Addison’s Disease in dogs - What do lab results tell us

Hypoadrenocorticism (Addison’s disease) reflects the condition of the organism caused by a deficiency in production / secretion of glucocorticoids and/or mineralocorticoids by the adrenal cortex. The destruction of the adrenal cortex is termed primary hypoadrenocorticism.

Clinical signs of primary hypoadrenocorticism are dominated by the failure of production of all adrenocortical hormones. The breakdown of the glucocorticoid- as well as the mineralocorticoid production and secretion is the result of the destruction of more than 90% of the adrenal tissue. Etiologically an immune-mediated destruction due to auto - antibodies is discussed (idiopathic adrenocortical atrophy). Analogical to human primary hypoadrenocorticism it is assumed that in dogs 21-hydroxylase may be the responsible autoantigen. 21-hydroxylase plays an important role for the synthesis of cortisol and aldosteron. A number of immune-mediated disorders such as thyroid hypofunction, diabetes mellitus and hypoparathyroidism in dogs are believed to be due to autoantibodies against adrenal tissue as well. Young to middle-aged, intact female dogs (2 months up to 4-6 years of age) are predisposed for primary hypoadrenocorticism.

A breed disposition has been reported for great Danes, Portuguese water dogs, Rottweilers, Poodles, West Highland white terriers and soft coated Wheaten terriers, whereas cats do not show a breed disposition. In bearded Collies, Leonbergers and standard Poodles a heritable component is suspected, the exact mechanism however has not yet been determined. Another cause of primary hypoadrenocorticism is the destruction of the adrenal cortex by drugs. In about 5% of dogs treated with Mitotane for Cushing’s disease a complete, irreversible destruction of the adrenal cortex requires a life long replacement of mineralo- and glucocorticosteroids. Treatment with Trilostane (reversible inhibitor of the 3-hydroxysteroid dehydrogenase), though not common, has been reported to cause adrenocortical necrosis, necessitating a continuous monitoring of the patient by means of the ACTH-stimulation test

Other possible causes of primary hypoadrenocorticism are bilateral adrenalectomy and the destruction of the adrenal glands by neoplasias, infarction or amyloidosis.

Secondary hypoadrenocorticism is marked by a reduction of the ACTH production and secretion resulting in atrophy of the adrenal cortex and subsequent reduced secretion of glucocorticoids. Primary cause for secondary hypoadrenocorticism is the continuous suppression of ACTH secretion associated with drug therapy with glucocorticoids, progesteron or megestrol acetate. The concentration of mineralocorticoids (aldosterone) remains nearly unaffected by the reduced release of ACTH.

For the major part the regulation of aldosteron release is effected by the renin-angiotensin system and adjustments of the plasma potassium concentration. Aldosteron is considered the “main mineralocorticoid” of the adrenal cortex. It promotes the renal excretion of potassium and the reabsorption of sodium, chlорid and water. Rare causes for secondary hypoadrenocorticism are tumors in the hypothalamus or pituitary.

Clinical signs of hypoadrenocorticism often are indistinct. They may be acute or chronic, appear episodic for weeks or even months and intensify in stressful situations. Alternately the patient shows periods of obvious illness and total health. The lack of corticosteroids results in decreasing tolerance to stress, anorexia, vomiting, diarrhea, lethargy and abdominal pain. Following the administration of corticosteroids commonly a temporary symptomatic improvement occurs. Additional deficiency of aldosteron causes hyponatremia, hyperkalemia and water loss to result in lethargy, hypovolemia, hypotension and bradycardia, decreased renal perfusion, weakness and tremor. Addisonian crisis is the most dramatic form of hypoadrenocorticism. The inadequate release of glucocorticoids and mineralocorticoids during a period of stress finds the animal in a life threatening state,
collapsing with bradycardia, a weak pulse, vomiting, dehydration and often abdominal pain. These patients must be treated as absolute emergencies and often die without immediate fluid therapy. Therapy must be determined on a case to case basis. However, in addition to the replacement of glucocorticosteroids, mineral-corticosteroids (Fludrocortison) must also be administered.

**Laboratory findings** in primary hypoadrenocorticism are elevated plasma ACTH concentrations (>500 pg/ml) due to the lack of the negative feedback of cortisol on the pituitary. On the contrary dogs with secondary hypoadrenocorticism demonstrate extremely low or almost undetectable levels of ACTH (<5 pg/ml). A careful sample handling on part of the submitting veterinarian is absolutely crucial (cooled EDTA plasma!!) to avoid falsely low values and incorrect interpretations. The clinical/chemical findings are just as confusing as the clinical signs. In healthy animals stress (cortisol release) triggers eosinopenia and lymphopenia. An animal suffering from hypoadrenocorticism lacks these changes in the blood profile, because the adrenal cortex is incapable of an adequate reaction. The blood profile reflects the lacking adaptation to stress by lymphocytosis and/or eosinophilia or both parameters within reference range.

**Laboratory findings**

- eosinophilia
- lymphocytosis
- neutropenia
- normocytic, normochromic anemia
- azotemia (increased blood urea / creatinine/phosphate)
- hyponatremia (<135 mmol/l)
- hyperkalemia (>5.5 mmol/l)
- sodium/potassium ratio <25:1
- hypochloremia (<100 mmol/l)
- hypoglycemia (rare)
- hypercalcemia
- hypoalbuminemia
- USG 1.015 – 1.030

Further diagnostic evidence for Addison’s disease is azotemia secondary to a reduced renal perfusion and decreased glomerular filtration rate. The impaired renal blood flow results from hypovolemia, hypotension and bradycardia. Vomiting and diarrhoe as well as renal loss of fluids and reduced water intake stress the characteristics of prerenal azotemia. The urine concentration (USG) in prerenal azotemia normally is relatively high (>1.030). The USG in animals with hypoadrenocorticism however is between 1.015 and 1.030, because the kidneys lose the ability to concentrate because of the chronic loss of sodium. Azotemia is reversible with efficient fluid therapy which confirms its prerenal origin. Increased urea levels may also be the result of gastrointestinal hemorrhaging. A helpful diagnostic parameter is a narrow sodium/potassium ratio. A healthy dog shows a ratio from >27:1 to 40:1, whereas the ratio in dogs suffering from Addison’s disease is <27:1 (<25:1). In so called atypical Addison’s disease about 10 % of dogs with primary hypoadrenocorticism have serum levels of sodium and potassium within the normal range. To avoid incorrect interpretations the submitted serum sample must be free of hemolysis and spun down when sent to the lab. Pseudohyperkalemia can falsify the result and is caused by hemolysis, prolonged shipping and is seen in dogs with extreme thrombocytosis and leucocytosis. Other illnesses associated with electrolyte abnormalities (i.e.hepatic diseases, renal failure, gastrointestinal hemorrhage, blood loss and tumors). In 2008, ACTH stimulation tests performed by LABOKLIN showed 104 patients with cortisol base and stimulation values of <60ng/ml. 29% of these patients demonstrated a decreased sodium/potassium ratio (<27:1). It was not possible to distinguish patients tested for Addison’s disease from those suspected of suffering from Cushing’s disease or being under triostane therapy because case histories were not furnished.
Elevated serum calcium levels are often seen in dogs with hypoadrenocorticism and are most probably the result of the interaction of reduced glomerular filtration, increased tubular reabsorption and hemoconcentration. In a study of 40 dogs with hypercalcemia in 25% of animals hypoadrenocorticism was the cause. Occasionally dogs with hypoadrenocorticism display reduced serum albumin levels (6-39%). Gastrointestinal hemorrhage, reduced synthesis and absorption as well as renal loss are possible causes. In some Addison’s patients a mild increase of AST and AP is found, possibly due to a reduced cardial output and impaired blood circulation.

How is Addison’s disease being diagnosed?
The diagnostic gold standard is the ACTH stimulation test. To rule out cross reactions with cortisol, corticosteroids should not be given 12-24 hours prior to testing. Hydrocortison, prednisolon and prednison can cause cross reactions and falsely elevated cortisol values, depending on the test methods used. Dexamethason does not influence the measured cortisol concentration but does suppress the cortisol secretion in dogs with an intact hypothalamus-pituitary-adrenal cortex axis by up to 33%, resulting in falsely low cortisol concentrations. A distinction between primary and secondary hypoadrenocorticism is not possible with the ACTH stimulation test.

**ACTH Stimulation test: test protocol**

1. blood sample for basal cortison concentration (serum, plasma).
2. injection (i.v.) of 0,25 mg synthetic ACTH (0,125 mg for dogs weighing < 5kg).
3. after 60 minutes collect second blood sample for cortisol concentration.

Hypoadrenocorticism: undetectable or very low cortisol stimulation after administration of ACTH.

In 2008 LABOKLIN evaluated 3388 ACTH stimulation tests performed in dogs. Approx. 37% of the patients displayed basal and stimulation cortisol concentrations of <50 nmol/l, in 43% of dogs both values were between 50-150 nmol/l and 19% of animals tested with stimulation concentrations of >150 nmol/l.

According to literature citations 85% of dogs with hypoadrenocorticism have basal and stimulation cortisol concentrations of <30 ng/ml and even 90% of affected dogs showed basal and stimulation cortisol concentrations of <60 ng/ml. In 2008, of all ACTH stimulation tests carried out at LABOKLIN 41% had basal and stimulation cortisol concentrations <60 ng/ml. The inconsistency with the literature citations results from the lack of knowledge of case histories.

Therefor a distinction of patients suspected of suffering from Addison’s disease and those under triostane therapy was not possible.