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Canine Hypoadrenocorticism: **General considerations and diagnosis**

Introduction

- Hypoadrenocorticism is an uncommon endocrine disorder of dogs with an estimated prevalence between 0.06 and 0.28%.
- If it is not appropriately diagnosed and treated, hypoadrenocorticism is associated with significant mortality due to severe hyperkalemia, hyponatremia, dehydration and hypovolaemic shock.[1]

Definition

- Hypoadrenocorticism is the umbrella term for a range of naturally occurring or iatrogenic disorders that cause reduced function of the adrenal cortex and results in a state of glucocorticoid deficiency, mineralocorticoid deficiency or both.[2]

Classification and pathogenesis

- Primary hypoadrenocorticism is due to adrenocortical injury. It can be naturally occurring (most commonly immune-mediated) or iatrogenic due to surgery (bilateral adrenalectomy) or drugs (e.g., trilostane, mitotane).
  - Addison's disease is a term synonymous with "primary hypoadrenocorticism."
  - Most dogs with primary hypoadrenocorticism have both glucocorticoid and mineralocorticoid deficiency and usually present with hyponatremia and/or hyperkalemia.
  - Some dogs with mineralocorticoid deficiency maintain electrolyte concentrations within reference intervals through an as of yet unknown mechanism. The following sub-classification is based on the electrolyte alterations:
    - **Hyponatremic and/or hyperkalemic hypoadrenocorticism** (defined as hypoadrenocorticism with hyperkalemia and/or hyponatremia).
    - **Eunatraemic, eukalemic hypoadrenocorticism** (hypoadrenocorticism with normal concentrations of potassium and sodium in the blood).
- Secondary hypoadrenocorticism is a state of glucocorticoid or, less likely, mineralocorticoid deficiency due to lack of ACTH or renin, respectively. Secondary glucocorticoid-deficient hypoadrenocorticism can be naturally-occurring or iatrogenic due to surgery (e.g., hypophysectomy, post-adrenalectomy of a cortisol-producing adrenal tumor) or abrupt discontinuation of drugs with glucocorticoid activity, including progestins.
  - Dogs with secondary hypoadrenocorticism usually have eunatraemic, eukalemic hypoadrenocorticism.

Cortisol and aldosterone deficiency

- Glucocorticoids have numerous vital functions in the body; they play a crucial role in metabolism, gluconeogenesis, immune system function, erythrocytosis, maintenance of endothelial integrity, control of blood volume and pressure through catecholamine responsiveness, and much more. Without cortisol, patients may develop hypoglycemia, hypotension, gastrointestinal symptoms, lack of energy, and inability to respond to stress.
- Aldosterone's primary role is maintaining normovolemia by promoting sodium, chloride, and water reabsorption while facilitating potassium excretion in the renal distal tubule. Lack of aldosterone commonly results in hyponatremia, hypochloremia, hypovolemia, and hyperkalemia. As mentioned above, some dogs with mineralocorticoid deficiency maintain electrolyte concentrations within reference intervals through an as of yet unknown mechanism.

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Signalment

- Hypoadrenocorticism has been reported in dogs aged from 2 months to 14 years, with a median age between 3 and 6 years.[3-5]
- The disease is more common in pure-breed dogs.
- It has a strong heritable component in standard poodles, Portuguese water dogs, Nova Scotia duck tolling retrievers, soft-coated wheaten terriers and bearded collies.
- Other breeds have been shown to have an increased risk of hypoadrenocorticism, e.g., great Dane, Pyrenean mountain dog, and West Highland white terrier.

Clinical features

- Hypoadrenocorticism causes vague and nonspecific clinical signs that could also be due to many other disorders, including gastrointestinal disease, renal failure, or neurological disease.
- Features that should raise suspicion of hypoadrenocorticism include a waxing and waning course of chronic gastrointestinal signs, especially if rapidly responsive to symptomatic fluid or glucocorticoid therapy, or where such signs are exacerbated by stressful situations.
- The group of clinical signs includes, but is not limited to, vomiting, diarrhea, inappetence, weight loss, lethargy, weakness, collapse, polyuria, polydipsia, shaking, abdominal pain, melena or hematochezia, and hematemesis. Physical examination findings are usually nonspecific and can include thin-body condition, dehydration, and a painful abdomen.
- In dogs with acute hypoadrenocortical crisis, observed in approximately 30% of the cases, signs of hypovolemic shock, including bradycardia or tachycardia, collapse, hypothermia, weak pulses, and poor capillary refill time, are observed.

Laboratory findings

- Hyperkalemia, hyponatremia, and hypochloremia represent the most consistent blood chemistry abnormalities among dogs with primary hypoadrenocorticism.
- Hyperkalemia occurs in up to 95% of dogs with primary hypoadrenocorticism.
- The normal sodium to potassium ratio lies between 27:1 and 40:1. Dogs with primary hypoadrenocorticism frequently (95%) have a ratio below 27:1.
- The electrolyte abnormalities mentioned above suggest hypoadrenocorticism but are not pathognomonic. The differential diagnosis for hyperkalemia with hyponatremia includes gastrointestinal diseases (including pancreatitis), renal failure, parasitic infection (whipworms), urinary obstruction, chronic effusion with repeated drainage and congestive heart failure.
- Hypercalcemia occurs in up to 30% of dogs with hypoadrenocorticism.
- Other biochemical abnormalities that may be observed include azotemia, hyperphosphatemia, hypoalbuminemia, hypercholesterolemia, hypoglycemia and increased liver enzymes.
- Hematologic abnormalities may include anemia, eosinophilia, and lymphocytosis.
- The absence of a stress leucogram (neutrophilia, lymphopenia, monocytosis, and eosinopenia) in a sick patient should prompt consideration of hypoadrenocorticism.
- Urinalysis often reveals impaired urine concentration ability; in patients with concurrent azotemia and isosthenuria, hypoadrenocorticism can easily be misinterpreted as primary renal disease.

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Electrocardiography and diagnostic imaging

- Electrocardiography can reveal findings consistent with hyperkalemia (e.g., bradycardia, lack of P waves, wide QRS complexes and tall T waves).
- Radiographs may reveal microcardia, narrowed vena cava and hypoperfused lung vessels.
- Ultrasound findings in dogs with hypoadrenocorticism may be normal, but usually the adrenal glands appear smaller (shorter and thinner) than in healthy dogs.

Endocrine tests

- ACTH stimulation test (serum cortisol concentration measured before and one hour after administration of synthetic ACTH (5 µg/kg IV or IM in dogs) is considered the most appropriate test to confirm hypoadrenocorticism.
- The ACTH stimulation test is considered positive when pre- and post-ACTH cortisol concentrations are within or less than the bottom quartile of the reference interval for basal cortisol; e.g., if the reference interval for basal cortisol concentration is 30-120 nmol/L (1.1-4.4 ug/dL), a post-ACTH cortisol concentration of 53 nmol/L (1.9 ug/dL) or less is diagnostic for hypoadrenocorticism.[2]
- **It is essential to confirm that no exogenous glucocorticoids or progestins are being or have been administered by any route, including topical.** The administration of such medications can produce false positive results up to two months after their discontinuation.
- The ACTH stimulation test can be performed during initial stabilization and treatment if dexamethasone (one single administration) is used because it does not cross-react with the cortisol assay; more extended periods of treatment with dexamethasone will result in suppression of the hypothalamus-pituitary-adrenal axis and a false positive result for hypoadrenocorticism.
- Measurement of endogenous ACTH should ideally be performed. Plasma ACTH concentrations are high with primary hypoadrenocorticism and undetectable to low with secondary hypoadrenocorticism.
- Basal serum cortisol ≥2 µg/dL (55 nmol/L) allows to rule out hypoadrenocorticism. Basal serum cortisol ≤2 µg/dL (55 nmol/L) should NEVER be used to confirm the diagnosis due to the low specificity (63—78%).[6-8] When basal serum cortisol ≤2 µg/dL (55 nmol/L) is detected, an ACTH stimulation test should always be performed.
- The urinary cortisol is low in dogs with hypoadrenocorticism and can be considered as a screening test.[9]
- Rare cases of isolated aldosterone deficiency exist for which cortisol concentrations are within the reference interval. Diagnosis is made by documentation of hyponatremia and hyperkalemia and exclusion of all other causes. For these cases, measurement of pre and post-ACTH aldosterone concentrations is advised.

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