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Hypoadrenocorticism – Diagnostic Tips and Pitfalls

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What exactly is hypoadrenocorticism? Why don't we refer to it as Addison's disease anymore?

The term "Addison's disease" is no longer recommended in the current ALIVE guidelines (ALIVE: Agreeing Language in Veterinary Endocrinology) because it refers only to primary hypoadrenocorticism. The preferred term "hypoadrenocorticism" (hypoA) describes any form of adrenal cortex insufficiency. The causes can be both natural and iatrogenic and can be either adrenal (primary hypoA) or pituitary (secondary hypoA). In the classic case, primary hypoA is triggered by an immune-mediated loss of adrenal cortex function. The deficiency usually affects both glucocorticoids (primarily cortisol) and mineralocorticoids (primarily aldosterone), although isolated cortisol deficiency is also possible.
In contrast, in secondary hypoA, the hormones that stimulate the adrenal gland (primarily ACTH) are absent. This is almost always accompanied by a pure cortisol deficiency, as aldosterone can be produced and secreted independently of ACTH.

How do I diagnose hypoadrenocorticism?

The diagnostic process consists of the following steps:

a) Clinical suspicion
   - Description: Hypoadrenocorticism can occur in any age, gender, or breed. However, young dogs between the ages of 3 and 4 years, as well as certain breeds, are predisposed (Table 1). In some studies, bitches were affected more frequently, but this does not appear to apply to all breeds.
   - Clinical signs: The clinical signs can vary greatly and resemble those of other diseases, meaning that hypoA can be the cause of the symptoms in almost every case. However, hypoA should definitely be included in the differential diagnoses if polyuria/polydipsia, gastrointestinal symptoms, and weakness are present, especially if these symptoms occur recurrently and respond quickly to infusion therapy.

b) Suitable laboratory changes
   - Haematology: Cortisol deficiency is often associated with mild, non-regenerative anaemia. However, a more specific sign is the lack of a stress leukogram in a critically ill patient. In particular, attention should be paid to the presence of lymphocytosis.
   - Clinical chemistry:
     - *Changes in electrolytes:* Hyperkalaemia and hyponatraemia are typical of hypoadrenocorticism and are triggered by the lack of aldosterone.
       A pure cortisol deficiency will not be associated with hyperkalaemia, but it can also lead to hyponatraemia.

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Table 1: Breed predispositions in dogs for hypoadrenocorticism.

	Dog breeds
Hereditary component identified or highly presumed	Poodle, Portuguese Water Dog, Nova Scotia Duck Tolling Retriever, Soft Coated Wheaten Terrier, Bearded Collie
Familiar occurrence	Leonberger, Pomeranian
Increased risk	Great Dane, West Highland White Terrier, Rottweiler, Pyrenean Mountain Dog
Reduced risk	Golden Retriever, Yorkshire Terrier, Lhasa Apso

- *Prenatal azotaemia:* This is a consequence of reduced blood volume and reduced glomerular pressure due to an aldosterone deficit. Azotaemia usually is mild. However, in some patients with hypoA azotaemia can be unusually severe despite its purely prerenal nature.
- *Hypoglycaemia:* This can result from cortisol deficiency.
- *Hypercalcaemia:* The exact pathogenesis is unclear; usually it is an increase in total calcium, but increased concentrations of ionised calcium are also possible.

– Urinalysis: Despite the prerenal azotaemia, which should normally be associated with concentrated urine, hypoA results in a reduction in the urine-specific gravity (USG).

c) Cortisol screening
If hypoA is suspected, measuring serum cortisol can be helpful. If the serum cortisol concentration is above a laboratory-defined cut-off, hypoA is highly unlikely. This cut-off is often reported as 20 ng/ml (2.0 µg/dl, 55 nmol/l). If the value is below this, a confirmatory ACTH stimulation test (ACTH-Stim) needs to be carried out to diagnose hypoA.

d) ACTH-Stim
The ACTH-Stim is the test procedure necessary for the diagnosis of hypoA. Following an initial blood sample (serum), 5 µg/kg tetracosactide/cosyntropin is injected. Intramuscular injection is possible, but intravenous administration is preferred in order to standardise the test. A second blood sample (serum) is taken one hour after the injection. Cortisol concentration is determined in both serum samples. If the cortisol values before and after the injection are in the lower quartile of the reference range for cortisol or below, hypoA is confirmed.

The Na/K ratio as a screening method

A low ratio of sodium (Na) and potassium (K) (Na/K ratio) can be indicative of hypoA. However, the specificity is not particularly high, as there are many differential diagnoses (Table 2). Adequate specificity is only present at Na/K < 20.

Table 2: Differential diagnoses for a low Na/K ratio

Low Na/K ratio
Hypoadrenocorticism
Gastrointestinal o Parasites (Ancylostoma spp, Trichuris spp) o Salmonellosis o Parvovirosis, distemper o Severe malabsorption o Duodenal perforation o Gastric torsion
Pyometra
Mycotoxins
Hepatic failure
Chylothorax
Congestive heart failure
Primary polydipsia

It should also be kept in mind that hypoA is not always associated with hyperkalaemia.

Even healthy dogs can show very low basal cortisol concentrations

Due to the pulsatile release of cortisol, concentrations measured at any given time may be randomly low. Even in healthy dogs, serum cortisol concentrations may be below the detection limit. An ACTH stim is therefore necessary in any case for values below the cut-off.

Why cortisol should be sent to a laboratory for measurement?

The ALIVE committee of the ESVE (European Society of Veterinary Endocrinology) points out the necessity of correct test validation and reliably performed quality controls when measuring cortisol. Measurement of cortisol in a reference laboratory is therefore recommended.

Serum is the preferred sample material

Cortisol can also be measured in (heparinised) plasma. However, serum should be used to standardise hormone measurements. In any case, you should avoid using different sample materials within one functional test.

It doesn't always have to be "Addison's"

Insufficient stimulation of cortisol after an injection of tetracosactide/cosyntropin in patients with normal adrenal function may be caused by incorrect test performance. However, glucocorticoid pre-treatment is much more often the cause. Even small amounts, administered briefly, a long time ago, or applied topically (including eye drops and ear ointment), can influence the pituitary-adrenal axis. Exogenously administered glucocorticoids lead to feedback to the pituitary gland, which stops producing adrenocorticotropic hormone (ACTH). The adrenal glands react very sensitively to this lack of endogenous ACTH stimulation with atrophy of the adrenal cortex.
The time required for the adrenal cortex to recover varies from individual to individual. The same applies to progestagens, which also have a gluco-corticoid effect. The medical history regarding possible previous treatments must therefore be taken very conscientiously.

Can dexamethasone be given in an emergency if an ACTH stimulation test cannot be carried out immediately?

Dexamethasone is not detected by the widely used cortisol assays and therefore does not interfere with the measurement. If a patient requires immediate treatment with a glucocorticoid in an emergency, before an ACTH stim can be carried out, the use of dexamethasone is therefore often recommended. However, the ACTH stimulation must then be carried out immediately. Any delay (even a few hours) can negatively influence the assessability of the test result. Dexamethasone affects the pituitary-adrenal axis like any other glucocorticoid.

The patient pre-treated with glucocorticoids

In an experimental study, healthy beagles given prednisolone for three weeks recovered their adrenal function within just two weeks after withdrawal.However, observations from other studies have identified patients who, even after relatively small amounts of glucocorticoids, showed a abnormal response to tetracosactide/cosyntropin for several weeks after discontinuation. In general, a period of 6-8 weeks without glucocorticoids is recommended before performing stimulation testing. If this is not possible, endogenous ACTH measurement (eACTH) and/or measurement of stimulated aldosterone serum concentration may be considered.

Hypoadrenocorticism despite cortisol stimulation

The typical patient with hypoA will not show any increase in cortisol concentration in response to ACTH stimulation. However, it should be noted that a certain degree of stimulation of cortisol is quite possible. Usually, a stimulated cortisol concentration in the lower quartile of the reference range (often below 20 ng/ml) is defined as consistent with hypoA. However, in some patients higher stimulated cortisol concentrations may be encountered.
In case of reasonable clinical suspicion, hypoA may be diagnosed even if the given cut-off is exceeded. The consultation of a specialist in endocrinology is recommended in these cases.
Furthermore, an isolated aldosterone deficiency has been described that is associated with hyperkalaemia and hyponatraemia with physiological cortisol stimulability.
However, this is limited to case reports.

What to do with questionable results of an ACTH stim

A correlation of clinical signs and laboratory changes is essential. In any case, the differential diagnoses need to be checked carefully.
A precise medical history regarding possible exposure to glucocorticoids (including topical therapy in people that are in close contact with the patient) needs to be taken.
Measurement of **endogenous ACTH** (eACTH) can support the diagnosis of primary hypoA. In primary hypoA, eACTH should be measurable or elevated. In patients pre-treated with glucocorticoids no eACTH is released.
However, eACTH concentrations below the detection limit are not conclusive and need to be interpreted cautiously. They do not exclude hypoA. There are two reasons to it: First, eACTH is instable and can easily be destroyed when sample handling (including shipment) is suboptimal. Second, eACTH is released from the pituitary in a pulsatile manner. This means that low concentrations may occur at any given time. When this happens, a low concen-tration will be detected.

Canine eACTH is unstable. For reliable results, EDTA plasma needs to be separated shortly after sampling, refrigerated, and shipped cooled.
The EDTA plasma must arrive at the laboratory in a cooled state (temperature not exceeding 8°C) to avoid incorrect results.

In case ACTH stim is not available

If an ACTH stim is not available, the cortisol/eACTH quotient can provide helpful information. However, whether it can replace the ACTH stim as a diagnostic tool is still subject of discussion although some supporting study data is existing.
In order to avoid incorrect results arrival of EDTA plasma at the laboratory in a cooled state (temperature not above 8° C) is mandatory.

Eunatraemic/eukalaemic hypoadrenocorticism ('Atypical' Addison's Disease)

Hyperkalaemia in patients with hypoA develops due to a deficiency in aldosterone. However, not every patient with hypoA is hyperkalaemic. Eunatraemic/eukalaemic hypoA is seen in secondary hypoA (= pituitary disease = isolated cortisol deficiency), but secondary hypoA is rare. Absence of hyperkalaemia may also occur in patients with primary hypoA (= adrenal cortical insufficiency). Either this is because the immune mediated destruction of the adrenal cortex has not yet reached the aldosterone producing parts, i.e. those parts have not been fully destroyed, and there is still enough aldosterone production left to control the potassium concentration. Or other factors influencing the blood potassium concentration (e.g. decreased intake due to inappetence, compensation via the kidneys in a still adequately hydrated patient) are in place.
Eunatraemic/eukalaemic hypoA should be considered in any patient with gastrointestinal signs. The presence of measurement of the serum aldosterone concentration may indicate whether or not there is a corresponding, therapeutically relevant deficiency.

Hypoadrenocorticism also occurs in cats

Hypoadrenocorticism has also been described in cats, albeit rarely. In particular, cats of the British Shorthair breed are frequently mentioned in the literature. Diagnostic cut-off values are extrapolated from dogs, although some endocrinologists argue that they should be set higher as those for dogs.

The Laboklin parameters and profiles for the diagnosis of hypoadrenocorticism

Cortisol, eACTH, and aldosterone can be measured separately. In addition, measurement of cortisol as part of the ACTH stimulation test and the cortisol/eACTH ratio is offered. Two newly composed, helpful profiles are rounding out the Laboklin service with respect to hypoA: the intestinal profile and the "Addison's profile".
Since hypoA is often associated with non-specific gastrointestinal symptoms, the new intestinal profile also includes the measurement of cortisol, along with other important parameters such as pancreatic-specific lipase (PSL) and trypsin-like immunoreactivity (TLI).

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Literature

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Table 3: Revised profiles and parameter combinations at Laboklin that are of interest when hypoadrenocorticism is suspected

Designation	Specific Parameters	Required Material
ACTH stimulation test	2 x cortisol	2 x 0.5 ml serum
Addison's profile	cortisol, potassium, sodium, chloride, glucose, albumin, creatinine	1 ml serum
Cortisol/ACTH ratio	eACTH cortisol	1 ml EDTA-plasma (cooled) 1 ml serum
Intestinal profile	protein, albumin, globulins, Alb/Glob ratio, potassium, sodium, chloride, cortisol, PLI, TLI, vitamin B12, folate, haematology	1 ml serum whole blood blood smear