Cushing's Disease

Introduction and Overview

Cushing's disease is the term commonly used to identify a condition that results from the over-production of cortisol by the adrenal glands, two small glands located near the kidneys. Cortisol, a hormone that is important for regulating the metabolism of proteins, fats and carbohydrates, is produced by specialized cells comprising the outer or cortical portion of the adrenal glands. As a result, this condition also is called hypercortisolism (hyper = excessive, cortisolism = involving cortisol) or hyperadrenocorticism (hyper = excessive, adrenocorticism = involving the adrenal cortex). The term 'Cushing's Disease' often is used to describe this condition, which is named in honor of Harvey Cushing, an American neurosurgeon who first described the clinical syndrome in people in 1932. In his original publication, the underlying problem was a tumor in the pituitary gland in the brain that affected the adrenal glands and caused a variety of clinical signs and symptoms including high blood pressure, weight gain, fatigue, impaired immune function, and excessive deposition of fat on the sides of the face.

Cushing's disease typically occurs in middle-aged and older dogs of all breeds, with no predilection for either gender. The most common symptoms associated with the condition related to the urinary system include increased thirst (polydipsia) and urination (polyuria). Affected dogs also have changes in the musculoskeletal system, which include decreased muscle mass, muscle weakness, obesity, excessive fat on the neck and shoulders, a pot-bellied abdomen, and lack of energy. Skin manifestations of the condition include hair loss (alopecia), thin skin, bruising, hyperpigmentation, and white scaly patches on the elbows.

Pathogenesis of Cushing's Disease

Under normal conditions, cortisol production is indirectly controlled by a hormone, corticotropin-releasing hormone (CRH), released by a region of the brain called the hypothalamus. The hypothalamus releases this hormone under two circumstances. One is governed by the animal's diurnal rhythm, which is related to the normal sleep-wake cycle. Early in the morning, the hypothalamus releases CRH, which then stimulates the pituitary gland, which is located at the base of the brain, to release adrenocorticotropic hormone or ACTH into the blood, which then results in an increase in production of cortisol by the adrenal gland. As a result, blood levels of cortisol are highest in the morning, and these increased circulating concentrations of cortisol result in negative feedback on both the hypothalamus and the pituitary gland to reduce both CRH and ACTH. As a result, circulating concentrations of cortisol decrease and reach their lowest values at night. The other stimulus for increased cortisol secretion is stress, which again stimulates the hypothalamus to release CRH, which enhances ACTH production, and eventually increases cortisol production.

Cushing's disease occurs commonly in dogs, with more than 80% of cases being the result of a pituitary tumor called an adenoma that secretes ACTH. In dogs with pituitary adenomas, production of ACTH no longer responds to the negative feedback signal normally associated with cortisol production.

Common Clinical Findings
Middle-Aged and Older Dogs
Polydipsia
Polyuria
Obesity
Pot-Bellied Abdomen

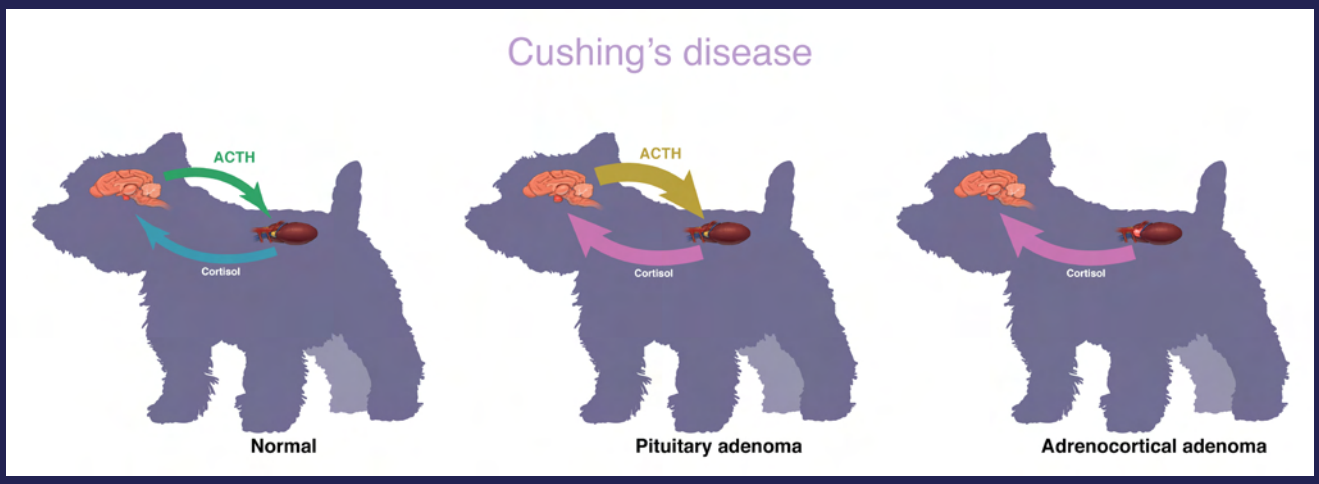

Figure 1 - This illustration depicts the normal interaction between the pituitary and adrenal glands, the effect of a pituitary adenoma on secretion of both ACTH and cortisol, and the effect of an adrenocortical adenoma on secretion of cortisol.

As a result, the cells in the adrenal cortex continue to secrete cortisol, resulting in hypercortisolism and Cushing's disease (***Figure 1***).

In a relatively small number of dogs, typically reported to be ~15% of cases, hypercortisolism occurs independent of ACTH secretion and is due to a cortisol-secreting tumor in the adrenal gland. In rare instances, the condition may occur secondary to chronic administration of corticosteroids used in the treatment of diseases caused by allergies, autoimmune or inflammatory responses, or neoplasia.

Clinical Signs and Symptoms of Cushing's Disease

Cortisol has important effects on metabolism of carbohydrates, proteins and fats. For example, it increases blood concentrations of glucose by inhibiting the uptake of glucose into cells and by stimulating the production of new glucose molecules by the liver. It also stimulates the degradation of protein and adipose tissue. When production of cortisol is excessive, as occurs in animals with Cushing's disease, the end result is very high blood concentrations of glucose, loss of glucose into the urine, which also occurs in dogs with diabetes mellitus, loss of structural proteins, muscle weakness and fatigue. For reasons that are unclear, some of the extra glucose is converted into fat and is deposited in the abdomen. Cortisol also interferes with kidney function, causing increased urination which in turn causes the animal to drink large amounts of water in order to replace what is lost in the urine.

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Laboratory Diagnosis of Cushing's Disease

Based on the animal's history and physical examination findings, veterinarians suspecting that the underlying problem might be Cushing's disease measure cortisol concentrations in plasma or urine samples. It is important to note, however, that some dogs may have less obvious clinical signs and symptoms. Other findings that occur frequently in dogs with Cushing's disease include increased plasma activity of the alkaline phosphatase enzyme, high levels of lipids in the blood, and a reduced concentration of thyroxine (T4).

A diagnosis of hypercortisolism is based on a combination of the clinical signs, increased circulating concentrations of cortisol or the presence of cortisol in the urine, and a reduced sensitivity of the pituitary-adrenocortical system to the negative feedback effect that normally occurs in response to administration of a synthetic cortisol-like compound, referred to as a glucocorticoid. To perform this latter test, the veterinarian will measure blood concentrations of cortisol before, 4 and 8 hours after administering a synthetic glucocorticoid, such as dexamethasone. In healthy dogs, dexamethasone will exert a

negative feedback on the production of ACTH by the pituitary gland and significantly reduce blood concentrations of cortisol at the later time points. In contrast, an ACTH-producing pituitary tumor will not respond to the synthetic glucocorticoid and circulating cortisol concentrations will remain unchanged or be decreased only at the 4-hour time point. Because some dogs with illnesses unrelated to the adrenal glands may respond similarly, this test is not 100% reliable for making a diagnosis of hypercortisolism.

In many practices, additional emphasis is placed on the measurement of cortisol in the urine. This is because urine accumulates in the bladder before being voided, which minimizes the concern over potential fluctuations in concentrations of cortisol that may occur as the result of other stresses (e.g., a visit to the veterinarian's office). In most instances, urine concentrations of cortisol are related to those of creatinine and these measurements are made in urine samples collected on several consecutive days.

While it would appear logical that dogs with ACTH-producing pituitary tumors could easily be identified by measuring concentrations of ACTH in the circulation, this is not the case. This is because some dogs with hypercortisolism secondary to a pituitary tumor have normal circulating concentrations of ACTH. If, however, the hypercortisolism has developed as the result of a tumor in the adrenal cortex, this laboratory test is extremely important. Dogs with adrenocortical tumors will have extremely low circulating concentrations of ACTH, which makes it much easier to distinguish between hypercortisolism caused by a pituitary tumor or an adrenocortical tumor.

Treatment of Cushing's Disease

Many factors enter into the decision about how best to treat dogs with hypercortisolism. These include the underlying cause, other diseases that might exist (e.g., neoplasia), cost of treatment, and the client's preference. Fortunately, immediate treatment is not required in all dogs with hypercortisolism, particularly those exhibiting mild clinical signs.

When hypercortisolism is the result of a pituitary tumor, the condition can be treated either medically or surgically. Medical treatment of the condition involves administration of drugs that either reduce the production of ACTH by the pituitary tumor or the production of cortisol by the adrenal cortex. The most commonly used drug is trilostane, a synthetic steroid that inhibits one or more of the enzymes responsible for the synthesis of cortisol by cells in the adrenal cortex. The duration of effect (i.e., how long circulating concentrations of cortisol remain decreased) varies among dogs, which accounts for why once-daily administration is not effective in some dogs. As a result, the dosage may need to be increased or the drug administered more often to achieve the desired effect. Adjustments in the dose of trilostane are based on repeated assessments of clinical signs and the results of routine blood tests, such as determination of alkaline phosphatase concentrations. Typically improvements in the dog's status will be apparent in 7 to 10 days, but associated skin problems may require months to resolve.

The other drug that is commonly used to treat dogs with hypercortisolism is mitotane, a drug that causes destruction of the cells in the adrenal cortex that produce cortisol. To determine whether or not treatment with mitotane has achieved the desired results, the veterinarian will perform ACTH stimulation tests. The ultimate goal of treatment with mitotane is to reduce resting concentrations of cortisol and to see little, if any, increase after the administration of ACTH. When this has been achieved, it may be necessary to provide exogenous glucocorticoids during periods of high stress or illness.

Hypercortisolism in dogs with pituitary tumors also can be treated surgically or with radiation therapy. The surgical procedure is performed by cutting through the sphenoid bone beneath the pituitary gland and removing the tumor. Response to surgical treatment has been reported to be very good, and compares favorably with those reported for dogs treated medically as described above. The other approach involves the use of radiation therapy to reduce the size of the tumor. Outcomes with radiation therapy have been variable, with optimal responses occurring in dogs with small tumors.

When hypercortisolism is caused by a functional adrenocortical tumor, treatment is surgical removal of the tumor. If the entire tumor cannot be removed, mitotane can be administered to cause destruction of the tumor and associated adrenal cortical cells.

Current Research About Cushing's Disease

Cushing's disease affects about 100,000 dogs each year in the US. Because this condition also occurs in people, the approaches used to treat humans have been applied to dogs. While these approaches have markedly improved the prognosis in humans, questions remain about how best to treat the condition in dogs, how to improve the results obtained with surgical intervention, and how to more fully understand the effects of the disease. For these reasons, in this section we review three recent studies related to the most common form of the disease, namely pituitary-dependent hypercortisolism.

van Rijn SJ, Galac S, Tryfonidou MA, Hesselink JW, Penning LC, Kooistra HS, Meij BP. The Influence of Pituitary Size on Outcome After Transsphenoidal Hypophysectomy in a Large Cohort of Dogs with Pituitary-Dependent Hypercortisolism. J Vet Intern Med. 2016 Jul;30(4):989-95.

Surgical treatment of dogs with pituitary-dependent hypercortisolism consists of removal of the pituitary gland by a transsphenoidal approach, which is similar to the approach used in humans with the disease. Since the early 1990s, this surgery has been performed on dogs with this condition, with remission rates exceeding 80%. In earlier studies, one of the main prognostic factors for long-term remission in dogs was pituitary gland size. Consequently, the goal of this project was to further investigate the influence of pituitary gland size on outcome in a large number of dogs treated using this surgical approach over a 20-year period. To do this, the investigators determined survival times and recurrence rates for 306 dogs and related these variables to the pituitary gland size. Four weeks after surgery, 91% of dogs were alive and remission was confirmed in 92%. The median survival time was 781 days, median disease-free interval was 951 days. Over time, hypercortisolism recurred in 27% of dogs after a median period of 555 days. Dogs with recurrence had a significantly higher ratio of the area of the pituitary height to the area of the brain area. The survival time and disease-free interval of dogs with enlarged pituitary glands was significantly shorter than that of dogs with a nonenlarged pituitary gland. The size of the pituitary at the time of surgery significantly increased over the 20-year period. Although dogs with larger tumors have a less favorable prognosis, the outcome for dogs with larger tumors improved over time. These findings suggest that pituitary gland surgery remains an option for treatment of dogs with large tumors, and that success rates increase with increasing experience.

Fracassi F, Malerba E, Furlanello T, Caldin M. Urinary excretion of calcium and phosphate in dogs with pituitary-dependent hypercortisolism: case control study in 499 dogs. Vet Rec. 2015 Dec 19;177(24):625.

Pituitary-dependent hypercortisolism in dogs often is characterized by high circulating concentrations of phosphate. The goal of this study was to compare serum and urinary concentrations of phosphate and the degree to which phosphate and calcium are excreted into the urine in healthy dogs and 167 dogs with this disease. Serum concentrations of phosphate in dogs with pituitary-dependent hypercortisolism were significantly greater than those either in healthy dogs or in dogs with other diseases. Serum concentrations of calcium also were significantly higher in dogs with hypercortisolism than in dogs with other diseases. Dogs with hypercortisolism excreted less phosphate but more calcium than either healthy dogs or dogs with other diseases, whereas excretion of calcium was higher. These findings suggest that the high serum concentrations of phosphate in dogs with pituitary-dependent hypercortisolism are due, at least in part, to retention of phosphate by the kidneys.

Mamelak AN, Owen TJ, Bruyette D. Transsphenoidal surgery using a high definition video telescope for pituitary adenomas in dogs with pituitary dependent hypercortisolism: methods and results. Vet Surg. 2014 May;43(4):369-79.

Even though surgical removal of pituitary adenomas has been performed successfully in dogs for many years, it has not been used widely because it is both technically challenging and expensive. The two most commonly encountered difficulties are accurately defining the appropriate borders of the basisphenoid bone and illuminating the surgical site. To address these problems, these investigators used a new high definition video telescope to remove tumors from 26 dogs with pituitary dependent hypercortisolism. They modified the traditional surgical approach, observed the procedure using a high definition video telescope, and improved their ability to localize the site by drilling pilot holes in the basisphenoid bone followed by computed tomography. Overall, the mortality rate was 19%, with 0 deaths occurring in the last 16 dogs. The investigators reported sustained tumor remission and normalization of laboratory findings in 20/21 (95%) dogs at 1-year follow-up. They concluded that the modified trans-oral approach is a safe and effective strategy for long-term remission of hypercortisolism occurring secondary to pituitary adenomas.

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