Hypoadrenocorticism in Dogs

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Hypoadrenocorticism, also known as Addison's disease, is an uncommon but important endocrine disease of dogs. This disorder results from adrenal cortical failure, which is presumed in most cases to result from immune-mediated destruction of the adrenal cortex. However, this has rarely been shown to occur due to other causes in dogs, including bilateral adrenal neoplasia, infarction, or granulomatous disease due to systemic fungal infections.[1] In most dogs with hypoadrenocorticism, this destruction occurs in all layers of the adrenal cortex, resulting in signs of both glucocorticoid and mineralocorticoid deficiency. These patients are commonly referred to as having typical or classic hypoadrenocorticism. However, in up to 30% of patients with hypoadrenocorticism, there are no electrolyte abnormalities that would suggest a mineralocorticoid deficiency, and the signs are exclusively due to glucocorticoid deficiency; these patients are referred to as having atypical or glucocorticoid-deficient hypoadrenocorticism.[1] Although it was long assumed that patients with atypical hypoadrenocorticism had selective destruction of the adrenal cortex that resulted in sparing of the zona glomerulosa, the layer that produces mineralocorticoids, studies have shown variable aldosterone levels in patients with atypical hypoadrenocorticism. These have ranged from very low levels consistent with classic mineralocorticoid deficiency,[2] to normal aldosterone levels that would suggest sparing of the zona glomerulosa.[3] Patients with atypical hypoadrenocorticism may progress to typical hypoadrenocorticism over time. However, this is only reported in 9 to 14% of patients, indicating that most atypical dogs will remain atypical. [3,4]

Hypoadrenocorticism in dogs is most common in young to middle-aged dogs, although it has been reported in patients ranging from four months to 14 years of age.[1] A female sex predilection has generally been described, although it is not replicated in all studies.[1,5,6] One recent study showed that spayed or neutered dogs had a significantly higher risk of developing hypoadrenocorticism than intact dogs.[7] Certain breeds have a much higher risk of developing hypoadrenocorticism. Hypoadrenocorticism is inherited as an autosomal recessive trait in the Standard Poodle, Nova Scotia Duck Tolling Retriever, and Portuguese Water Dog. Other breeds at increased risk include the Bearded Collie, Great Dane, West Highland White Terrier, and Wheaten Terrier, among others.[1]

Clinical signs of hypoadrenocorticism are generally non-specific, including lethargy, reduced appetite, vomiting, diarrhea, weakness, and shaking. Patients with typical hypoadrenocorticism frequently present in an acute crisis, with signs of hypovolemic shock, collapse, or severe dehydration. Patients with atypical hypoadrenocorticism are more likely to present with chronic or waxing and waning clinical signs and have been shown to have a longer duration of signs preceding diagnosis compared to patients with typical hypoadrenocorticism.[3] Less commonly, hypoadrenocorticism may result in melena or hematochezia.[1,8] Rarely, megaesophagus may occur in patients with hypoadrenocorticism,[9] and there have been recent case reports of patients with hypoadrenocorticism that have an acquired dilated cardiomyopathy similar to what has been described in some human Addisonian patients.[10,11]

Typical hypoadrenocorticism will result in classic electrolyte disturbances secondary to aldosterone deficiency, including hyperkalemia, hyponatremia, hypochloremia, and metabolic acidosis. The lack of aldosterone leads to renal sodium wasting and, thus, an inability to conserve water, which is what results in the marked hypovolemia and dehydration often noted in these patients. Although patients with typical hypoadrenocorticism often present in hypovolemic shock, their hyperkalemia may cause bradycardia, leading to heart rates much lower than expected for a patient in shock. Therefore, bradycardia in the face of hypotension or hypovolemia should increase the index of suspicion for hypoadrenocorticism. Prerenal azotemia secondary to hypovolemia is common in patients with typical hypoadrenocorticism. However, this may be easily mistaken for a renal azotemia due to reduced urine concentrating ability secondary to the washout of sodium from the kidneys. Hypercalcemia is seen in approximately 34% of patients with hypoadrenocorticism and is more common in patients with typical vs. atypical disease.[12] Other common biochemical abnormalities include hypocholesterolemia, hypoalbuminemia, and hypoglycemia. Hypocholesterolemia and hypoalbuminemia are more common in dogs with atypical hypoadrenocorticism,[3] which may further complicate the diagnosis of hypoadrenocorticism in these cases as these abnormalities can also be seen with protein-losing enteropathy and hepatic dysfunction. Thirty percent of dogs with hypoadrenocorticism will have mild elevations in hepatic enzymes, and changes in complete blood count may include lymphocytosis, eosinophilia, non-regenerative anemia, and a lack of stress leukogram in an ill patient.[1]

A definitive diagnosis of hypoadrenocorticism is confirmed with an ACTH stimulation test. This test should be performed by measuring cortisol levels before and 1 hour after administration of a 5 µg/kg intravenous dose of synthetic ACTH (cosyntropin). Dogs with hypoadrenocorticism will fail to have any stimulation of cortisol production and thus will have pre- and post-ACTH cortisol levels <2 µg/dl, although most Addisonian patients will have a cortisol level <1 µg/dl for both pre- and post-ACTH cortisol levels.[1] It is important to keep in mind that recent or current corticosteroid administration may alter ACTH stimulation test results. This can occur if the patient has had a steroid medication that may read falsely as cortisol. Still, it can also occur if the recent administration of a steroid medication has resulted in suppression of endogenous cortisol production. In patients with severe illness or a very high suspicion of hypoadrenocorticism, the ACTH stimulation test should be the first-line test. However, in patients who are suspected of potentially having atypical hypoadrenocorticism or who have more mild or chronic clinical signs, starting with a single basal cortisol measurement can be a useful screening test. Multiple studies have shown that a single basal cortisol level >2 µg/dl effectively rules out hypoadrenocorticism.[13,14,15] In patients with a cortisol level ≤ 2 µg/dl, an ACTH stimulation test is required to determine whether hypoadrenocorticism is present.

Treatment of hypovolemic patients should focus on fluid resuscitation with crystalloids and emergency treatment of hyperkalemia if required. Historically, 0.9% saline was recommended for Addisonian patients. Still, many clinicians prefer a buffered replacement crystalloid solution such as lactated Ringer's solution or Normosol-R to avoid the acidifying effects of 0.9% saline.[1] Ideally, an ACTH stimulation test should be done before any glucocorticoid supplementation is given. However, if this is not possible or the patient is unstable, dexamethasone can be administered prior to an ACTH stimulation test, as it is not read as cortisol by most assays. Glucocorticoid supplementation in the acute phase of illness should be supraphysiologic to account for the patient's current state of illness and long-term lack of endogenous glucocorticoids leading up to presentation. Recommendations vary, but a 1 to 2 mg/kg/day prednisone equivalent dose is a reasonable starting dose for acute treatment, and this should be reduced over time as the patient improves. Typically, dexamethasone is used intravenously in the acute phase of treatment during hospitalization before the patient is transitioned to oral prednisone for long-term therapy. In the long term, patients should be administered a physiologic dose of prednisone daily. For most dogs, a physiologic dose of prednisone will be between 0.1 to 0.2 mg/kg/day, but some dogs are very sensitive to the effects of prednisone and may require even lower doses for physiologic glucocorticoid replacement.[1] The dose can be reduced until the patient shows no signs of steroid excess and clinical signs remain controlled. Because the normal daily prednisone dose is meant to mimic the physiologic production of cortisol, this dose may not be adequate for Addisonian dogs in stressful situations. Therefore, the daily steroid dose should be doubled in times of stress. What counts as a stressful situation

will vary from dog to dog and may include things like boarding, travel, having visitors to the family, and veterinary visits.

Mineralocorticoid supplementation in dogs with typical hypoadrenocorticism is best achieved with DOCP (desoxycorticosterone pivalate), a long-acting synthetic mineralocorticoid with no glucocorticoid activity. The published starting dose for this medication is 2.2 mg/kg IM or SC every 25 days.[1] However, multiple studies have shown that most dogs can be controlled on significantly lower doses of DOCP or with longer dosing intervals,[16,17] so a lower starting dose of 1.5 mg/kg every 25-28 days could be considered.[16] A lower dose may be a good option in patients >3 years of age, as one study showed that these dogs had a significantly lower DOCP requirement than younger patients.[16] Electrolytes should be rechecked two weeks after the first DOCP dose is administered to ensure normalization of sodium and potassium has occurred. Electrolytes should also be rechecked immediately prior to the next DOCP injection to ensure they remain normal; if they are normal at this time, the dosing interval can be increased by several days, with the goal for most patients being to achieve a monthly dosing interval as this is generally the best option for owner compliance. Once an ideal dosing regimen is established for DOCP, owners may opt to administer these injections subcutaneously at home, helping to reduce the overall cost of treatment. Fludrocortisone, an oral mineralocorticoid with some glucocorticoid activity, can be used instead of DOCP, but it tends to be more challenging. This is both because it results in less consistent control of electrolytes than DOCP in many patients and because the glucocorticoid activity may result in signs of iatrogenic hyperadrenocorticism even when prednisone is not administered concurrently.[1] Therefore, DOCP is recommended over fludrocortisone for mineralocorticoid supplementation in Addisonian dogs.

The prognosis for patients with hypoadrenocorticism is excellent, and prolonged survival is expected with appropriate treatment. Although hypoadrenocorticism is a relatively rare disease, it is an important differential diagnosis to consider in patients with consistent clinical signs and laboratory abnormalities, as it is a life-threatening but highly treatable disease with an excellent prognosis.

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