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Addison's disease

Diagnostic Brochure

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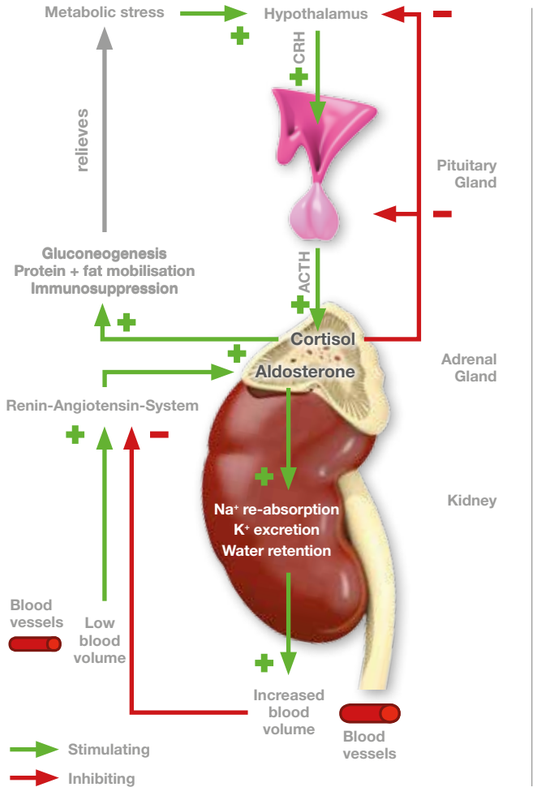
What is Addison's disease (hypoadrenocorticism)

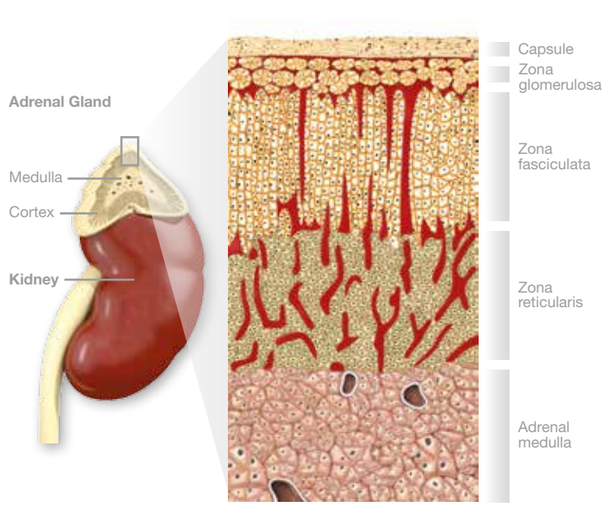
Addison's is a disease resulting from loss of production of corticosteroids, principally mineralocorticoids (mainly aldosterone) and glucocorticoids (mainly cortisol).

The most common cause of hypoadrenocorticism is primary hypoadrenocorticism, which is nearly always due to an immune-mediated destruction of the adrenal glands. This condition usually results in deficiencies of both glucocorticoids and mineralocorticoids, however cases of isolated glucocorticoid deficiency have been reported (atypical hypoadrenocorticism).

Secondary hypoadrenocorticism (caused by pituitary dysfunction) results in the deficiency of adrenocorticotropic hormone (ACTH). This is a very rare cause of canine hypoadrenocorticism and tends to result in glucocorticoid deficiency only.

Regulation of Cortisol and Aldosterone





Mineralocorticoids

The principal mineralocorticoid released by the zona glomerulosa of the adrenal cortex is aldosterone. The secretion of aldosterone is principally regulated by the renin-angiotensin system (which controls blood pressure in the body) and plasma potassium concentrations. Normally ACTH has only a permissive effect on aldosterone secretion. However pharmacological doses of ACTH, such as that used in an ACTH stimulation test, will induce the secretion of aldosterone. Aldosterone primarily acts on the proximal convoluted tubule in the kidney to increase sodium reabsorption and on the distal convoluted tubule to increase sodium reabsorption in exchange for potassium ions. Osmotic forces ensure that this results in an increase in water retention. Therefore aldosterone maintains blood volume by retaining sodium within the body and it also excretes potassium and hydrogen ions.

Aldosterone deficiency results in low sodium (hyponatraemia), high potassium (hyperkalaemia), increased hydrogen ions (acidosis) and low blood volume (hypovolaemia). Hypovolaemia causes poor renal perfusion and often pre-renal azotaemia. Acidosis, depression and microcardia can also develop. Ultimately ischaemic damage to the gastro-intestinal tract leads to severe vomiting, haemorrhagic diarrhoea and acute pancreatitis. Hyperkalaemia increases the threshold for action potential generation and causes depressed neuromuscular activity resulting in bradycardia and muscle weakness. The failure of sodium reabsorption in the nephron reduces the ability of the loop of Henle to maintain an effective concentration gradient leading to a polyuria and compensatory polydipsia. Importantly, the urine that is produced may be isosthenuric or only minimally concentrated in such circumstances.
This combination of relatively low urine concentration and azotaemia can easily be mistaken for renal disease.

Glucocorticoids

The principal glucocorticoid released by the zona reticularis and zona fasciculata layers of the adrenal cortex is cortisol. Its secretion is regulated by ACTH, which is produced by the pituitary gland. Cortisol acts on virtually every tissue in the body and produces a range of effects, which may be best explained as a group in terms of improving the body's defences against long term stress (particularly starvation), by mobilising amino acids and fat reserves. This leads to an increase in blood glucose by the breakdown of muscle and by acting against the body's major anabolic hormone (insulin), as well as increasing fat deposits in the liver and subcutaneous tissues by mobilising fat reserves. It stimulates appetite, red blood cell production and suppresses some aspects of the immune and inflammatory responses, thereby protecting the body from the more deleterious long-term consequences of these responses. Cortisol is the body's natural anti-pyretic and stimulates the production of scavenger proteins (such as albumin). Cortisol also has some effects on the amino acid metabolism and turnover of enterocytes as well as gastro-intestinal immunity.

Cortisol deficiency therefore results in anorexia, weight loss, anaemia, hypoalbuminaemia and hypoglycaemia. Depression is also associated with hypoadrenocorticism in humans and may be the result of the psychological effects of hypocortisolaemia as well as the metabolic abnormalities that have already been described. It is impossible to know if an animal is depressed but the behaviour of dogs with untreated hypoadrenocorticism would suggest that they suffer from something similar. Deficiency of cortisol may also affect gastro-intestinal motility and contribute to the vomiting, diarrhoea and inappetence seen in many cases of chronic hypoadrenocorticism.

Acute and chronic hypoadrenocorticism

Dogs with hypoadrenocorticism can present with a gradual onset of clinical signs e.g. intermittent bouts of vomiting and diarrhoea or they may present in an acute life-threatening state (hypoadrenocorticism crisis). Dogs presenting in crisis may also have had chronic clinical signs prior to the acute episode.

Clinical signs

Dogs with hypoadrenocorticism can display an array of clinical signs of varying severity that wax and wane, are non-specific and can be easily mistaken for other diseases e.g. renal disease, gastroenteritis including parvovirus infection, neuromuscular and metabolic diseases. Hypoadrenocorticism has been referred to as 'the great pretender'. The table below shows the variability of signs that may be reported by owners of dogs with hypoadrenocorticism.

Almost all cases	Common	Less common
Inappetence	Weakness	Diarrhoea
Lethargy/depression	Vomiting	Weight loss
		Shivering/muscle stiffness
		Polyuria
		Polydipsia
		Regurgitation
		Melena, haematemesis or haematochezia

Physical examination

Due to the variety both in type and severity of clinical signs in cases of hypoadrenocorticism, physical examination findings can range from signs consistent with hypovolaemic shock e.g. prolonged capillary refill times, weak peripheral pulses, weakness or collapse to more subtle changes such as abdominal pain and dehydration. Some cases may not even have any abnormalities noted on clinical examination.

It is worth noting that some dogs presenting in hypovolaemic shock may not have the expected tachycardia on examination due to the bradycardic effects of the hyperkalaemia.

The table below shows some of the physical examination findings that may be noted in dogs with hypoadrenocorticism[1].

Almost all cases	Common	Less common
Depression	Weakness	Painful abdomen
	Collapse	Prolonged capillary refill time
	Hypothermia	Bradycardia
	Dehydration	Weak pulse
		Melena

Differential diagnoses

As clinical signs/physical examination findings in canine hypoadrenocorticism can be non-specific, it can easily be confused with other diseases. Examples of these are shown in the table below[2].

Body system / organ	Examples	Similarities in presenting signs
Urinary tract	Acute renal failure	Dehydration Polyuria / polydipsia Vomiting Anorexia
Exocrine pancreas	Acute pancreatitis	Abdominal pain Dehydration Anorexia Vomiting Diarrhoea
Gastro-intestinal tract	Infectious enteritis (various)	Anorexia Vomiting Haemorrhagic diarrhoea
Hepatobiliary tract	Hepatitis (toxic, inflammatory)	Vomiting Diarrhoea
Neuromuscular system	Myasthenia gravis	Episodic weakness Regurgitation / vomiting
Cardiovascular system	3rd degree heart block	Bradycardia Episodic collapse
Endocrine system	Hypothyroidism	Bradycardia Dullness
Haematopoietic system	Anaemia	Pale mucous membranes Collapse

Haematology

Haematological changes that are most likely to raise suspicion for hypoadrenocorticism are:

1) Lymphocytosis
2) Eosinophilia
3) Lack of a "stress leukogram" i.e. a normal neutrophil count in an obviously unwell animal

Glucocorticoids inhibit neutrophil departure from the circulation: they cause demarginalisation of neutrophils; promote the movement of lymphocytes out of the circulation and cause lymphocytolysis; and suppress eosinophil numbers by a variety of mechanisms. This results in the typical stress leukogram picture of neutrophilia, eosinopenia and lymphopenia.

In the absence of glucocorticoids in hypoadrenocorticism, dogs can have higher lymphocyte and eosinophil counts than what would be expected for the degree of illness and stress. Therefore, normal or even high eosinophil/lymphocyte counts in a dog that is expected to be stressed due to illness, as well as absence of a neutrophilia should prompt the inclusion of hypoadrenocorticism in the differential diagnosis list. Very occasionally a reverse stress leukogram can be seen.

The haematocrit/PCV in dogs with hypoadrenocorticism is variable.
A non-regenerative anaemia is reported to occur in approximately 15% of cases, however dogs presenting in crisis tend to have higher values due to relative erythrocytosis secondary to dehydration/hypovolaemia[1].

Biochemistry

There are many biochemical changes of varying magnitudes that can occur in hypoadrenocorticism. One study assessing clinical parameters in 225 dogs with hypoadrenocorticism prior to treatment, found the abnormalities below (with the percentage of dogs with these abnormalities in brackets)[3]:

1) Increased urea (blood urea nitrogen) (88.4%) and increased creatinine (65.6%)

Azotaemia is common in hypoadrenocorticism due to poor renal perfusion caused by hypovolaemia. Hypovolaemia occurs as a consequence of the failure to preserve sodium and water due to the lack of aldosterone. Primary renal damage is uncommon in straightforward hypoadrenocorticism cases and the azotaemia is classified as “pre-renal”. In pre-renal azotaemia, urea (BUN) is commonly increased to a greater degree than is creatinine. Another possible explanation for a higher urea than would be predicted from the creatinine concentration is the presence of gastro-intestinal haemorrhage, which can also occur in these cases.

2) Metabolic acidosis (40.5%)

Mild metabolic acidosis is likely to be the consequence of reduced aldosterone mediated hydrogen excretion, hypovolaemia, hypotension and hypoperfusion.

3) Increased “liver” enzymes (ALKP, ALT, AST; 28.7-31.1%)

There are often mild increases in “liver” enzymes in dogs with hypoadrenocorticism. This may reflect the hepatic impact of reduced tissue perfusion perhaps in addition to portal challenges from compromised gastrointestinal mucosa. Primary hepatic pathology is unlikely to be a feature.

4) Hypoalbuminaemia (6.3%)

The mechanism by which some dogs with hypoadrenocorticism have low albumin is not understood. Interestingly, it is more often observed in dogs that have normal electrolyte concentrations (that are not in crisis when they present), suggesting that it could be a finding that is masked by dehydration and hypovolaemia in the classic cases.

5) Hypoglycaemia (16.7%)

Glucocorticoids promote hepatic gluconeogenesis and reduce insulin sensitivity. Consequently, in the absence of glucocorticoids, reduced gluconeogenesis and increased insulin mediated uptake result in lower circulating glucose concentrations. The hypoglycaemia is not caused by increased insulin concentrations[4].

6) Hypocholesterolaemia (7%)

The mechanisms by which a proportion of hypoadrenocorticoid dogs are hypocholesterolaemic are not clear. Glucocorticoids promote lipolysis and their absence may reduce the baseline level lipolysis and serum lipids. There may be reduced intestinal fat absorption. It has been noted that hypocholesterolaemia is more common in dogs with “glucocorticoid deficient” hypoadrenocorticism than typical hypoadrenocorticism[5].

7) Urine Specific gravity < 1.030 (57.6%)

In the classic description of pre-renal azotaemia due to reduced renal perfusion, concentrated urine with a high urine specific gravity (USG >1.030) would be expected. However, dogs with hypoadrenocorticism commonly have a USG < 1.030. It is believed that the mechanism for this is due to chronic loss of sodium caused by the lack of aldosterone mediated sodium resorption, resulting in reduced renal medullary sodium, a reduced medullary concentrating gradient and compromised concentrating ability of renal collecting ducts.

The combination of azotaemia and poorly concentrated urine can make the differentiation between renal disease and hypoadrenocorticism challenging and endocrine testing to assess for the presence of hypoadrenocorticism should be considered in these cases.

Electrolytes

The electrolyte changes that can be documented in hypoadrenocorticism (with the percentage of dogs with these abnormalities from one study on canine hypoadrenocorticism):[3]

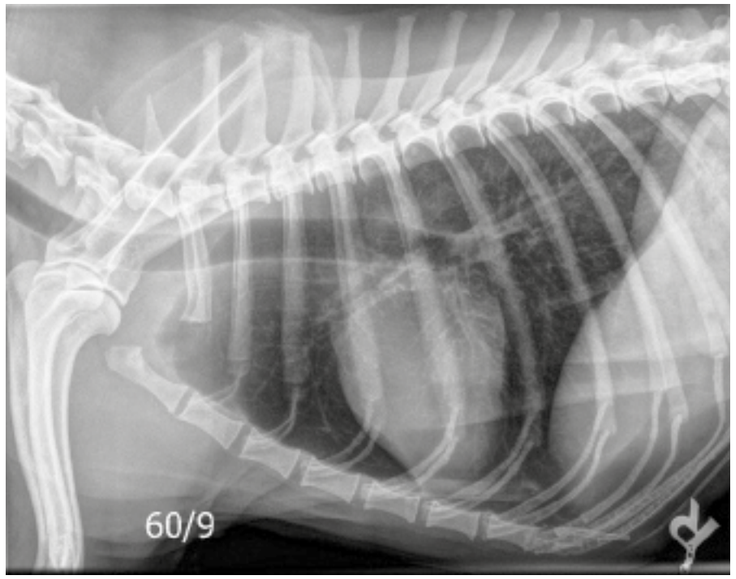
1) Decreased sodium to potassium ratio (95.6%)
2) Hyperkalaemia (95.6%)
3) Hyponatraemia (81.3%)
4) Hyperphosphataemia (68.3%)
5) Hypochloraemia (41.7%)
6) Hypercalcaemia (30.7%)

A very high proportion of dogs with primary hypoadrenocorticism will have hyperkalaemia, hyponatraemia and/or reduced sodium to potassium ratio (< 27). The presence of a low sodium to potassium ratio raises suspicion for hypoadrenocorticism, however, there are other non-adrenal causes of low sodium to potassium ratios, so this finding is not diagnostically specific[6,7]. Diagnostic specificity does increase progressively with lower sodium to potassium ratios, with a specificity of 96% reported at < 24 and 100% reported with a ratio < 23[8,9]. It should be remembered however that dogs with atypical primary hypoadrenocorticism or secondary hypoadrenocorticism will not have electrolyte abnormalities, as their aldosterone production is unaffected. Electrolyte abnormalities are also not present in all cases of primary hypoadrenocorticism.

Hypercalcaemia is observed in a significant proportion of cases of hypoadrenocorticism, particularly in those that present in crisis. The mechanism is not clearly understood and different authors have recorded different findings concerning total and ionised calcium results. The hypercalcaemia documented can be due to total hypercalcaemia with or without concomittant ionized hypercalcaemia but ionized hypocalcaemia can also occur[3,8,10]. Decreased glomerular filtration rate and decreased urinary excretion of calcium have been suggested to occur but there are rarely derangements of PTH, PTHrP or vitamin D[11].

Radiographs

Radiography may be indicated as part of the investigation of many of the presenting signs associated with hypoadrenocorticism. Radiographic findings in primary hypoadrenocorticism can include a small cardiac silhouette (microcardia) due to volume depletion, reduced diameter of the caudal vena cava and cranial lobar pulmonary artery and a small liver[12]. On very rare occasions a megaoesophagus may be seen.



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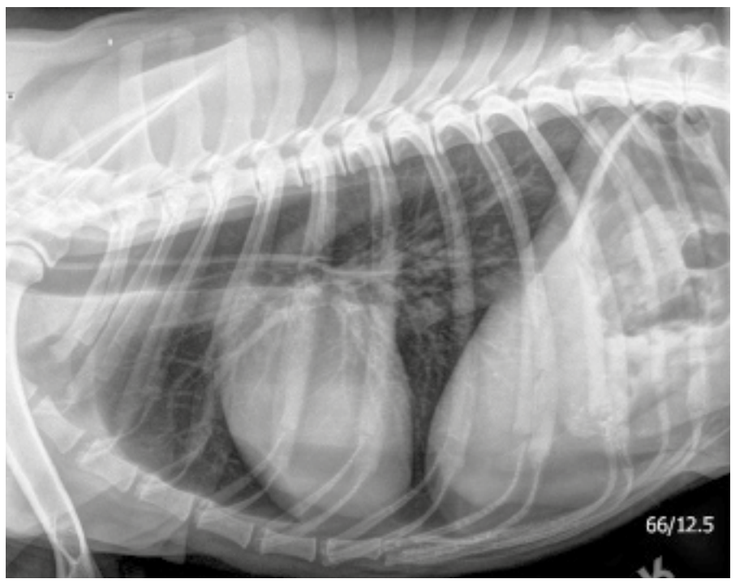
A thoracic radiograph of a dog with hypoadrenocorticism demonstrating microcardia.

This dog was in hypovolaemic shock at the time of presentation.



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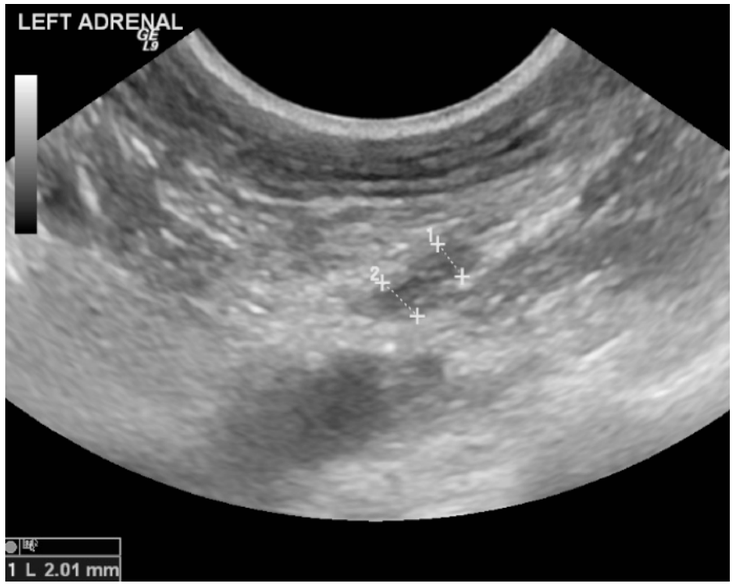
A thoracic radiograph of a dog with hypoadrenocorticism with megaoesophagus.

This dog presented with regurgitation as one of its main clinical signs.

Ultrasonography

Abdominal ultrasonography may also be indicated as part of the investigation of many of the presenting signs associated with hypoadrenocorticism e.g. to assess the pancreas with cases presenting with abdominal pain. It can be used to demonstrate a reduction in adrenal size, however such changes are not consistent[13,14]. Identification of adrenal glands can be technically challenging and therefore this can be operator dependent. The main modality of ultrasonography in these cases is mainly to assess for other disease processes that could be confused with hypoadrenocorticism e.g. pancreatitis and gastro-intestinal disease.



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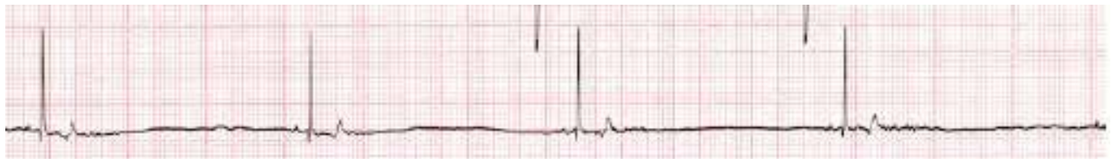
Ultrasound of a thin left adrenal gland in a dog with primary hypoadrenocorticism.

ECG

Electrocardiographic (ECG) changes are apparent in some cases of hypoadrenocorticism and develop because of the reduced conduction caused by the hyperkalaemia. ECG changes correlate poorly with the absolute potassium concentration because of the effects of hypercalcaemia (which protects the heart to some extent) and acidosis (which increases the extra-cellular potassium concentration).

ECG changes include sinus bradycardia, a reduction (and eventual loss) of the P wave, an increase in T wave amplitude and a widening of the QRS interval. The absence of a bradycardia does not exclude hypoadrenocorticism.



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ECG demonstrating sinus bradycardia (paper speed 25 mm/sec)

Basal cortisol

Basal cortisol has been shown to be an effective screening test for hypoadrenocorticism in cases where this condition is considered as a differential. The use of a cortisol value ≤ 55 nmol/L resulted in a 100% sensitivity for diagnosing hypoadrenocorticism, however due to the poor specificity at this value (63.3%), an ACTH stimulation test should then be performed to confirm the presence of the disease[15]. Cases with a basal cortisol > 55 nmol/L are unlikely to have the disease and so other disease processes should be considered in these cases.

ACTH stimulation test

The ACTH stimulation test is the gold standard for diagnosing hypoadrenocorticism in dogs.

Interpretation of ACTH stimulation

- Post-ACTH cortisol results < 55 nmol/L (< 2 µg/dL) are positive.
- Most cases have pre- and post-ACTH cortisol < 27 nmol/L (< 1 µg/dL)

Subnormal responses

In some cases of naturally occurring hypoadrenocorticism, adrenal function can deteriorate more gradually and so, as the disease progresses, there may be varied stages of subnormal cortisol responses to ACTH. These subnormal responses may not be sufficiently abnormal to result in clinical signs. If there is sufficient dysfunction to result in clinical signs, it is expected that post-ACTH cortisol will be less than 55 nmol/L (< 2 µg/dL).

False positives

It should be remembered that individual dogs have differing degrees of hypothalamic-pituitary adrenal axis sensitivity to the suppressive effects of glucocorticoids (and glucocorticoid acting substances such as progestogens). Some dogs are very sensitive and reduce their production of cortisol in response to very low doses of exogenous glucocorticoids. All history relating to recent glucocorticoid exposure must be considered in the interpretation of a positive ACTH response test result including “minor” exposure such as topical, eye, ear and skin treatments including over the counter owner-sourced products. False positive results are seen commonly in these circumstances.

Exaggerated responses

When the cortisol response to ACTH is exaggerated, e.g. post-ACTH cortisol > 600 nmol/L, hypoadrenocorticism is excluded. However this exaggerated response should not be used as the basis for considering a diagnosis of hyperadrenocorticism. Dogs that are sufficiently ill to be suspected of hypoadrenocorticism will be sufficiently ill to generate abnormally high cortisol as part of the stress response to their illness, i.e. generate a false positive result for hyperadrenocorticism.

Aldosterone

The traditional analyte of interest in ACTH stimulation is cortisol. However, this only assesses glucocorticoid production and not mineralocorticoid production. The inclusion of aldosterone measurement assists with

1) determining the need for mineralocorticoid supplement and
2) the differentiation of primary from atypical primary or secondary hypoadrenocorticism.
   - In primary hypoadrenocorticism, there will be no aldosterone response
   - In secondary (pituitary) hypoadrenocorticism or atypical primary hypoadrenocorticism, there will be an aldosterone response

Endogenous ACTH

In primary hypoadrenocorticism, the adrenal cortex has failed and both mineralocorticoid and glucocorticoid production are affected. However in atypical primary hypoadrenocorticism and secondary (pituitary dependent) hypoadrenocorticism, only the adrenal production of glucocorticoids but not mineralocorticoids is affected.

Endogenous ACTH (eACTH) can therefore be used to differentiate between atypical primary hypoadrenocorticism and secondary hypoadrenocorticism cases.

- In primary atypical hypoadrenocorticism (adrenocortical failure) eACTH will be high
- In secondary hypoadrenocorticism (pituitary failure) as well as iatrogenic hypoadrencorticism, eACTH will be low
- Beware of possible false low results due to sample handling and shipping

Endogenous ACTH should be interpreted with the results of the ACTH stimulation test and not used in isolation to diagnose hypoadrenocorticism. Animals that are sick/stressed because of non-adrenal illness will have high values (but will not have a failure to stimulate cortisol by ACTH).

Recent updates on diagnosis, treatment and monitoring hypoadrenocorticism

1) Atypical or glucocorticoid-deficient hypoadrenocorticism:

Not all dogs diagnosed with primary hypoadrenocorticism have the expected electrolyte abnormalities i.e. hyponatraemia, hyperkalaemia or sodium to potassium ratio < 27 (or a combination of these) noted on presentation. These cases have been classified as 'atypical or glucocorticoid deficient hypoadrenocorticism', with the assumption that only glucocorticoids were deficient in these dogs but mineralocorticoid production was unaffected, resulting in the lack of electrolyte changes on blood work.

Previous studies have detected that there may be additional differences in atypical versus typical cases of primary hypoadrenocorticism. Atypical cases tend to be older at presentation (mean age 7 years vs 4.4 years), have a longer mean duration of clinical signs (4.38 months vs 1.16 months) and be less likely to have vomiting as a presenting sign[16]. Another study documented that atypical cases tended to involve larger breed dogs > 20 kg[5]. Haematological and biochemical differences results have also been noted, with atypical cases being more likely to have anaemia, hypoalbuminaemia and hypocholesterolaemia[16]. Hypoglycaemia is also commonly noted in these cases[5].

Electrolyte abnormalities and therefore progression to typical primary hypoadrenocorticism can occur in atypical cases following diagnosis but this does not appear common[5,16].

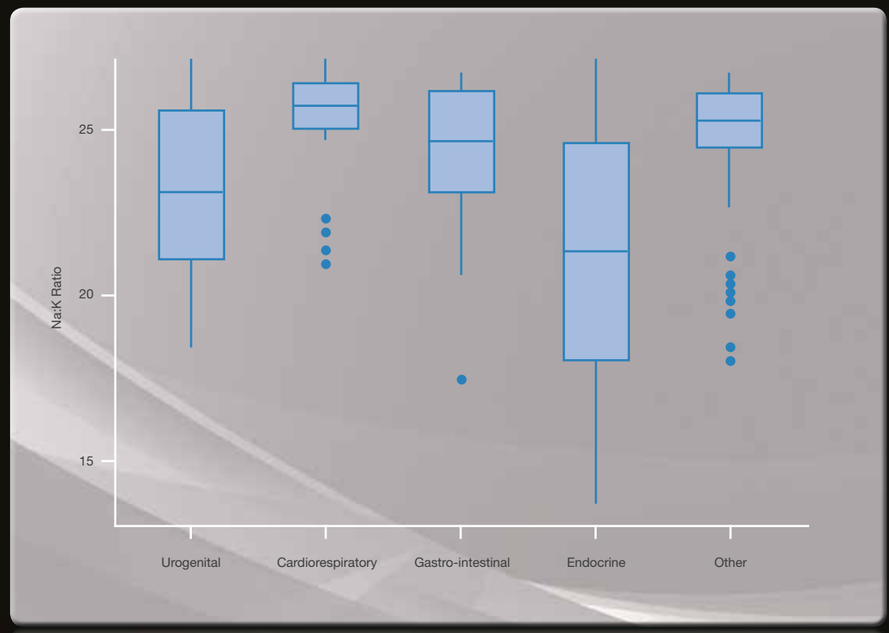
A recent study has shed potential doubt on classifying dogs with atypical primary hypoadrenocorticism using lack of electrolyte abnormalities alone. This study identified 3/70 dogs that were diagnosed with hypoadrenocorticism but had normal sodium/potassium concentrations at presentation, but which also had undetectable levels of aldosterone, consistent with abnormal function of the zona glomerulosa of the adrenal glands[17]. As historically aldosterone has not been routinely measured in all cases of hypoadrenocorticism with lack of electrolyte abnormalities, it may be possible that previous cases of atypical hypoadrenocorticism have been misclassified and were, in fact, aldosterone deficient as well. In humans, similar cases of primary hypoadrenocorticism have been identified with a lack of sodium/potassium abnormalities; however renin measurement in these cases has been consistent with a failing zona glomerulosa of the adrenal glands.

In cases of primary hypoadrenocorticism without electrolyte changes, measurement of aldosterone, endogenous ACTH (to differentiate atypical from secondary hypoadrenocorticism) and potentially plasma renin (to assess the function of the zona glomerulosa) should be considered in order to correctly classify the type of hypoadrenocorticism and therefore determine the need for mineralocorticoid supplementation in addition to glucocorticoids.

2) Screening tests for hypoadrenocorticism:

a) Sodium to potassium ratio and white blood cell count

A sodium to potassium ratio < 27 in dogs has been used to increase a clinician's suspicion of hypoaldosteronism, however there are many other diseases which can result in low ratios e.g. gastro-intestinal disease and cardiorespiratory disease[6,8]. The serum sodium and potassium levels and therefore the sodium to potassium ratio can also be very varied in cases of hypoadrenocorticism[17].



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The box plot above shows the different disease categories that were associated with low sodium to potassium ranges in dogs, as well as the ranges of the ratios seen in each category. There were 20 dogs in the urogenital group, 21 dogs in the cardiorespiratory group, 30 dogs in the gastro-intestinal group, 37 dogs in the endocrine group (of which 27 had hypoadrenocorticism) and 54 dogs in the other group[6].

One study has documented however that combining the sodium to potassium ratio with the lymphocyte count to identify dogs with hypoadrenocorticism, is superior to using either the ratio or the lymphocyte count alone[9]. The same study also documented that the neutrophil to lymphocyte ratio is significantly lower in dogs with hypoadrenocorticism (median value 3.0) compared to dogs without the disease (median value 9.51). A more recent study documented a specificity of 68% of diagnosing hypoadrenocorticism in cases where both the sodium to potassium ratio was ≤ 22 and the neutrophil to lymphocyte ratio was ≤ 2.3, as this combination of results wasn't seen in cases with non-adrenal illness[19]. Clinicians should therefore consider assessing haematological values as well as the sodium to potassium ratio to increase their suspicion of hypoadrenocorticism being present.

b) Aldosterone to renin ratio

The aldosterone to renin ratio was found to be significantly lower in dogs with hypoadrenocorticism compared to healthy dogs and there was also no overlap between the two groups[20]. However due to the absence of a group of dogs with disease mimicking hypoadrenocorticism in this study, the usefulness of this as a screening test cannot be currently assessed. Renin assays are also technically difficult to run and currently not widely available.

c) Cortisol to ACTH ratio

The cortisol to ACTH ratio has also been assessed as a screening test in canine hypoadrenocorticism in several studies[20,21,22]. The first studies did show promise with no overlap noted when compared to both healthy dogs and dogs with disease mimicking hypoadrenocorticism[20,22]. The results from the most recent study assessing this (which also had much larger case numbers) documented that the cortisol to ACTH ratio was the best parameter for diagnosing hypoadrenocorticism when compared to plasma ACTH levels, basal cortisol and the sodium to potassium ratio[21]. However there was overlap noted between dogs with hypoadrenocorticism and dogs with disease mimicking hypoadrenocorticism, which could result in misdiagnosis and inappropriate therapy being instituted if an ACTH stimulation test was not performed to confirm hypoadrenocorticism. Measuring ACTH is quite difficult as it can be rapidly decreased due to haemolysis/proteolysis post-sampling. Therefore samples must be handled in a very specific manner to allow the results to be interpreted reliably.

d) Endogenous ACTH

Endogenous ACTH has also been assessed as a tool for diagnosing primary hypoadrenocorticism by itself. Using a cut-off of > 50 pmol/L, it was found to have a sensitivity of 96% and a specificity of 100% for correctly diagnosing hypoadrenocorticism in a study assessing dogs with clinical signs suggestive of hypoadrenocorticism (n = 145). However these results would not be applicable to cases of secondary hypoadrenocorticism and this study did only include a small number of dogs with hypoadrenocorticism (n = 38)[19].

3) Monitoring mineralocorticoid replacement in cases of primary hypoadrenocorticism:

Dogs diagnosed with hypoadrenocorticism and receiving treatment are generally monitored and their treatment tailored using a combination of their clinical signs, physical examination findings and serum sodium and potassium levels, as well as their calculated sodium to potassium ratios.

Mineralocorticoid replacement is assessed in humans using a combination of clinical examination, blood pressure measurement to assess for orthostatic hypotension, serum sodium and potassium levels and measurement of plasma renin activity (PRA)[23]. The recommended target level for PRA is either within the reference range or just above the upper normal limit of reference.

A recent study was performed to assess the use of PRA as a monitoring tool for mineralocorticoid supplementation in dogs with primary hypoadrenocorticism[18]. This study found that PRA was (as expected) increased in cases of primary hypoadrenocorticism and decreased significantly with mineralocorticoid supplementation, confirming that as in humans, this could be used as a monitoring tool for mineralocorticoid supplementation in dogs and is a promising tool for the future.

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