought their dog was just getting old and slowing down, but discovered the changes were all due to the effects of the Cushing's disease. Most dogs tolerate the medications well, despite all of the warnings listed above (we just want you to know what to look out for!).

On occasion, removal of the daily excess of cortisol will reveal an underlying inflammatory condition such as arthritis, skin allergies, inflammatory bowel disease etc that must then be treated separately.

Overall, while Cushing's is usually not curable, it is manageable for many years, with most dogs having much improved quality of life once the condition is controlled.

If at any time you are concerned about your pet with Cushing's disease, it is best to discuss it with your veterinarian instead of guessing on your own. These patients can be complex, and may need more frequent monitoring or more extensive monitoring than above if there are concurrent conditions like diabetes.