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Hypoadrenocorticism is a syndrome that results from a deficiency of both glucocorticoid and mineralocorticoid secretion from the adrenal cortices. Destruction of more than 95 per cent of both adrenal cortices causes a clinical deficiency of all adrenocortical hormones and is termed primary hypoadrenocorticism (Addison’s disease). Secondary hypoadrenocorticism is caused by a deficiency in ACTH, which leads to atrophy of the adrenal cortices and impaired secretion of glucocorticoids. The production of mineralocorticoids, however, usually remains adequate.

PRIMARY HYPOADRENOCORTICISM (ADDISON’S DISEASE)

Primary hypoadrenocorticism occurs more frequently in the dog than is recognised but it is much less common than hyperadrenocorticism (Cushing’s disease). Hypoadrenocorticism is rare in the cat and only 8 cases have been reported. The clinical signs, diagnosis and treatment of hypoadrenocorticism in the dog and cat are similar.

Primary hypoadrenocorticism in the dog has been associated with the following conditions:

*Idiopathic adrenocortical insufficiency.* This is the commonest cause in the dog and is thought to result from immune-mediated destruction of the adrenal cortex. The presence of anti-adrenal antibodies in two dogs and characteristic histopathological findings in another support this hypothesis. In humans, hypoadrenocorticism has been found to be associated with other immune-mediated endocrine disorders such as thyroiditis, diabetes mellitus, hypoparathyroidism, primary gonadal failure and atrophic gastritis. A similar autoimmune polyglandular disease has also been recognised in dogs.

*Mitotane-induced adrenocortical necrosis.* Although mitotane usually spares the zona glomerulosa and therefore mineralocorticoid secretion, cases of complete adrenocortical failure can occasionally occur (see under treatment of hyperadrenocorticism).
Trilostane-induced adrenocortical necrosis. Although trilostane is a competitive inhibitor of steroid synthesis, it can cause acute adrenal necrosis, which can lead to complete adrenocortical failure (see under treatment of hyperadrenocorticism).

Bilateral adrenalectomy, haemorrhage or infarction of the adrenal cortex or mycotic or neoplastic involvement of the adrenal gland can also lead to adrenal insufficiency, but these are rare causes.

The loss or damage to the adrenal cortex leads to mineralocorticoid and glucocorticoid deficiency. Aldosterone is the major mineralocorticoid and deficiency causes impaired ability to conserve sodium and water and failure to excrete potassium leading to hyponatraemia and hyperkalaemia. Hyponatraemia induces lethargy, depression, nausea and leads to the development of hypovolaemia, hypotension, reduced cardiac output and decreased renal perfusion. Hyperkalaemia causes muscle weakness, hyporeflexia and impaired cardiac conduction. Glucocorticoid deficiency causes decreased tolerance of stress, loss of appetite and a mild normocytic, normochromic, anaemia.

Clinical signs

There are no breed predilections but the possibility of an hereditary factor has been suggested in some breeds, for example standard Poodles. Hypoadrenocorticism appears to be a disease of the young and middle-aged dog with an age range of 3 months to 9 years and a median age of 4 to 5 years. Approximately 70 per cent of reported cases are female.

The progression of adrenocortical insufficiency may be acute or chronic. Chronic hypoadrenocorticism is far more common than the acute disease in the dog.

Acute primary hypoadrenocorticism. The clinical appearance of the acute form is that of hypovolaemic shock (adrenocortical crisis). The animal is usually found in a state of collapse or collapses when stressed. Other signs include weak pulse, profound bradycardia, abdominal pain, vomiting, diarrhoea, dehydration and hypothermia. The condition is rapidly progressive and life-threatening. Aggressive fluid therapy will help most patients and allow more time to make a diagnosis.

Chronic primary hypoadrenocorticism. The clinical signs in the chronic form are often vague and non-specific. The diagnosis should be considered in any dog with a waxing and waning type of illness or that shows episodic weakness and collapse. The most consistent clinical signs include anorexia, vomiting, lethargy depression and/or weakness. The severity of each sign can vary during the course of the disease and may be interspersed with periods of apparent good health often following non-specific veterinary therapy, usually consisting of corticosteroid medication and/or fluid administration. Other common clinical signs include dehydration, bradycardia and weak femoral pulses. In a few cases, severe gastrointestinal haemorrhage can occur resulting in profound anaemia. Hypoadrenocorticism can easily be mistaken for chronic renal insufficiency, primary neuromuscular disorders and diseases which cause weight loss, weakness, anorexia, vomiting and diarrhoea.

Laboratory findings

Haematological changes may include lymphocytosis, eosinophilia and mild normocytic, normochromic,
non-regenerative anaemia. However, these findings are not as consistent as those changes seen in hyperadrenocorticism. Normal or elevated eosinophil and lymphocyte counts in an ill animal with signs compatible with hypoadrenocorticism are significant, because the expected response to stress is eosinopenia and lymphopenia. The mild anaemia may not be obvious until the dog has been rehydrated since dehydration may mask the anaemia.

The most consistent laboratory findings in hypoadrenocorticism are prerenal azotaemia, hyponatraemia and hyperkalaemia. Blood urea and serum creatinine are increased as a result of reduced renal perfusion and decreased glomerular filtration rate. Reduced renal perfusion results from hypovolaemia, reduced cardiac output and hypotension, which in turn result from chronic fluid loss through the kidneys, acute fluid loss through vomiting and/or diarrhoea, and inadequate fluid intake.

Prerenal azotaemia is usually associated with concentrated urine (specific gravity > 1.030) whereas the urine in primary renal failure is often isosthenuric or only mildly concentrated (1.008 to 1.025). Some severe cases of hypoadrenocorticism, however, may develop impaired concentrating ability because the chronic sodium loss reduces the renal medullary concentration gradient. Therefore the laboratory findings may resemble those of chronic renal failure. With adequate fluid therapy, the blood urea will return to normal in cases of hypoadrenocorticism.

Sodium is usually less than 135 mmol/l and potassium greater than 5.5 mmol/l. The ratio of sodium to potassium may be more reliable than the absolute values. The normal ratio of sodium to potassium varies between 27:1 and 40:1, whereas in patients with hypoadrenocorticism, the ratio is commonly less than 25:1 and may be below 20:1. Blood samples must be collected before intravenous fluids are administered otherwise the electrolyte concentrations may quickly return to normal. Even so, approximately 10 per cent of cases may have normal electrolyte concentrations at the time of presentation and these are usually thought to be early cases of hypoadrenocorticism.

Mild to moderate hypercalcaemia is seen in about a third of cases of hypoadrenocorticism, usually those dogs which are most severely affected by the disease. Hypercalcaemia is caused by haemoconcentration, increased renal tubular reabsorption and decreased glomerular filtration. Cases of hypoadrenocorticism have a tendency to develop hypoglycaemia because glucocorticoid deficiency reduces glucose production by the liver and peripheral cell receptors become more sensitive to insulin. Severe hypoglycaemia is uncommon but the potential should remain a concern for the clinician.

**Electrocardiographic findings**

Hyperkalaemia impairs cardiac conduction which can be assessed by electrocardiography (ECG). Although the ECG changes do not correlate directly with serum potassium levels, the following guidelines have proved helpful:

- > 5.5 mmol/L - peaking of the T wave
- shortening of the Q-T interval
- > 6.5 mmol/L - increased QRS duration
- > 7.0 mmol/L - P wave amplitude decreased
P-R interval prolonged
> 8.5 mmol/L - P wave absent
severe bradycardia (sinoventricular rhythm)

Electrocardiography can also be used for monitoring the patient during treatment.

Radiographic findings
Dogs with hypoadrenocorticism may show radiographic signs of hypovolaemia which include: microcardia, decreased size of pulmonary vessels and reduced size of the caudal vena cava. The changes are not specific and only represent changes associated with hypovolaemia and dehydration irrespective of the cause. A few dogs with hypoadrenocorticism develop oesophageal dilatation as a result of generalised muscle weakness and this can be seen on thoracic radiographs (Burrows, 1987).

Endocrine testing
The ACTH stimulation test is commonly used to confirm the presence of hypoadrenocorticism. The intravenous preparation of ACTH (tetracosactin) should be used as absorption by other routes cannot be relied on if the patient is collapsed or severely hypotension. In hypoadrenocorticism, the resting cortisol concentration will be low with a subnormal or negligible response to ACTH. The test can also be used to measure aldosterone. The ACTH stimulation test, however, does not distinguish between primary and secondary hypoadrenocorticism.

Plasma ACTH concentrations are required to differentiate primary and secondary hypoadrenocorticism. Plasma ACTH concentrations are low in secondary hypoadrenocorticism and markedly raised in primary hypoadrenocorticism.

Treatment
**Acute primary hypoadrenocorticism.** Aggressive intravenous fluid therapy using normal saline should be used in the acute crisis to treat the hyperkalaemia, which is life-threatening. The response to treatment is usually predictable and often dramatic. Monitor the circulating sodium concentration and ensure it does not increase by more than 10-12 mmol/l in the first 24 hours. Glucose and insulin therapy or calcium administration are therefore not usually required for the treatment of hyperkalaemia due to hypoadrenocorticism. The serum potassium falls because of the dilution effect of the saline and the improvement in renal perfusion. The increased renal blood flow allows further excretion of potassium into the urine. Dextrose may be required rarely if the patient is hypoglycaemic.

Glucocorticoid therapy should be used early in the treatment of the acute crisis. Once the animal has improved with saline and glucocorticoids, maintenance therapy with mineralocorticoids can be instigated. Glucocorticoids of choice in the acute crisis include:
- hydrocortisone sodium succinate 10 mg/kg IV repeated every 3 - 6 hours or as a constant rate infusion of 0.5 mg/kg/hour
- prednisolone sodium succinate 5 mg/kg IV repeated every 3 - 6 hours
- dexamethasone sodium phosphate 0.5 - 1.0 mg/kg IV given once
If plasma cortisol concentrations are to be measured for the diagnosis of hypoadrenocorticism, then dexamethasone should be used as the other preparations cross-react with cortisol in the assay.

**Chronic primary hypoadrenocorticism (maintenance therapy).** Fludrocortisone acetate (Florinef, Squibb) is an oral synthetic adrenocortical steroid with mineralocorticoid effects and is the treatment of choice for maintenance therapy in the dog. An initial dose of 15 mcg/kg/day of fludrocortisone is given and serum electrolytes measured after 5 to 7 days. The dose rate should then be adjusted until the sodium and potassium levels are within the normal range. The daily maintenance dose required is usually between 15 to 30 mcg/kg/day. The dose often has to be increased during the first 6 to 18 months of therapy and the drug may need to be administered twice daily in a few cases.

Daily glucocorticoid supplementation is not required after initial treatment in the majority of cases. However the owners of animals with hypoadrenocorticism should be given a supply of prednisolone tablets to be administered if the patient appears unwell. Prednisolone at a dose of 0.1 to 0.2 mg/kg daily should be sufficient as a physiological replacement for those cases that do require glucocorticoid medication.

Salt supplementation using salt tablets or salting the food should be instigated initially to help correct hyponatraemia but can be gradually reduced and phased out as it is not usually required long term. Dogs requiring unusually high doses of fludrocortisone, however, may respond to oral salt and fewer fludrocortisone tablets.

The prognosis for hypoadrenocorticism is generally excellent providing owner education is adequate.