DANADA VETERINARY HOSPITAL, P.C.

# Cushing's Disease (Hyperadrenocorticism)

Cushing's disease, or hyperadrenocorticism, is a disorder in which the adrenal glands overproduce the hormone cortisol. To understand the disease, one must first understand the normal function of the adrenal system.

The body contains two adrenal glands which sit next to each of the kidneys. Each gland is divided into two layers: the medulla and the cortex. The medulla makes hormones that help the dog respond to stress, regulate metabolism, and maintain the tone of blood vessels. The most significant medullary hormone is adrenaline (epinephrine). The cortex has three layers, and each has its own function. These include regulation of sodium and potassium balance and production of testosterone, estrogen, and steroid (cortisol) hormones.

The adrenals work in combination with the head hormonal gland of the body, the pituitary gland. When more hormones are necessary, the pituitary sends stimulatory signals to the adrenals and hormone production begins. When enough hormones are present, a signal is sent back to the pituitary to let it know the work is done. This feedback stops the stimulatory signals from the pituitary and prevents overproduction of any hormones in the body.

### *Causes of Cushing's*

There are three mechanisms by which this disease can occur. Regardless of the cause, the clinical signs are the same. However, identification of the underlying cause may impact the efficacy of treatment, as well as prognosis for the condition.

**Pituitary-Dependent Hyperadrenocorticism (PDH)** - The most common cause of Cushing's disease (80 - 85% of all cases) is a benign tumor of the pituitary gland. Malignant (cancerous) tumors are rare. The tumor causes the pituitary to overproduce a hormone that, in turn, stimulates the adrenal glands to overproduce cortisol. The tumor may be either microscopic (called a microadenoma) or quite large (called a macroadenoma). Depending on the size of the tumor, the presence of non-Cushing's related signs will be variable. Many dogs with this form of Cushing's disease can live normal lives for many years. However, growth of the pituitary tumor can lead to a poorer prognosis.

**Adrenal Tumor Hyperadrenocorticism (ATH)** - In 10-15% of cases, Cushing's disease is the result of a benign or malignant tumor of the adrenal gland. The tumor continuously produces cortisol regardless of the signals it gets from the pituitary. If benign, surgical removal cures the disease. If malignant, surgery may help for a while, but the prognosis is less favorable than for a benign tumor.

**Iatrogenic** - Iatrogenic Cushing's disease refers to a condition where the over-abundance of cortisol has resulted from excessive administration of a cortisone-containing (steroid) drug. This form often results from chronic high doses of medication used to treat allergies, and auto-immune disorders. Usually most of the signs of Cushing's will resolve if the medication is safely discontinued.

## *Prevalence*

Spontaneous Cushing's is common in dogs over 6 years of age. The average age of onset is approximately ten years of age.

For pituitary-dependent Cushing's (PDH), there are breeds which have an increased incidence of the disease. These breeds include all Poodle breeds, German Shepherd dogs, Beagles, Labrador Retrievers, Dachshunds, Boxers, and some Terrier breeds, including Boston Terriers. It occurs with equal frequency in male and female dogs.

For adrenal tumor Cushing's (ATH), the disease is more common in female dogs and in the larger breeds. These breeds which appear most often affected with ATH include Poodles, German Shepherd dogs, Dachshunds, Labrador Retrievers, and terriers.

## *Clinical Signs*

The most reported clinical signs associated with Cushing's disease are an increase in appetite, water consumption, and urination. Lethargy (lack of activity), panting, and muscular weakness are also seen in many cases. Problems related to the skin and hair coat include thin, easily bruised skin, loss of hair (alopecia), poor healing, and excessive pigmentation.

Many of these dogs develop a bloated appearance. This happens because of liver swelling (hepatopathy) along with weakening of the abdominal muscles. Infrequently, neurologic signs are seen. These signs include but are not limited to seizures, altered behavior, and incoordination.

Many Cushing's patients may experience frequent or recurrence infections of the skin, ears, urinary tract, and/or sinuses as a result of steroid suppression of the immune system.

## *Diagnosis*

A number of tests are necessary to diagnose and confirm Cushing's disease. Initially, routine blood chemistry is done to rule out other similar conditions such as hypothyroidism, kidney disease, etc. Commonly the liver enzyme Alkaline Phosphatase (ALP) is elevated because of excess steroids in the body. While this finding is not diagnostic for Cushing's, an elevated ALP coupled with clinical signs raises the level of suspicion and warrants testing to confirm the disease.

A urine test can be performed to measure the resting level of cortisol in the body. This test is only useful for ruling out, rather than confirming Cushing's. If the cortisol level is normal, the patient does not have Cushing's disease. However, stress and other factors often push resting cortisol levels above normal limits, so if the test is elevated, further confirmation tests are needed.

There are two common tests that are used to confirm a diagnosis of hyperadrenocorticism. The first is an **ACTH Stimulation Test**. This test involves administration of a stimulating hormone followed by measurement of cortisol levels in the blood. Cushing's patients usually have an exaggerated level of cortisol in the blood following administration of ACTH. ACTH Stimulation is a good screen test for Cushing's, but false negative results can occur. It remains the best test for monitoring therapy of Cushing's and for diagnosing iatrogenic Cushing's when suspected.

An alternative option for testing is a **Low Dose Dexamethasone Suppression Test (LDDST)**. The patient is given a dose of steroid which typically suppresses the naturally occurring (endogenous) cortisol of the body. The test then measures the endogenous cortisol at four and eight hours after drug administration. Cushing's patients will have little or no suppression of cortisol levels at either interval. This test is the gold standard for diagnosis of Cushing's due to its accuracy and ability to sometimes distinguish PTH from ATH.

In some cases, additional tests may be necessary to decipher the cause of Cushing's. These may include a High Dose Dexamethasone Suppression Test or abdominal ultrasound.

### *Treatment*

**Pituitary Dependent Cushing's**-There is no cure for PDH, but treatment is very effective at controlling symptoms. Medication is given to limit the release of cortisol, or in some cases destroy a portion of the adrenal cortex responsible for cortisol production. The treatment does not limit the signals from the pituitary, and therefore effective control requires life-long treatment. There are multiple drugs available to treat PDH, but the most common are Trilostane (Vetoryl) and Mitotane (Lysodren).

**Trilostane** is an enzyme inhibitor that decreases the adrenal gland's ability to make cortisol. It must be dosed once or twice daily to remain effective. ACTH Stimulation tests are required at periodic intervals to monitor progress. This is the most utilized treatment in the United States.*

**Lysodren** (also known as mitotane or o'p'-ddd) is a tissue-specific chemotherapy that slowly destroys the layer of the adrenal cortex responsible for steroid production. This medication is also very effective and can be weaned down to a point where doses can be given one or two times each week. However, if too much drug is used, most or all of the adrenal cortices will be destroyed. This can lead to a condition where cortisol levels become dangerously low. Therefore, careful monitoring of the dog is necessary to achieve good results.**

**Adrenal Tumor** -With some adrenal tumors, especially the benign form (adenoma), good results can be achieved with drug therapy alone. Trilostane is the drug of choice, but Lysodren can also be used. While surgery can be curative for some forms of adrenal tumors, it is potentially very dangerous to the dog, even when performed by skilled surgeons, because the tumor is typically surrounded by large blood vessels.

**Iatrogenic Cushing's Disease**-Treatment of this form requires discontinuation of the cortisone-containing medication. This must be done in a very controlled manner so that side-effects do not

occur from withdrawal of the drug. When a prolonged course of cortisone therapy is necessary, the adrenal glands will atrophy and need time to “relearn” their normal functions. Abrupt stoppage of the steroid medication will not allow the adrenals the time they need to acclimate, and signs of low steroid levels (profound lethargy, vomiting, diarrhea) may result.

## *Prognosis*

Dogs with ADH caused by a benign tumor have a good prognosis whereas the prognosis is guarded with the malignant form (adenocarcinoma). The prognosis with PDH is variable depending upon whether the tumor is a small tumor (microadenoma) or large tumor (macroadenoma), presence of concurrent medical problems, and willingness of the owner to continue with treatment and monitoring. Most issues impacting prognosis revolve around whether the patient experiences an adequate quality of life with their level of symptom control.

### **Typical Trilostane Therapy*

Start on Trilostane once to twice daily as prescribed by your veterinarian.

Recheck in 10-14 days for an ACTH Stimulation test 4-6 hours following the dosing of medication.

ACTH Stimulation testing is performed every 10-14 days until the proper dose is determined. At that time, the dose will be continued, and ACTH stimulation testing will be repeated 30, and 90 days after therapy is started. After that, ACTH Stimulation is performed every 3-4 months in most cases unless symptoms are not well controlled.

### ***Typical Lysodren Therapy*

Treatment with Lysodren involves an initiating phase and a maintenance phase.

The **initiating phase** arrests the disease and restores the dog to a more normal state. Some of the clinical signs, especially increased food, and water intake, should stop within the first 1-3 weeks. Other signs, such as a poor hair coat or a bloated abdomen, may take several weeks or months to correct.

1) During this phase, Lysodren is given twice daily until one of the following occurs:

a. Your dog's water intake drops to the 1 oz per pound (14 cc per kilogram) per day.

b. Your dog's appetite returns to normal, or it takes 15-30 minutes to eat when it would normally eat in much less time.

c. Your dog does not finish a regular meal.

d. Your dog vomits, has diarrhea, or is unusually listless.

e. You reach the 9-day mark from which you started the Lysodren dosing.

2) When one of the above criteria is met, your pet should return for another ACTH stimulation test. This test should be done early in the morning and will require your dog to be in the hospital for about two-three hours. If the test is abnormal, the initiating phase will continue. If the test is normal, the maintenance phase will begin.

3) Prednisolone/Prednisone Rescue Therapy - During the initiation phase clinical signs of illness are attributable to the drop in cortisol. If loss of appetite, vomiting, diarrhea, or listlessness occurs, oral prednisolone is started to help manage these symptoms, and the Lysodren therapy is stopped until testing can be performed. If vomiting prevents oral administration, your dog must be seen by a veterinarian for administration of proper medication by injection.

4) Report Any Other Changes in Your Dog's Behavior-This disease and this treatment can result in several abnormal behaviors. However, your dog can also have other diseases that occur concurrently but independently of Cushing's disease. It is important that we differentiate between the two situations so that proper treatment can be taken.

The **maintenance phase** represents the phase of long-term therapy. This phase lasts the rest of the dog's life. You must continually monitor your dog's food and water intake. We expect both to return to a normal level. Water intake should be less than 1 oz per pound of body weight per day, but do not limit the water if your dog needs to drink more. The food amount should be measured each day to determine how much your dog is finishing. At least two feedings per day are preferred. When regulated, most dogs will only need to take Lysodren approximately once weekly, and side effects from both the medication and the Cushing’s should be minimal. An ACTH stimulation test will be necessary about every 3-6 months to be sure that regulation is satisfactory.