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DIAGNOSING CANINE HYPERADRENOCORTICISM

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Hyperadrenocorticism is associated with excessive production or administration of glucocorticoids and is one of the most commonly diagnosed endocrinopathies in the dog.

Aetiology

Hyperadrenocorticism can be spontaneous or iatrogenic. Spontaneously occurring hyperadrenocorticism may be associated with inappropriate secretion of ACTH by the pituitary (pituitary-dependent hyperadrenocorticism) or associated with a primary adrenal disorder (adrenal-dependent hyperadrenocorticism).

Pathophysiology

Pituitary-dependent hyperadrenocorticism

Pituitary-dependent hyperadrenocorticism accounts for over 80% of dogs with naturally occurring hyperadrenocorticism. Excessive ACTH secretion results in bilateral adrenocortical hyperplasia and increased cortisol secretion. There is a failure of the negative feedback mechanism of cortisol on ACTH. However, episodic secretion of ACTH results in fluctuating cortisol concentrations that may at times be within the normal range.

Pathological changes in pituitary-dependent hyperadrenocorticism include microadenomas and macroadenomas of the corticotroph cells and a primary failure of the negative feedback response. Microadenomas are less than 1 cm in diameter. In one study using immunocytochemical staining, more than 80% of dogs with pituitary-dependent hyperadrenocorticism were positive for pituitary adenomas.

Macroadenomas are larger than 1 cm in diameter and only a small percentage of dogs have large corticotroph adenomas. These may compress the remaining pituitary gland and extend dorsally into the hypothalamus. However, they are generally slow growing and do not always produce neurological signs. Malignant pituitary tumours are rare.
Adrenal-dependent hyperadrenocorticism

The remaining 15–20% of spontaneous cases of hyperadrenocorticism in dogs and cats are caused by unilateral or bilateral adrenal tumours, which can be benign or malignant.

Adrenocortical adenomas are small, well-circumscribed tumours that do not metastasise and are not locally invasive. Approximately 50% are partially calcified. Adrenocortical carcinomas are usually large, locally invasive, haemorrhagic, and necrotic. Tumour calcification also occurs in about 50% of dogs. The tumours frequently invade the phrenicoabdominal vein and caudal vena cava and metastasise to the liver, lung and kidney.

In dogs, adrenocortical adenomas and carcinomas occur in approximately equal proportions. The cortex contiguous to the tumour and that of the contralateral gland become atrophied in the presence of functional adenomas and carcinomas. This is important if the tumour is removed surgically as post-operatively the animal may not be able to secrete sufficient glucocorticoids.

Clinical signs

Any breed of dog can develop hyperadrenocorticism but Poodles, Dachshunds and small terriers, for example the Yorkshire Terrier, Jack Russell Terrier, and Staffordshire Bull Terrier, appear more at risk at developing pituitary-dependent hyperadrenocorticism. Adrenocortical tumours occur more frequently in larger breeds of dog. No breed predisposition has been recorded in cats.

Pituitary-dependent hyperadrenocorticism is usually a disease of the middle-aged to older dog, with an age range of 2–16 years and a median age of 7–9 years. Dogs with adrenal-dependent hyperadrenocorticism tend to be older with a range of between six and 16 years and a median age of 10–11 years.

There is no significant difference in sex distribution in pituitary-dependent hyperadrenocorticism; however, female dogs are three times more likely to develop adrenal tumours than males.

Hyperadrenocorticism has an insidious onset and is slowly progressive over many months or even years. Many owners consider the early signs as part of the normal ageing process of their dog. In a few cases, clinical signs may be intermittent, with periods of remission and relapse and in other cases there may be rapid onset and progression of clinical signs.

Polydipsia and polyuria are seen in virtually all cases of hyperadrenocorticism. Excessive thirst, nocturia and/or urination in the house are usually noted by owners. The polydipsia occurs secondary to the polyuria, which is only partially responsive to water deprivation.

Increased appetite is common but most owners often assess this as a sign of good health. A voracious appetite, scavenging or stealing food, however, may give rise to concern especially if the dog previously had a poor appetite.

A pendulous abdomen is very common in hyperadrenocorticism but may be so gradual that owners fail to recognise its significance. The abdominal distension is associated with redistribution of fat to the abdomen, liver enlargement and abdominal muscle wasting and weakness.

The gradual onset of lethargy and poor exercise tolerance are usually considered by most owners to be compatible with ageing. Lethargy, excessive panting and poor exercise tolerance are probably an expression of muscle wasting and weakness.

Occasionally, dogs with hyperadrenocorticism develop myotonia, characterised by persistent active muscle contractions that continue after voluntary or involuntary stimuli. All limbs may be affected, but the signs are usually more severe in the hindlimb. The animals with myotonia walk with a stiff stilted gait. The affected limbs...
are rigid and rapidly return to extension after being passively flexed.

The skin particularly over the ventral abdomen becomes thin and inelastic. Striae can form as a result of this inelasticity. The abdominal veins are prominent and easily visible through the thin skin. There is often excessive surface scale and comedones are seen especially around the nipples. Hyperpigmentation of the skin is rare in canine hyperadrenocorticism.

Protein catabolism causing atrophic collagen also leads to excessive bruising either following venepuncture or other minor trauma. Healing wounds often undergo dehiscence and even old scars may start to breakdown.

Calciosis cutis is a frequent finding in biopsy material from the skin, however clinical evidence of calcnosis cutis is less common. The gross appearance can vary but the predilection sites are the neck, axilla ventral abdomen and inguinal areas. Calcinosis cutis usually appears as a firm, slightly elevated, white or cream plaque surrounded by a ring of erythema. The exact pathogenesis is unknown but plasma calcium and phosphorus concentrations are usually normal.

Thinning of the haircoat, leading to bilaterally symmetric alopecia, is frequently seen with hyperadrenocorticism and occurs because of the inhibitory effect of cortisol on the anagen or growth phase of the hair cycle. The remaining hair is dull and dry because it is in the telogen or resting phase of the hair cycle. The alopecia is non-pruritic and affects mainly the flanks, ventral abdomen and chest, perineum and neck. The head, feet and tail are usually the last areas to be affected. The coat colour is often lighter than normal.

Entire bitches with hyperadrenocorticism usually cease to cycle. The length of anoestrus, often years, indicates the duration of the disease process. In the intact male both testes become soft and flabby.

A few cases develop neurological signs in associated with large expanding functional pituitary tumours. The most common clinical signs are dullness, depression, loss of learned behaviour, anorexia, aimless wandering, head pressing, circling, ataxia, blindness, anisocoria and seizures. More often, however, neurological signs develop during initial treatment of pituitary-dependent hyperadrenocorticism with trilostane or mitotane. This is thought to involve removal of the negative feedback of cortisol, which can cause some pituitary tumours to enlarge rapidly.

Systemic hypertension occurs in more than 50% of dogs with untreated hyperadrenocorticism.

**Laboratory findings**

The most consistent haematological finding is a stress leucogram with a relative and absolute lymphopenia (< 1.5 x10^9/L) and eosinopenia (< 0.2 x10^9/L). The red cell count is usually normal, although mild polycythaemia may occasionally be noted. Platelet counts may also be elevated. These findings are thought to result from stimulatory effects of glucocorticoids on the bone marrow.

Glucocorticoids, both endogenous or exogenous, induce a specific hepatic isoenzyme of alkaline phosphatase in the dog. The increase in serum alkaline phosphatase is commonly 5–40 times the normal level and is perhaps one of the most reliable indicators of hyperadrenocorticism.

Alanine aminotransferase (ALT) is commonly elevated in hyperadrenocorticism, but the increase is usually only mild and is believed to result from liver damage caused by swollen hepatocytes due to glycogen storage.

Blood glucose is usually in the high normal range, but about 10% of canine cases will develop overt diabetes mellitus. The gluconeogenic effect of glucocorticoids results in insulin antagonism and subsequent development of pancreatic islet cell exhaustion. The cat appears more prone to developing hyperglycaemia and overt diabetes.

Blood urea is usually below normal due to the continual urinary loss associated with glucocorticoid-induced
diuresis. Serum creatinine concentration also tends to be in the low to normal range.

Cholesterol and triglyceride concentrations are usually increased due to glucocorticoid stimulation of lipolysis. Cholesterol is usually greater than 8 mmol/L but this is not a specific finding as cholesterol is also raised in hypothyroidism, diabetes mellitus, chronic liver disease and chronic renal disease, all of which may be differential diagnoses.

The specific gravity of the urine is usually less than 1.015 and is often hyposthenuric (< 1.010) provided water has not been withheld. Dogs with hyperadrenocorticism can concentrate their urine if water is deprived, but their concentrating ability is usually reduced. Glucosuria is present in the 10% of cases with diabetes mellitus. Urinary tract infection is common and occurs in about half the cases of hyperadrenocorticism.

Basal thyroxine concentrations are decreased in about 70% of dogs with hyperadrenocorticism. The response to stimulation by TSH usually parallels normal dogs but thyroxine concentrations both before and after stimulation with TSH are subnormal.

**Diagnostic imaging**

**Radiography** Radiographic examination of the thorax and abdomen is advisable in all cases of suspected or proven hyperadrenocorticism. Although positive diagnostic information is only obtained in the small number of cases in which adrenal enlargement can be detected, the number and frequency of radiological changes consistent with hyperadrenocorticism provide a useful aid to diagnosis. In addition, survey radiographs may reveal significant concurrent disease.

Hepatomegaly is the most consistent radiographic finding in hyperadrenocorticism. Good radiographic contrast permits easy identification of the abdominal structures because of the large deposits of intrabdominal fat. Hepatomegaly may be mild to severe and the ventral lobe borders vary in shape between distinctly rounded and sharply wedged-shaped. The pot-bellied appearance is usually very obvious on the recumbent lateral projection.

Adrenal enlargement is the least common finding on abdominal radiographs. Gross enlargement is suggestive, though not diagnostic, of an adrenocortical carcinoma. Unilateral mineralisation in the region of an adrenal gland suggests the possibility of an adrenal tumour. Both adrenocortical adenomas and carcinomas can become calcified.

Calcinosis cutis tends to have a nodular mineralisation pattern, whereas calcification in the fascial planes, for example just dorsal to the thoracolumbar spine, tends to be linear. Mineralisation may also be seen in the renal pelvis, liver, gastric mucosa and abdominal aorta.

A grossly distended urinary bladder may be seen radiographically even when the animal has been allowed to urinate prior to the radiographic examination. Cystic calculi may also be present and are usually associated with urinary tract infection.

Occasionally, the impression of osteopenia is gained from a distinct reduction in radiographic density of the lumbar vertebral bodies relative to the vertebral end plates.

**Ultrasonography** Abdominal ultrasonography has been used to examine the adrenal glands. It is a challenge for the ultrasonographer to consistently distinguish between normal and hyperplastic adrenal glands since the diagnosis of adrenal hyperplasia is somewhat subjective. The measurement of the thickness (ventrodorsal dimension) of the adrenal gland has been shown to be more sensitive than the either the length or width of the
gland. A thickness of greater than 7.5 mm for the left adrenal gland would be suggestive of adrenal hyperplasia. If both adrenal glands are of similar size and normal shape in a dog or cat with hyperadrenocorticism, it suggests the disease is pituitary-dependent.

Abdominal ultrasonography can also detect adrenocortical tumours. Adrenal masses are diagnosed by the location of the mass and clinical signs exhibited by the animal. There is a propensity for adrenal tumours to invade nearby vessels and surrounding tissues, therefore a thorough ultrasonographic examination of adjacent vessels and tissues should be performed. Mineralisation is frequently associated with benign and malignant adrenocortical tumours in the dog and acoustic shadowing may aid in localising the adrenal tumour.

**CT and MR imaging** Computed tomography (CT) and magnetic resonance (MR) imaging have also proved helpful in the diagnosis of adrenal tumours, adrenal hyperplasia and large pituitary tumours but these techniques are more expensive.

**Endocrine screening tests**

A presumptive diagnosis of hyperadrenocorticism can be made from clinical signs, physical examination, routine laboratory tests, and radiographic findings, but the diagnosis must be confirmed by either ACTH stimulation test or a low-dose dexamethasone suppression test.

**ACTH stimulation test** The ACTH stimulation test is the best screening test for distinguishing spontaneous from iatrogenic hyperadrenocorticism and reliably identifies more than 50% of dogs with adrenal-dependent hyperadrenocorticism and about 85% of dogs with pituitary-dependent hyperadrenocorticism. It is a simple test to perform and the only one that documents excessive production of glucocorticoids by the adrenal cortex. The information gained also provides a baseline for monitoring trilostane and mitotane therapy.

However, the ACTH stimulation test does not reliably differentiate adrenal-dependent from pituitary-dependent hyperadrenocorticism. It is less sensitive, but more specific than the low-dose dexamethasone test. A diagnosis of hyperadrenocorticism should not be excluded on the basis of a normal ACTH response if the clinical signs are compatible with the disease. Occasionally, an animal under chronic stress may develop some degree of adrenal hyperplasia, which produces an abnormal or equivocal ACTH response result. The author has seen this in a number of severe systemic diseases, for example uncontrolled diabetes mellitus and pyometra and has documented a normal ACTH response after treatment in each case.

**Low-dose dexamethasone suppression test** The low-dose dexamethasone suppression test is more reliable than the ACTH stimulation test in confirming hyperadrenocorticism, since the results are diagnostic in all adrenal-dependent cases and in 90–95% of dogs with pituitary-dependent hyperadrenocorticism. However, it is not as useful as the ACTH stimulation test for the detection of iatrogenic hyperadrenocorticism. It is also affected by more variables, takes eight hours to complete, and does not provide pre-treatment information that may aid in monitoring the effects of trilostane or mitotane therapy. The low-dose dexamethasone suppression test is more sensitive, but less specific than the ACTH stimulation test. Like the ACTH stimulation, the low-dose dexamethasone test does not reliably differentiate pituitary-dependent from adrenal-dependent hyperadrenocorticism.

Interpretation of the results of a low-dose dexamethasone suppression test must be based on the laboratory’s normal range of cortisol values for the dose and preparation of dexamethasone administered. If the dose of
Dexamethasone fails to adequately suppress circulating cortisol concentrations in a dog with compatible clinical signs, a diagnosis of hyperadrenocorticism is confirmed. While basal and 8-hour post-dexamethasone samples are most important for interpretation of the test, one or more samples taken at intermediate times during the test period may also prove helpful. If a plasma cortisol concentration determined 2–6 hours after dexamethasone injection is suppressed to below 40 mmol/L, while the 8-hour sample shows escape from cortisol suppression, then a diagnosis of pituitary-dependent hyperadrenocorticism can be made. Whilst some cases of pituitary-dependent hyperadrenocorticism will not suppress at any stage during a low-dose dexamethasone suppression test, any suppression during the 8-hour period essentially rules out a diagnosis of adrenal-dependent hyperadrenocorticism.

**Other screening tests** Evaluation of urinary corticoid/creatinine ratio rather than the more laborious 24-hour urinary corticoid excretion has been shown to be a simple and valuable screening test, but lacks specificity.