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Third Thursday Rounds
Lecture Notes

The Greatest Pretender: Challenging Adrenal Insufficiencies

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Introduction

Adrenocortical insufficiency can be life threatening and may be difficult to identify. This is because of a multitude of factors including uncommon patient signalments, vague clinical signs, normal hemograms, co-morbidities, and variances in types of adrenal insufficiency. To highlight these difficulties we will go through four unique cases and how they were diagnosed and successfully treated for adrenal insufficiency.

Hypoadrenocorticism is an endocrine disease of the adrenal gland, due to failure of the secretion of glucocorticoid and mineralocorticoids. The most important glucocorticoid and mineralcorticoid is cortisol and aldosterone, respectively. The most common form of this disease is primary adrenal failure (**Typical Hypoadrenocorticism or Addison's disease**) causing deficiency of both cortisol and aldosterone from the adrenal cortex. The more rare form of this disease is pituitary based dysfunction causing subsequent failure of adrenocorticotropin hormone (ACTH) release and subsequent pure glucocorticoid deficiency. This is called **Atypical Hypoadrenocorticism or Addison's Disease**.

Signalment

The signalment of dogs are most commonly young to middle aged female dogs (average 4-5 years of age). This disease is heritable in certain breeds including the Standard Poodle, Portuguese Water Dog, Nova Scotia Duck Tolling Retriever, and the Bearded Collie. Despite there being a heritable association, any dog or cat breed can develop this disease and is considered to be from autoimmune destruction of the adrenal cortex. This condition is much more rare in cats but does occur, both in the Typical and Atypical forms[1,2] There have been a few case reports of cats developing adrenal lymphoma resulting in adrenal insufficiency.[3]

Clinical Signs

The onset of clinical signs are often chronic although it may be an acute exacerbation, with the appearance of episodic (waxing/waning) signs in up to half of cases. Each patient has an individual number, severity, and progression of clinical signs. Difficulty in identification starts with an uncommon signalment and continues with individual and variable clinical signs, while also struggling with biased client histories. To better investigate potential stressors consider a change in their usual routine, including boarding, moving, lifestyle changes, and even an appointment (grooming, daycare, hospital).[4]

Signs to trigger suspicion include, but are not limited to, gastrointestinal signs, such as vomiting, diarrhea, decreased appetite, abdominal discomfort, lethargy, weakness, weight loss, shaking, polyuria, and polydipsia. These signs are mainly due to the glucocorticoid deficiency. When the mineralocorticoid is also deficient then more obvious signs can manifest including dehydration, hypovolemia, collapse, electrolyte abnormalities, and circulatory shock. To keep things interesting, patients with more severe presentations can also be due to glucocorticoids alone since adrenergic receptors, which are an important cofactor for maintaining vascular tone, can become flaccid causing both distributive (vasodilatory) and hypovolemic circulatory shock. Glucocorticoids are also responsible for maintaining a normal blood glucose concentration and so hypoglycemia seen with adrenal insufficiency can result in weakness and even neurologic signs, such as seizures, ataxia, and an altered mentation.

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Diagnostic Testing

Diagnostic testing is required to confirm this disease process and prompt oral therapy. There are indirect hemogram abnormalities which can help prompt suspicion for adrenal insufficiency, but a definitive diagnosis requires an ACTH stimulation test. Below is a list of laboratory abnormalities that can be seen with adrenal insufficiency. Variances are also provided to help point out how these values can be masked by co-morbidities and progressive consequences of adrenal insufficiency.

I. Complete Blood Chemistry

- Normocytic, normochromic anemia
- **Hemoconcentration (increased HCT or PCV%):** dehydration and hypovolemia can result in masking of the underlying anemia
- **Eosinophilia, neutrophilia, and lymphocytosis:** seen in only 25% of cases
- **Normal leukogram:** lack of a stress leukogram in a critically ill patient is a subtle finding that may be crucial in triggering suspicion
- **Inflammatory leukogram:** co-morbidities or secondary complications of adrenal insufficiency [such as GI translocation, initial inflammatory trigger to cause adrenal decompensation, critically-ill related-corticosteroid insufficiency (CIRCI)]

II. Chemistry

- **Hyponatremia:** lack of mineralocorticoids
  - Other differentials include gastrointestinal losses, diabetes mellitus, nephrotic syndrome, liver failure, medications (diuretics), primary hyperdipsia.
  - **Normal Na+:** hemoconcentration, hypovolemia, AKI, Atypical Addison's disease
- **Hyperkalemia**: lack of mineralocorticoids
  - Other differentials include acute renal or post-renal failure, gastrointestinal disease, liver failure, metabolic/respiratory acidosis, post-ischemic reperfusion, hemoconcentration, hypoaldosteronism, medications (potassium-sparing diuretics, ACE inhibitor)
  - **Normal K+:** Atypical Addison's disease, CKD, anorexia, gastrointestinal disease, hyperaldosteronism, medications (insulin therapy).
  - Cats with Typical Addison's disease tend to have lower potassium elevations when compared to dogs[5]
- **Elevated Calcium, Chloride, Phosphorus:** Typical or Atypical Addison's disease b/c of lack of mineralocorticoids causing inability to retain sodium renally, or Atypical form with hemoconcentration and hypovolemia.
- **Hypoalbuminemia, Hypocholesterolemia, Hypoglycemia, and elevated liver enzymes:** Typical and Atypical Addison's disease d/t lack of glucocorticoids.
  - Other differentials include liver failure, sepsis, gastrointestinal disease, insulinomas, and renal failure
- **[Na+]/[K+]:** helps to decipher through artificially altered electrolyte values. Should be less than 30 with Typical Addison's disease. Usually normal ratio with Atypical Addison's disease.

III. Imaging

- **Chest Radiographs:** microcardia, narrow posterior vena cava, microhepatica. Can be normal if only mildly hypovolemic or normovolemic.
- **Abdominal imaging:** gastroenteritis signs, pancreatitis, small adrenal glands bilaterally. Can be normal.

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IV. ACTH Stimulation test

- **Baseline cortisol:** 2 ug/dL or above will exclude the diagnosis of hypoadrenocorticism. < 2 ug/dL should increase suspicion and prompt ACTH stimulation testing
  - **Cosyntropin injection for ACTH stimulation test:** 250 ug in dogs and 125 ug in cats IM or IV.
- **Post-30 minute Cortisol:** low laboratory reference range. This additional test is usually performed in cats due to decreased ACTH hormone circulation time. Other differential is CIRCI.[1]
  - Laboratory sample collection methods vary so consult with laboratory
- **Post-60 minute Cortisol:** low laboratory reference range in dogs. Cats may have a normal level by this time. Other differential is CIRCI.[4]

Due to the difficulty in identifying this condition, the possibility of other metabolic conditions that cause similar signs, and the ability for the patient to improve without direct treatment for adrenal insufficiency, this disease should be considered in any systemically ill dog or cat. Also consider with waxing and waning illness, improvement with conservative management, and the improvement once glucocorticoids are initiated. Overall the type of adrenal insufficiency, severity of secondary consequences, species variances, and co-morbidities all make blood work abnormalities quiet variable. Keep this in mind when interpreting hemograms and the patient's clinical scenario.

Treatment

Treatment should be provided immediately if Addison's disease is suspected, since electrolyte derangements, hypoglycemia, and circulatory shock (both distributive and hypovolemia) can cause life-threatening complications. Initially stabilization includes intravenous fluid resuscitation, correction of electrolyte derangement and acidosis, supplementation if hypoglycemia, and the initiation of glucocorticoids. The initial treatment is usually an injectable form of Dexamethasone (0.1 to 0.25 mg/kg q12-24 hours) since it does not disrupt the interpretation of the ACTH stimulation testing. Oral steroids will affect these results and are not recommended until post-cortisol samples are drawn. The lower end of the dose may be administered if the patient is showing signs of sepsis or if Addison's disease is considered less likely while the ACTH stimulation test is pending.

Starting with an isotonic crystalloid for fluid resuscitation is reasonable since any formulation will provide a decrease in potassium through dilution, improving renal perfusion, and correcting metabolic acidosis. It is important to be cognizant of the patient's sodium level when choosing and administering isotonic crystalloid therapy. Do this by ensuring the sodium does not change more than 0.5-1 mEq/L/hr if there is any consideration for this change occurring for longer than 24 hours. This is to prevent the potential for central pontine myelinolysis. Start by choosing the isotonic crystalloid that most closely matches the patient's current sodium level and recheck sodium levels every 4-6 hours to reassess the fluid plan. If the potassium elevation is of concern it may be wise to consider the initial bolus with normal saline followed by ongoing resuscitation with a different isotonic crystalloid. Please see the table above for information regarding isotonic crystalloid and colloid fluids and their respective sodium and potassium concentrations. Fluid therapy is discontinued when dehydration, azotemia, and electrolyte derangements resolve and the patient is eating and drinking. Mineralocorticoid support is provided by administering either IM or SQ desoxycorticosterone pivalate (DOCP) 2 mg/kg q23-30 days or oral fludrocortisone acetate 0.1 mg q 24 hours. Since there is no rapid-acting version of this medication and the electrolytes often are corrected by providing a combination of fluids and glucocorticoids, it is recommended to administer after the patient is hemodynamically stable, azotemia has resolved, and electrolyte derangements are corrected.[6]

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Be aware that cats with adrenal insufficiency tend to respond slower than dogs, and can take up to 3 to 5 days to appreciate improvement. If there is ongoing lack of response in cats, lymphoma of the adrenal glands should be considered.[2] Once stabilization has occurred and the patient's parameters have improved or normalized, long term therapy for Atypical Addison's disease is prednisone (prednisolone in cats) to replace the glucocorticoids. The patient should be tapered to the lowest effective dose. Prior to an anticipated stressful event the client should be instructed to double the physiologic steroid dose starting the day before and continuing until 1-2 days after the event. Cats have also been found to require DOCP injections at closer to the 30 days, where dogs are on average anywhere from 23-30 days. This warrants electrolyte testing every 3-5 days after 23 days in both species until electrolytes derangements are appreciated. Monitoring the patient long term is very important for quick identification of further destruction of the adrenal gland and potential electrolyte derangements (eg. Atypical Addisonian can transition into a Typical Addisonian). In addition, monitoring for signs of iatrogenic hyperadrenocorticism is important.[6]

Critically-Ill Related Adrenal Insufficiency (CIRCI)

The last notable difficulty in diagnosing and treating adrenal insufficiency is that there is a condition that can mimic Atypical Hypoadrenocorticism. It is a condition vaguely defined as an inadequate cortisol production or response during periods of severe stress such as critical illness, most notable during sepsis and septic shock.[7] It was first recognized in critically-ill humans that would respond hemodynamically to low physiologic doses of steroids versus patients without any steroids or high-dose steroids.[8] There is no test to truly discern between these two disease processes and this comes from critically-ill patients having lack of cellular response to circulating cortisol or cortisol concentrations that are not adequate for the illness at hand but could be normal or even elevated for laboratory references. The major difference is that CIRCI is secondary to a serious illness that needs to be identified and treated aggressively, while both diseases require steroids to regain hemodynamic stability. The key difference in treatment is that Atypical Addisonian causes life-long steroid dependency, where CIRCI is a temporary deficiency, and thus steroids can be tapered and then discontinued.

References

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