Canine Hypercortisolism (Cushing's Syndrome): **Diagnosis**

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Introduction

- Hyperadrenocorticism is defined as hypersecretion of adrenocortical hormones and can be subclassified in hyperaldosteronism (also known as Conn's syndrome), hypercortisolism (also known as Cushing's syndrome) and hyperandrogenism.
- Cushing's syndrome may be iatrogenic (due to the administration of pharmacological doses of steroids) or spontaneous.
- Spontaneous hypercortisolism is one of the most common endocrine disorders of middle-aged and elderly dogs, with an estimated incidence of 1 per 1000 dogs per year. In about 85% of cases it is due to a pituitary (micro- or macro-) adenoma that hypersecretes ACTH. In about 15% of cases it is due to a functional adenoma or (more often) carcinoma of the adrenal cortex. Rare cases of ectopic ACTH secretion and food-dependent hypercortisolism have been reported in dogs.
- The possibility that a dog has Cushing's syndrome is based on the history and physical examination.
- Endocrine tests should be performed only when clinical signs are consistent with hypercortisolism.
- Testing for hypercortisolism should be avoided if serious illness exists.

Clinical signs

- The primary indication for pursuing a diagnosis of hypercortisolism is the presence of one or more of the common clinical signs. The more clinical signs identified, the stronger the indication to pursue testing for hypercortisolism.
- If only one clinical sign is present, it is usually polyuria/polydipsia. Other common clinical signs of hypercortisolism include polyphagia, panting, lethargy, abdominal distension, endocrine alopecia (and skin changes suggestive of endocrine disease), muscle atrophy (and muscle weakness), hepatomegaly and arterial hypertension.
- Less common clinical signs of hypercortisolism include calcinosis cutis (pathognomonic for Cushing's syndrome), urinary incontinence, thromboembolism, ligament rupture, persistent anoestrus, testicular atrophy, facial nerve palsy and pseudomyotonia.
- It is very rare that a dog with hypercortisolism has a decrease in appetite; anorexia is a major negative indicator for the presence of hypercortisolism. Poor appetite in a dog with hypercortisolism should raise the suspicion of a pituitary macroadenoma or a serious co-morbidity.
- Clinical signs may develop secondary to mass-occupying effects of a pituitary or adrenocortical tumour.

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Routine laboratory changes

- Whenever hypercortisolism is suspected, it is important to perform a complete blood count, a biochemical profile and a urinalysis before proceeding with specific endocrine tests.
- The results of a complete blood count, a biochemistry panel, and a urine examination may further support the diagnosis of hypercortisolism. Above all, these analyses allow to exclude conditions with similar clinical signs (e.g., diabetes mellitus, hypercalcaemia, renal disease)
- Complete blood count in dogs with hypercortisolism may reveal neutrophilia, lymphopenia, eosinopenia (i.e., a stress leukogram), thrombocytosis, and (mild) erythrocytosis.
- A biochemistry panel in dogs with hypercortisolism may reveal increased liver values (especially alkaline phosphatase), hyperglycaemia, hyperphosphatemia and hyperlipidaemia.
- Urine examination in dogs with hypercortisolism may reveal a low specific gravity, indicators for urinary tract inflammation and glucosuria. Proteinuria is a common finding and can be mild to severe.
- In about 10% of dogs with Cushing's syndrome, the glucocorticoid excess may result in diabetes mellitus.

Endocrine tests: introduction

- The goal of a screening test is to differentiate dogs with hypercortisolism from dogs without hypercortisolism. The goal of a differentiation test is to distinguish pituitary tumours and adrenocortical tumours in dogs known to have hypercortisolism.
- A screening test for hypercortisolism depends on the demonstration of either 1) inappropriately high cortisol secretion or 2) decreased sensitivity of the hypothalamic-pituitary-adrenal cortex axis to negative glucocorticoid feedback.
- None of the screening tests for hypercortisolism has 100% diagnostic accuracy. If only dogs are included for a screening in which history, physical examination and routine laboratory examination clearly point to hypercortisolism, the disease prevalence is high, indicating that all screening tests will be more accurate.
- Measurement of a single basal circulating cortisol (or ACTH) concentration has no diagnostic value, due to the pulsatile hormone secretion.
- Stress and nonadrenal illness may result in increased cortisol secretion. Consequently, stress and nonadrenal disease may result in false-positive screening test results.
- Any screening test may be negative in a dog with hypercortisolism. If a screening test is negative but suspicion of hypercortisolism remains high, another screening test must be performed.
- Cortisol concentrations vary by assay and among laboratories using the same method. Each laboratory must establish reference values and cut-off values.

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Screening test: low-dose dexamethasone suppression test (LDDST)

- The LDDST is considered the screening test of choice to diagnose spontaneous hypercortisolism.
- In dogs without hypercortisolism, dexamethasone administration causes rapid and prolonged suppression of cortisol secretion.
- Resistance to dexamethasone suppression is a continuum; slight resistance may be present in early or mild cases and more severe resistance may be present in advanced cases of hypercortisolism.
- Blood samples for determination of the cortisol concentration are collected immediately before and at 3-4 hours and at 8 hours after the intravenous administration of 0.01 mg dexamethasone per kg body weight.
- The finding of a circulating cortisol concentration > 40 nmol/l (> 1.4 µg/dL) at 8 hours after dexamethasone is consistent with hypercortisolism. Some endocrinologists use a cut-off value of 28 nmol/l (1.0 µg/dL).
- Lack of suppression at 3-4 hours after dexamethasone is also highly suspicious for hypercortisolism.
- Suppression of > 50% at 3-4 hours and/or 8 hours after dexamethasone in dogs with hypercortisolism indicates that the hypercortisolism is pituitary-dependent.

Screening test: ACTH stimulation test

- The ACTH stimulation test assesses adrenocortical reserve and is the gold standard for diagnosing iatrogenic Cushing's syndrome.
- Because of its low sensitivity, the diagnostic usefulness as a screening test for spontaneous hypercortisolism is inferior to the LDDST.
- Blood samples for determination of the cortisol concentration are collected immediately before and at 60-90 minutes after intravenous (or intramuscular) administration of 5 µg synthetic ACTH per kg body weight.
- An exaggerated cortisol response after ACTH stimulation may be consistent with hypercortisolism.
- With the ACTH stimulation test about 40% of the dogs with hypercortisolism due to an adrenocortical tumour and about 15% of the dogs with pituitary-dependent hypercortisolism will be missed.
- A positive ACTH stimulation test may be found in dogs with chronic stress (due to nonadrenal disease).
- Progestagens, glucocorticoids and ketoconazole suppress the hypothalamic-pituitary-adrenocortical axis and, consequently, decrease the cortisol response to ACTH.

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Screening test: urinary corticoid to creatinine ratio (UCCR)

- The UCCR provides an integrated reflection of corticoid production, adjusting for fluctuations in blood concentrations.
- The UCCR is a very sensitive test to detect hypersecretion of cortisol. If cortisol is measured by chemiluminescence method (e.g., Immulite®) the sensitivity of the test is lower than measured by radioimmunoassay.
- Stress results in elevated UCCRs. Consequently, urine samples should not be collected in veterinary clinics, but have to be collected at home (by the owner), at least two days after a visit to a veterinary clinic.
- Determination of basal UCCRs is ideally performed in tandem with an oral high-dose dexamethasone suppression test.
- Owners have to collect morning urine samples on three consecutive days. After collection of the second morning urine sample, the owner has to administer 0.1 mg dexamethasone per kg body weight orally at 12.00, at 18.00 and at 24.00h.
- Basal UCCRs above the cut-off of the laboratory, in a dog with clinical signs and biochemical changes consistent with hypercortisolism, strongly point to Cushing's syndrome.
- A very low basal UCCR makes spontaneous hypercortisolism very unlikely.
- In mild cases of hypercortisolism, a basal UCCR below the cut-off value may be found.
- Lack of suppression (< 50%) in the UCCR of day three points to hypercortisolism.
- Suppression of > 50% in the UCCR of day three (compared to the basal UCCRs), in a dog with hypercortisolism, indicates that the hypercortisolism is pituitary-dependent.
- Nonadrenal disease may cause endogenous stress and result in elevated basal UCCRs.
- Glucocorticoids and other drugs that suppress cortisol secretion, such as progestogens, can decrease the basal UCCR.

Differentiation

It is important to differentiate pituitary-dependent hypercortisolism and hypercortisolism due to an adrenocortical tumour because treatment and prognosis differ.

Differentiation: endogenous ACTH concentration

- Measurement of the circulating endogenous ACTH concentration is the most accurate stand-alone biochemical differentiation test.
- The circulating endogenous ACTH concentration is suppressed in dogs with hypercortisolism due to an adrenocortical tumour. Dogs with pituitary-dependent hypercortisolism will not have undetectable circulating endogenous ACTH concentrations, but commonly have values within the reference interval (for healthy dogs).
- Blood for determination of the endogenous ACTH concentration should be collected into chilled, silicon-coated tubes containing EDTA, centrifuged within 15 minutes (preferably in a cooled centrifuge), and the plasma frozen immediately. Samples must stay frozen until analysis.

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Differentiation: high-dose dexamethasone suppression test (HDDST)

- Intravenous HDDST: blood samples for determination of the cortisol concentration are collected immediately before and at **3-4 hours** after the intravenous administration of 0.1 mg dexamethasone per kg body weight.
- HDDST using the UCCR: after collection of the morning urine samples for the basal UCCRs, the owner administers 0.1 mg dexamethasone per kg body weight orally at 12.00, at 18.00 and at 24.00h.
- In dogs with hypercortisolism due to an adrenocortical tumour, dexamethasone at any dosage does not suppress cortisol secretion; i.e. suppression is < 50%.
- In about 75% of dogs with pituitary-dependent hypercortisolism, cortisol values (either circulating cortisol concentration or UCCR) decrease at least 50% after administration of a high dose (0.1 mg/kg) of dexamethasone. In dogs with pituitary-dependent hypercortisolism that do not suppress, a large pituitary tumour is more likely.

Differentiation: diagnostic imaging

- The diagnosis of hypercortisolism cannot be performed solely with imaging, but must rely on hormone tests.
- **Radiography** in a dog with hypercortisolism may reveal abdominal distension, hepatomegaly, bladder distension, mineralization of the lungs and dermis, and metastases of an adrenocortical carcinoma. A small liver makes hypercortisolism unlikely. An adrenal mass may be visualized either because of mass effect or tumoral calcification.
- The presence of an adrenal tumour can be determined by **abdominal ultrasonography**. Moreover, ultrasonography can be used to estimate the size of the adrenal tumour, and to identify possible vascular or local soft tissue invasion, metastases (for example in the liver) and contralateral adrenocortical atrophy.
- Symmetrical, normal sized or enlarged adrenal glands are found in dogs with pituitary-dependent hypercortisolism, but mild asymmetry may also occur. Adrenal gland width is the most informative parameter. Breed and body size-related differences must be taken into consideration.
- Pituitary imaging (by contrast-enhanced **CT or MR**I) provides valuable information regarding treatment options and prognosis. Pituitary macrotumours may result in headache (or neurological signs), therefore pituitary imaging is recommended in all dogs at the time of diagnosis of pituitary-dependent hypercortisolism.
- An adrenal tumour and pituitary tumour may occur simultaneously. Consequently, visualization of both the pituitary area and the adrenals is recommended in dogs with hypercortisolism.

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