The Emergency Approach to the Great Pretender: Addison's Disease
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Hypoadrenocorticism is an endocrine disease process that results from a deficiency of both glucocorticoid and mineralocorticoid secretion from the adrenal gland. A majority of our clinical hypoadrenocorticism patients suffer from primary hypoadrenocorticism, also known as Addison's disease. The main cause of hypoadrenocorticism is theorized to be an autoimmune destruction of the adrenal cortex. At least 90-95% of adrenocortical tissue must be destroyed before clinical signs develop. Typically, the destruction involves all three zones of the adrenal cortex and results in both glucocorticoid (cortisol) and mineralcorticoid (aldosterone) deficiency.

Pathophysiology of Hypoadrenocorticism
The adrenal gland is comprised of an outer cortex and the inner medulla, with the outer cortex subdivided into three layers. The outer layer (zona glomerulosa) is involved with synthesis and secretion of the mineralocorticoid hormone, aldosterone. The middle layer (zona fasciculata) synthesizes glucocorticoids, and the inner layer (zona reticularis) produces adrenal sex steroids. The adrenal medulla, which is not affected in hypoadrenocorticism, secretes catecholamines such as epinephrine and norepinephrine.

Hypoadrenocorticism results from atrophy or destruction of the adrenal cortex and may be classified as either primary or secondary. Primary hypoadrenocorticism results from bilateral destruction of the adrenal cortices presumed in most cases to result from immune-mediated destruction of the adrenal gland. Less common causes of primary hypoadrenocorticism include trauma (e.g., surgical versus other), infections (e.g., fungal or bacterial), neoplasia, or following medical therapy (e.g., mitotane, trilostane, ketoconazole, megestrol acetate, etc.). Secondary hypoadrenocorticism results from lack of adrenal gland stimulation due to hypothalamic-pituitary-adrenal axis dysfunction, which most commonly results from inflammation, tumors, or trauma. Exogenous steroid administration may also suppress ACTH release, resulting in adrenal atrophy.

Signalment
With hypoadrenocorticism, certain breeds of dogs are over-represented, including Standard Poodles, Great Danes, Rottweilers, West Highland White terriers, Wheaten terriers, Leonbergers, Portuguese Water Dogs, Labrador Retrievers, Bearded Collies, Old English Sheepdogs, and Standard Schnauzers. Hypoadrenocorticism is also seen more in young to middle aged female dogs.

Clinical Signs
Common clinical signs include lethargy, inappetence, vomiting, diarrhea, bradycardia, hypotension, weight loss, and rarely, death. Cortisol is required in almost all tissues of the body and its deficiency is associated with stress intolerance, weakness, gastrointestinal signs, and hypotension.

Clinicopathologic findings
Clinicopathologic findings seen with hypoadrenocorticism include the failure to mount a stress leukogram (resulting in eosinophilia, lymphocytosis, and normal overall white blood cell and neutrophil count) and electrolyte abnormalities secondary to direct aldosterone effects (e.g., hyperkalemia, hyponatremia, hypochloremia, metabolic acidosis). Other common laboratory abnormalities include azotemia, isosthenuria (from osmotic diuresis secondary to sodium losses), hypoglycemia (due to impaired gluconeogenesis), hypercalcemia (due to altered renal excretion, reduced gastrointestinal absorption, and decreased resorption of calcium from bone), hypoalbuminemia, and hypocholesterolemia.
**ENDOCRINE TESTING**

The ACTH stimulation test is commonly used to confirm the presence of hypoadrenocorticism. Typically, a cortisol level is drawn followed by intravenous ACTH (tetracosactrin) administration. This is followed by a paired cortisol sample following ACTH administration.

**TREATMENT**

Treatment for the critically ill hypoadrenocorticism patient should include symptomatic supportive care, aggressive fluid therapy, correction of electrolyte abnormalities and hypoglycemia, anti-arrhythmic therapy (if needed), steroid administration and mineralocorticoid supplementation, if needed.

Aggressive intravenous fluid therapy using an isotonic crystalloid should be used in the acute crisis. While some prefer the use of 0.9% NaCl, the author understands that not all practices will have an array of isotonic crystalloid options. Regardless of which crystalloid is chosen, it is important to monitor the sodium concentration and ensure it does not increase by more than 10–15 mmol/l in the first 24 hours. Dextrose may be required if the patient is hypoglycemic.

Glucocorticoid therapy should be used early in the treatment of the acute crisis. Glucocorticoid options 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:** 0.1–0.2 mg/kg IV given once

The author prefers to perform the ACTH stimulation test prior to the use of glucocorticoid therapy. If the patient health status does not permit waiting, dexamethasone sodium phosphate should be used as the other preparations cross-react with cortisol in the assay.

**Chronic Primary Hypoadrenocorticism (Maintenance Therapy)**

Once the patient is more stable, and the ACTH stimulation test confirms the diagnosis, the author will institute mineralcorticoid therapy. Options include fludrocortisone acetate (e.g. Florinef) and DOCP. Fludrocortisone acetate is an oral synthetic adrenocortical steroid with mineralocorticoid effects. 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. Alternatively, desoxycortisone pivivate (DOCP) is a slowly absorbed mineralocorticoid administered subcutaneously or intramuscularly at 21–28 day intervals. The dose for DOCP is 2.2mg/kg per treatment. Mineralocorticoid dose should be adjusted to maintain normal sodium and potassium.

**In Summary**

Clinicians should be able to rapidly recognize the “great pretender” based on history, signalment, clinical signs, and classic clinicopathologic testing. Rapid and appropriate diagnostic workup should be performed (e.g., baseline cortisol, ACTH cortisol evaluation) to rule out other "lookalike" diseases such as metabolic disorders (e.g., renal disease, pancreatitis), toxicosis (e.g., grapes, etc.), infectious disease (e.g., Leptospira, urinary tract infection, pyelonephritis), etc.

Without treatment, hypoadrenocorticism can be life threatening due to dehydration, hypovolemia, severe electrolyte derangements, and ongoing fluid losses. In order to ensure the best outcome, the rapid identification and recognition of the hypoadrenocorticism state should be made. Appropriate use of steroids needs to be weighed as not to impair diagnostic testing for baseline cortisol levels or for future ACTH stimulation tests.

While long-term management may be cumulatively expensive (e.g., prednisone, periodic electrolyte monitoring, and mineralocorticoid supplementation), the prognosis for hypoadrenocorticism is good to excellent with medical management.
References: