

# Diagnosis of hyperadrenocorticism in dogs

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**ABSTRACT:** *Hyperadrenocorticism is a common condition in older dogs. It arises when feedback mechanisms within the hypothalamic-pituitary-adrenal axis fail, resulting in a chronic excess of blood cortisol. The most common cause of canine hyperadrenocorticism is a microscopic, benign, pituitary gland tumour, with fewer cases caused by adrenal tumours or chronic corticosteroid administration. Diagnosis of the condition can be challenging. Clinical findings are varied, and many are common to other conditions. Screening tests are also non-specific, and there is no single test available for its definitive diagnosis. Consequently, a combination of history, clinical signs, and laboratory findings are important in diagnosing hyperadrenocorticism.*

## INTRODUCTION

Commonly known as Cushing's disease, hyperadrenocorticism describes a condition in which there is chronic exposure to high levels of glucocorticoids, whether of endogenous or exogenous origin. Although rare in cats, this disorder is possibly the most common endocrinopathy of older dogs, and studies have estimated its incidence at one or two cases per 1000 dogs annually. Most affected dogs tend to be middle-aged or older, although cases do occur in younger dogs too. This article will highlight some of the main aspects of the pathogenesis of this disease in dogs, as well its clinical features and some of the tests used in its evaluation.

## PATHOPHYSIOLOGY

The hypothalamic-pituitary-adrenal (HPA) axis represents the primary control centre for cortisol production, and knowledge of this integrated endocrine unit is critical in order to understand hyperadrenocorticism and its diagnosis.

The hypothalamus serves as the integrating centre for most of the body's endocrine systems, and its paraventricular nuclei produce corticotropin releasing factor (CRF). This subsequently binds to receptors in the anterior pituitary gland, leading to adrenocorticotrophic hormone (ACTH) production. Following its transport to the adrenal glands, ACTH then stimulates production of cortisol by the *zona fasciculata* and *zona reticularis* of the adrenal cortices. Control of CRF and ACTH release is by negative feedback by cortisol at both the hypothalamic and pituitary levels.

## CAUSES

When presented with a patient with hyperadrenocorticism, it is important to determine its cause. This is a treatable condition, and differentiating between a pituitary and adrenal origin is necessary because the underlying cause will ultimately influence the treatment regime.

There are several possible causes of hyperadrenocorticism, and the condition can be either **spontaneous** or **iatrogenic**.

### Spontaneous cases

#### **Pituitary-dependent**

Most cases of canine hyperadrenocorticism arise spontaneously as a result of excess levels of endogenous cortisol. Approximately 80% of these are pituitary-dependent, arising due to an adenoma or hyperplasia of the pituitary gland (usually of the *pars distalis*, although some originate in the *pars intermedia*). In these cases, the hyperadrenocorticism is ACTH dependent, resulting from hypersecretion of ACTH by the abnormal pituitary gland. Excess ACTH then results in bilateral adrenocortical hyperplasia and hypertrophy, with subsequent cortisol hypersecretion.

#### **Adrenal-dependent**

The remaining 20% of cases are adrenal-dependent, arising from hypersecretion of cortisol by an adrenocortical tumour (adenoma or carcinoma), or even bilateral adrenocortical nodular hyperplasia. Of those dogs with adrenal-dependent disease, half of the cases are due to malignant tumours and half are due to benign cases.

In these cases, the hyperadrenocorticism is ACTH independent, arising due to excess cortisol from the abnormal adrenal gland. Here, the HPA axis feedback loop performs normally, inhibiting secretion of ACTH and CRF, causing atrophy of the uninvolved adrenocortical tissue.

### Iatrogenic cases

Some cases of hyperadrenocorticism arise as a result of excess levels of cortisol of exogenous origin, caused by long-term therapy with drugs that contain corticosteroids.



## HISTORY, CLINICAL FEATURES AND LABORATORY FINDINGS

Cortisol affects the function of many body systems, so the signs of hyperadrenocorticism are varied. Prolonged exposure to excessive concentrations of free plasma cortisol leads to various biochemical and physical changes, and these give rise to the characteristic features of the disease.

### Signalment

Spontaneous hyperadrenocorticism occurs predominantly in middle-aged and older dogs. There is no gender predilection, and although all breeds can be affected, there may be a higher incidence in smaller breeds such as miniature poodles, small terriers and dachshunds.

### Clinical signs

Characteristic clinical signs in dogs include polyuria and polydipsia, polyphagia, weight gain, muscle atrophy and weakness. The most common physical abnormalities include abdominal enlargement and hepatomegaly, as well as dermatological changes such as symmetrical alopecia, thinning of the skin, seborrhoea, pyoderma and comedone formation.



**Fig. 1:** Bichon Frise showing typical signs of hyperadrenocorticism. (Image courtesy of Grant Petrie.)

### Laboratory findings

#### Haematology

A stress leukogram due to excess cortisol is a common finding in dogs with hyperadrenocorticism. This comprises: mature neutrophilia, monocytosis, lymphopenia and eosinopenia.

#### Biochemistry

Dogs with hyperadrenocorticism commonly have increases in blood glucose, cholesterol and serum alkaline phosphatase.

#### Urinalysis

Typical urinalysis findings include low specific gravity and proteinuria. Urine may also culture positive for bacteria. The excess levels of cortisol suppress the immune system, and secondary bacterial infections are common, especially in the urinary tract.

## DIAGNOSTIC EVALUATION

If the history, clinical signs and laboratory findings are suggestive of hyperadrenocorticism and there is no evidence of an iatrogenic aetiology, subsequent diagnostic evaluation is necessary.

Unfortunately, there is no single, best test to detect hyperadrenocorticism. Measuring plasma cortisol concentration on a single occasion is of no diagnostic value because ACTH release is pulsatile. This results in variable plasma cortisol concentrations that can lie within the normal range at times.

Consequently, diagnostic evaluation of hyperadrenocorticism involves initial screening tests followed by differentiating tests.

### SCREENING TESTS

Screening tests detect whether or not hyperadrenocorticism is present. Some, but not all, can additionally help to differentiate between an adrenal and pituitary origin of the condition.

#### Urinary cortisol:creatinine ratio (UCCR)

The UCCR measures urinary corticosteroids. Excess circulating corticosteroids spill over into the urine, and therefore urinary cortisol concentration is a reflection of their production by, and circulation from the adrenal cortex. Creatinine measurements are used to adjust for urine dilution.

The sensitivity of this test is high, but it has a low specificity. Consequently it is considered useful to rule out hyperadrenocorticism, but not to rule it in. Confirmation of the disease in patients with an increased UCCR therefore requires further evaluation using the low-dose dexamethasone suppression test (LDDST) or ACTH stimulation test.

The UCCR is becoming increasingly used in favour of the LDDST. It requires little time for the veterinary surgeon or the owner, requires no blood collection and has a high diagnostic accuracy. Certainly in cases where there is just a slight possibility of hyperadrenocorticism, this test may be the quickest and least expensive one to use initially.

#### Low dose dexamethasone suppression test (LDDST)

This test measures and compares the levels of cortisol in an animal's bloodstream before and after an injection of dexamethasone. The low dose of dexamethasone will inhibit cortisol production by the adrenal cortex in normal dogs. Failure of cortisol suppression, on the other hand, is indicative of hyperadrenocorticism in the patient.

This test also has a high sensitivity, and a higher specificity than the UCCR. If you are relatively certain that your patient has hyperadrenocorticism,

based on history, clinical signs and other test results, the LDDST or combined dexamethasone suppression/ACTH stimulation test may be the best option to screen for the condition (and also to differentiate its origin).

#### **ACTH stimulation test**

The ACTH stimulation test evaluates the adrenocortical reserve capacity, and therefore its main use is to differentiate between primary and secondary adrenal insufficiency. It is also the only test that distinguishes between iatrogenic and spontaneous hyperadrenocorticism, although it cannot differentiate between a pituitary and adrenal origin. It is also used to monitor the effectiveness of therapy.

This test measures and compares levels of cortisol in an animal's bloodstream, before and after an injection of ACTH. Post-injection plasma cortisol concentrations that are below normal represent a reduced response to ACTH administration, indicative of adrenocortical atrophy, as occurs in iatrogenic hyperadrenocorticism or hypoadrenocorticism (Addison's disease). On the other hand, concentrations that are higher than in normal dogs represent an exaggerated response to ACTH administration, indicative of spontaneous hyperadrenocorticism.

Of all the screening tests, this has the highest specificity, as well as a relatively high sensitivity. It is also the only screening test that can be performed on animals with clinical signs of hyperadrenocorticism who have had recent or are currently receiving corticosteroid therapy.

#### **Combined dexamethasone suppression/corticotropin stimulation test**

This test screens for the presence of hyperadrenocorticism (via the ACTH stimulation test) and may also differentiate between cases of pituitary or adrenal gland origin (via a shortened version of the high-dose dexamethasone suppression test [HDDST]). It measures and compares levels of cortisol in an animal's bloodstream before and after an injection of dexamethasone and a subsequent ACTH injection once the post-dexamethasone blood sample is obtained.

In an animal that responds normally to the ACTH stimulation portion of the test, but resists dexamethasone suppression, hyperadrenocorticism is confirmed.

This test is favoured less than its counterparts though, since the shortened version of the HDDST is less reliable than the standard version. Additionally, administration of dexamethasone 4–6 hours prior to ACTH stimulation can influence the cortisol levels seen in response to the ACTH. Consequently there is more variability in the ACTH-stimulated cortisol response to ACTH with this combined test, than with the standard ACTH stimulation test alone.

#### **DIFFERENTIATING TESTS**

Once a diagnosis of hyperadrenocorticism is confirmed via screening tests, differentiating tests are necessary to determine whether the origin of the disease lies in the pituitary or adrenal gland.

#### **High dose dexamethasone suppression test (HDDST)**

As with the LDDST, this test measures and compares the levels of cortisol in an animal's bloodstream before and after an injection of dexamethasone. In this case, however, the higher dose of dexamethasone will inhibit production of cortisol in animals with pituitary-dependent disease, but not adrenal-dependent disease. However, approximately one in four dogs with pituitary-dependent hyperadrenocorticism fail to suppress cortisol levels in response to the high dose of dexamethasone, so a failure to suppress cannot be interpreted as a definitive diagnosis of an adrenal tumour. As mentioned earlier, too, although the LDDST and combined dexamethasone suppression/corticotropin stimulation test are used as screening tests, they may also serve as differentiating tests.

Currently, the tests most commonly used to differentiate between pituitary- and adrenal-dependent hyperadrenocorticism are the ACTH stimulation test and the HDDST.

#### **Corticotropin (ACTH) assay**

This assay measures endogenous concentrations of ACTH and is considered to be the most accurate means of differentiating between pituitary-dependent and adrenal-dependent hyperadrenocorticism. Additionally, it has the advantage of requiring only a single blood sample.

In dogs with an adrenal tumour, ACTH levels are low-normal to undetectable. In dogs with pituitary-dependent disease, however, ACTH levels are high-normal to high.

#### **DIAGNOSTIC IMAGING**

Radiography, abdominal ultrasonography, computed tomography and magnetic resonance imaging of the brain or adrenal glands can also be used to differentiate between the different origins of hyperadrenocorticism. Although all have advantages and disadvantages for this purpose, abdominal ultrasonography tends to be the technique most readily available, and therefore most widely used, to evaluate the cause of hyperadrenocorticism in dogs. This procedure allows for ready detection of small, unilateral adrenal gland tumours, as well as detection of bilateral adrenal enlargement in dogs with pituitary-dependent hyperadrenocorticism.

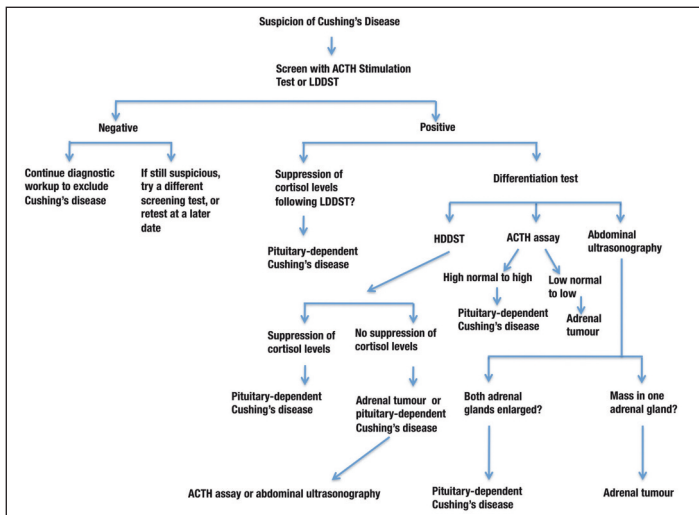


Fig. 2: Diagnostic Algorithm for Canine Hyperadrenocorticism.

## SUMMARY

Initially, testing is typically directed at confirming excessive production of glucocorticoids. Unfortunately though, there is no single ideal screening test for hyperadrenocorticism.

Adding to the complexity of diagnostic screening, however, is the fact that all of the tests can produce false positive or false negative results. Thus, multiple tests may be necessary for optimal diagnostic evaluation. Importantly too, the practitioner's level of clinical suspicion also plays an essential role in interpreting the test results and subsequently diagnosing hyperadrenocorticism.

Despite the numerous tests, each with its own limitations, the predictive value of a positive screening test result increases in proportion to the number and severity of clinical signs and laboratory changes suggestive of the disease. So the importance of using history, clinical signs and other laboratory findings in making a diagnosis of hyperadrenocorticism cannot be underestimated.

## FURTHER READING

DUESBERG, C. and PETERSON, M. E. (1997) Adrenal disorders in cats. *Veterinary Clinics of North America Small Animal Practice* 27:321-347.

WILLEBERG, P., PRIESTER, W. A. (1982) Epidemiological aspects of clinical hyperadrenocorticism in dogs (canine Cushing's syndrome). *Journal of the American Veterinary Medical Association* 18:717-724.

ZERBE, C. (1999) The hypothalamic-pituitary-adrenal axis and pathophysiology of hyperadrenocorticism. *Compendium on Continuing Education for the Practising Veterinarian* Vol 21 (12): 1134-1137.

ZERBE, C. (2000) Differentiating tests to evaluate hyperadrenocorticism in dogs and cats. *Compendium on Continuing Education for the Practising Veterinarian* Vol 22 (2): 149-156.

ZERBE, C. (2000) Screening tests to diagnose hyperadrenocorticism in cats and dogs. *Compendium on Continuing Education for the Practising Veterinarian* Vol 22 (1): 17-31.

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These multiple choice questions are based on the above text. Answers appear on page 47 of the print version, and as supporting information in the online version of this article.

**1. Which test(s) differentiate(s) between iatrogenic and spontaneous cases of hyperadrenocorticism:**

- Low dose dexamethasone suppression test
- High dose dexamethasone suppression test
- Urinary cortisol:creatinine ratio
- ACTH stimulation test

**2. All are common dermatological manifestations of hyperadrenocorticism, except:**

- Thickening of the skin
- Seborrhoea
- Comedones
- Pyoderma

**3. Which serves as both a screening and differentiating test for hyperadrenocorticism:**

- ACTH stimulation test
- Combined dexamethasone suppression/corticotropin stimulation test
- High dose dexamethasone suppression test
- Urinary cortisol:creatinine ratio