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## ISSUES IN ENDOCRINOLOGY

# Diagnosis and Management of Hypoadrenocorticism in Dogs

*Pamela Galati, BVetMed, MRCVS*

*Patty Lathan, VMD, MS, DACVIM (SAIM)*

*Mississippi State University College of Veterinary Medicine, Starkville, Miss.*

Primary hypoadrenocorticism, also known as Addison's disease, is a syndrome caused by bilateral dysfunction of the adrenal cortices. The adrenal glands are located in the abdomen medial to the kidneys and are composed of the cortex (outer portion) and medulla (inner portion). Within the adrenal cortex are 3 distinct layers, which are responsible for production of different hormones. From the outermost to the innermost, these layers are the zona glomerulosa, zona fasciculata, and zona reticularis. Cells in these layers produce aldosterone, cortisol, and adrenal androgens, respectively.

Hypoadrenocorticism is primarily a disease of dogs and occurs only rarely in cats. This condition is heritable and most commonly affects dogs of 4 breeds: standard poodles,<sup>1</sup> Portuguese water dogs,<sup>2</sup> Nova Scotia duck tolling retrievers,<sup>3</sup> and bearded collies. Other commonly affected breeds include West Highland white terriers,<sup>4,5</sup> Great Pyrenees,<sup>6</sup> and wheaten terriers.<sup>4,5</sup> Although the most common cause is thought to be immune-mediated adrenalitis,<sup>7</sup> in the absence of a definitive diagnosis, most

hypoadrenocorticism is classified as idiopathic. However, it can also occur secondary to other disorders that result in bilateral adrenal gland destruction (e.g., amyloidosis, hemorrhage, and neoplasia).<sup>4</sup> A recent report described hypoadrenocorticism secondary to intravascular lymphoma in a 2-year-old German shepherd.<sup>8</sup>

Most cases of hypoadrenocorticism represent a deficiency of glucocorticoids (primarily cortisol) and mineralocorticoids (primarily aldosterone), but other manifestations can occur. Atypical Addison's disease causes signs of isolated glucocorticoid deficiency. Some affected dogs are in very poor condition and considered to be experiencing an Addisonian crisis. In addition to the more commonly reported gastrointestinal signs that may be evident from a thorough history, dogs experiencing an Addisonian crisis are in hypovolemic shock and may have collapsed. In this article, we describe the diagnosis and management of these manifestations of hypoadrenocorticism.

## THE GREAT PRETENDER

Because hypoadrenocorticism in the dog has the ability to mimic other common diseases, it can be challenging to make the proper diagnosis.



## PRESENTATION

The clinical signs of hypoadrenocorticism can vary along a continuum of severity and chronicity (**BOX 1**). Because glucocorticoids help counteract the effects of stress and maintain normal gastrointestinal mucosal integrity and function, many dogs with glucocorticoid deficiency initially display waxing and waning nonspecific signs such as episodic vomiting, diarrhea, melena (**FIGURE 1**), lethargy, and dehydration. These dogs may respond well to supportive care;<sup>9</sup> thus, underlying hypoadrenocorticism can initially go undiagnosed.

However, when mineralocorticoid deficiency accompanies glucocorticoid deficiency, clinical signs can become more severe. Aldosterone stimulates sodium, chloride, and water retention along with potassium excretion in the distal renal tubules; therefore, lack of aldosterone results in hypochloremia, hypovolemia, acidosis, and hyperkalemia.<sup>10</sup>

In patients with atypical Addison's disease, clinical signs result from cortisol deficiency alone.

Among patients experiencing Addisonian crisis, some have previously received treatment for nonspecific signs; others have not because they displayed no clinical signs.

## DIAGNOSTICS

For any dog suspected to have hypoadrenocorticism, an excellent screening test is resting cortisol levels. This test is sensitive in that if the resting cortisol level is greater than 2.0 mcg/dL, for almost all dogs you can rule out hypoadrenocorticism. However, a low resting cortisol level alone can be normal for some dogs and thus a definitive diagnosis requires further testing. Classic bloodwork abnormalities associated with hypoadrenocorticism are hyperkalemia, hyponatremia, and lack of a stress leukogram.<sup>4</sup>

### BOX 1 Classic and Potential Clinical Signs of Hypoadrenocorticism

- Decreased appetite
- Vomiting, hematemesis
- Diarrhea, melena
- Lethargy or decreased willingness to exercise



**FIGURE 1.** Melena is common in dogs with hypoadrenocorticism, although because of ileus, it may not be obvious until after the dog has been hospitalized for 2 to 3 days. It is often present when packed cell volume drops precipitously after an Addisonian crisis but no other cause for the drop can be found.

## Serum Chemistry

In a dog with compatible history and clinical signs, a sodium:potassium ratio of less than 27 should prompt definitive testing. Be aware that low sodium:potassium ratios can occur in dogs with other conditions (e.g., renal failure,<sup>11</sup> trichuriasis,<sup>12</sup> pregnancy,<sup>13</sup> and body cavity effusions<sup>11</sup>) (**BOX 2**).

Additional abnormalities on serum biochemistry panels can include azotemia, hypoalbuminemia, hypocholesteremia, hypoglycemia, hypercalcemia, and elevated liver enzyme levels (**BOX 3**). Most patients do not have all of these abnormalities but instead may have a few that are severe (e.g., hypoglycemia and/or azotemia). Most dogs with hypoadrenocorticism show

### BOX 2 Differential Diagnoses Other Than Hypoadrenocorticism for Low Sodium:Potassium Ratio

#### Digestive system

- Acute kidney injury (anuria or oliguria)
- Trichuriasis
- Cavitary effusions (e.g., chylothorax)
- Pregnancy and periparturient illness
- Receipt of angiotensin-converting enzyme drug



vague symptoms that can prompt investigation of other body systems, including the gastrointestinal tract and kidneys. The laboratory findings for dogs with hypoadrenocorticism are similar to those of acute kidney injury (e.g., azotemia, electrolyte changes, and isosthenuria); thus, hypoadrenocorticism should always be a major differential diagnosis for dogs with these laboratory findings.

In dogs with atypical Addison's disease, electrolyte derangements are absent; hence, we rely on the signs of hypocortisolism (e.g., vomiting, diarrhea, melena, lethargy) to raise suspicion and prompt testing. One study suggested that aldosterone levels in patients with atypical Addison's disease are low;<sup>14</sup> it is unclear as to why patients with atypical Addison's disease do not have electrolyte abnormalities.

## Complete Blood Count

Along with clues from the serum biochemistry, a normal lymphocyte count may further raise suspicion for hypoadrenocorticism because a dog ill from another cause should have lymphopenia secondary to cortisol release (stress leukogram).<sup>4</sup> One study found that for all dogs with hypoadrenocorticism, lymphocyte counts were greater than 750/mcL; thus, for dogs with fewer

### BOX 3 Common Clinicopathologic Abnormalities in Dogs With Hypoadrenocorticism

- Hyperkalemia
- Hyponatremia
- Hypochloremia
- Acidosis
- Azotemia
- Hypoglycemia
- Increased alanine and aspartate aminotransferase levels
- Hypercalcemia
- Hypoalbuminemia
- Hypocholesterolemia
- Anemia
- Eosinophilia
- Lack of stress leukogram

### BOX 4 Procedure for Performing ACTH Stimulation Test<sup>18</sup>

1. Collect a blood sample into a red top tube.
2. Administer 5 mcg/kg of synthetic ACTH IV (up to a maximum of 250 mcg/dog). Avoid use of compounded formulations.
3. After 60 minutes, collect a second blood sample.
4. Submit both serum samples for cortisol measurement.

than 750 lymphocytes/mcL (and no previous receipt of glucocorticoids), hypoadrenocorticism is unlikely.<sup>15</sup>

In addition to not showing a stress leukogram, dogs with hypoadrenocorticism can be mildly to severely anemic. Severe anemia is often accompanied by melena and/or hematochezia, caused by gastrointestinal bleeding resulting from increased vascular permeability in the absence of cortisol. The packed cell volume (PCV) in patients in Addisonian crisis may initially be within reference range or mildly decreased but 1 to 2 days later severely decreased after rehydration and further blood loss. Because of ileus, which is common in dogs with hypoadrenocorticism, melena may not be apparent for 2 to 3 days.

## Imaging

Diagnostic imaging is not typically required for the diagnosis of hypoadrenocorticism. However, because of the nonspecific signs of this disease, thoracic and abdominal imaging are often included in the diagnostic workup of these patients. Some ultrasonographic and radiographic signs can be helpful. As you might expect, ultrasonography has shown that the adrenal glands are shorter and thinner in affected dogs than in those of their unaffected counterparts.<sup>16</sup> Radiographs may indicate hypovolemia (e.g., small heart and liver and decreased diameter of the cranial lobar pulmonary artery and caudal vena cava).<sup>17</sup>

## Definitive Diagnosis

To confirm hypoadrenocorticism, an adrenocorticotropic hormone (ACTH) stimulation test (BOX 4) must be performed. This test is performed by



measuring serum cortisol concentrations before and 1 hour after administration of synthetic ACTH. Use of synthetic cosyntropin at 5 mcg/kg, compared with the previously used dose of 250 mcg/dog, helps reduce the costs associated with testing.<sup>18</sup> In addition, reconstituted cosyntropin can be stored in plastic (not glass) syringes and frozen for up to 6 months without affecting efficacy,<sup>19</sup> making it more cost-effective for practitioners who would otherwise not use an entire vial before effectiveness is affected. A definitive diagnosis of hypoadrenocorticism can be made when post-ACTH cortisol levels are less than or equal to 2 mcg/dL. A recent study evaluated dogs that were suspected of having hypoadrenocorticism but had higher cortisol concentrations (up to 10 mcg/dL) after ACTH stimulation testing.<sup>20</sup> For these dogs, hypoadrenocorticism was ruled out for the following reasons: another disease (inflammatory bowel disease) was diagnosed, they did not respond to glucocorticoid administration, or signs of hypoadrenocorticism did not return after discontinuation of glucocorticoids. In our experience, rare patients with confirmed hypoadrenocorticism may have post-ACTH stimulation cortisol results of 2 to 3 mcg/dL.

## TREATMENT

Some patients exhibit chronic clinical signs only; others, however, experience a life-threatening Addisonian crisis, requiring acute stabilization and intensive therapy. The rest of the patients lie somewhere in between; although their condition is not immediately life-threatening, they may require fluid therapy and other supportive care in addition to steroid supplementation.

### Chronic Disease

For most hypoadrenocorticism patients who are clinically stable, treatment consists of supplementation with a mineralocorticoid and a glucocorticoid.

### Mineralocorticoids

Mineralocorticoid supplementation is available in 2 forms: daily oral (fludrocortisone) and monthly injection (desoxycorticosterone pivalate [DOCP]).

**Fludrocortisone:** Fludrocortisone acetate (0.01 mg/kg PO q12h) possesses both glucocorticoid and mineralocorticoid activity.<sup>21</sup> Although the dual functions may seem like a benefit, they can make it

more difficult to titrate the drug to an acceptable dosage. For example, an increase in fludrocortisone dose may be necessary to keep sodium and potassium within normal parameters, but this increased dose may result in a higher than necessary glucocorticoid effect and precipitate undesirable consequences of hypercortisolemia.

**DOCP:** Because DOCP has only mineralocorticoid activity, concurrent glucocorticoid (e.g., prednisone) supplementation is always necessary. However, many clinicians prefer DOCP because of its efficacy and the ability to adjust glucocorticoid supplementation independently. In addition, DOCP is more likely than fludrocortisone to normalize renin activity, suggesting that DOCP is a more effective mineralocorticoid supplement for dogs with hypoadrenocorticism.<sup>16</sup> Two formulations of DOCP are available: Percorten-V (Elanco, elanco.com) and Zycortal (Dechra Pharmaceuticals, dechra.com). The U.S. Food and Drug Administration–approved label for each formulation recommends an initial dose of 2.2 mg/kg<sup>22,23</sup> every 25 days. However, 1 publication documents using lower doses,<sup>24</sup> and we often begin treatment with a dose of 1.5 mg/kg. Zycortal is labeled for SC administration; Percorten-V is labeled for IM administration only but can also be given SC<sup>25</sup> off-label.

After the initial dose of DOCP is given, electrolytes should be checked at 14 days to assess the dosage and at 25 days to assess the dosing interval. At 14 days, if hyponatremia or hyperkalemia is present, increase the next dose (at 25 to 28 days) by 10% to 15%; if hypernatremia or hypokalemia is present, decrease the next dose by 10% to 15%. At 25 days, if hyponatremia or hyperkalemia is present, decrease the dosing interval by 1 to 2 days. If electrolytes are within reference range, to make the dosing interval more convenient for the client we often extend the dosing interval to 28 days, at which time we confirm that the electrolytes are within reference range. One study demonstrated that the dosing interval can be extended as long as 90 days, but this study used a dose of 2.2 mg/kg and initially required up to weekly electrolyte assessments to determine the optimal dosing interval.<sup>26</sup> We prefer to adjust the dose rather than extend the dosing interval beyond 28 to 30 days, and we do not recommend adjusting both dose and dosing interval. After the optimal dose and interval are determined, most clients can be taught to give DOCP at home.



## Glucocorticoids

All patients receiving DOCP must receive supplemental glucocorticoids. Some patients receiving fludrocortisone do not require additional prednisone long-term, but these patients seem to stabilize more quickly when additional glucocorticoid is given initially and then tapered after stabilization.<sup>27</sup>

For glucocorticoid replacement, oral prednisone at a starting dose of 0.5 to 1.0 mg/kg/day is usually recommended. This dose should be gradually lowered (over several weeks) to an optimal dose that controls signs of hypoadrenocorticism and avoids side effects (e.g., polyuria, polydipsia, polyphagia, panting). Larger dogs seem to be more sensitive to the side effects of glucocorticoids. Although published maintenance doses are usually 0.1 to 0.22 mg/kg/day,<sup>4</sup> we have managed a number of patients with lower doses (as low as 0.03 mg/kg/day). Dosage adjustments should be based on clinical signs only; for dogs with confirmed naturally occurring hypoadrenocorticism, an ACTH stimulation test should not be repeated for monitoring purposes.

## Atypical Addison's Disease

Because dogs with atypical Addison's disease have signs of glucocorticoid deficiency only, they require glucocorticoid supplementation only, administered according to the guidelines described above. For some of these dogs, electrolyte abnormalities may eventually develop and require mineralocorticoid supplementation. Rechecking electrolytes is recommended 2 weeks after diagnosis, then every month for 3 months, then every 3 months for 1 year.



**FIGURE 2.** Administration of IV fluids is imperative for a dog experiencing an Addisonian crisis. ECG and blood pressure are monitored to look for indications of hyperkalemia and to determine response to therapy.

## Addisonian Crisis

Dogs experiencing Addisonian crisis may have arrhythmias and/or bradycardia as a result of hyperkalemia and require treatment specifically targeted at correcting the hyperkalemia. Hypoglycemia has been reported in up to 38% of dogs with hypoadrenocorticism,<sup>9</sup> so insulin therapy for treatment of hyperkalemia should be withheld until normal blood glucose levels are confirmed. If severe enough, hypoglycemia may lead to seizures.<sup>2</sup> Dogs experiencing Addisonian crisis often have moderate to severe prerenal azotemia.

Prompt recognition or suspicion of an Addisonian crisis and subsequent treatment (**BOX 5**) are paramount to a successful outcome. Fluid resuscitation (**FIGURE 2**) is of utmost importance and will address hypovolemia, hypotension, metabolic acidosis, and hyperkalemia.<sup>31</sup> The latest recommendation is to give a balanced crystalloid solution (e.g., Plasmalyte 148, lactated Ringer's, or Normosol-R).<sup>32</sup> The previous recommendation was to give 0.9% sodium chloride. However, neurologic signs in dogs receiving treatment for Addisonian crises are thought to be the result of myelinolysis secondary to rapid correction of hyponatremia;<sup>33,34</sup> this concern, however, is valid only if the hyponatremia is chronic. When the patient's sodium concentration is less than 120 mEq/L, we monitor sodium concentrations more often and may use a fluid with a lower sodium concentration than lactated Ringer's solution. Sodium concentration should not be increased by more than 12 mEq/L every 24 hours.<sup>34</sup> In addition, balanced crystalloids are more alkalizing than sodium chloride. Fluid resuscitation should be performed with boluses of 20 to 30 mL/kg over 15 to 20 minutes; after administration of each bolus, vital signs (heart rate, pulse quality, and blood pressure) should be reassessed. Fluid resuscitation is considered complete when vital signs have returned to reference range. Lactate levels can also be used as an objective measure.

After the patient has received appropriate fluid resuscitation, IV dexamethasone can be administered. Dexamethasone does not interfere with results of a subsequent ACTH stimulation test because it is not detected by the cortisol assay, whereas prednisone, prednisolone, and methylprednisolone are. The patient should remain hospitalized and receiving IV fluids until electrolyte abnormalities are stabilized and any clinical abnormalities are controlled with oral medications. Among these oral medications will be prednisone. In the acute phase immediately after recovery from crisis,

**BOX 5 Treatment of Addisonian Crisis****Correct the following:**■ **Hypovolemia and hypotension**

- Balanced crystalloids, 20 to 30 mL/kg; reassess and repeat if necessary.

■ **Acidosis**

- IV fluid therapy is almost always adequate.

■ **Hyperkalemia**

- Fluids are usually adequate unless severe (>8.5 to 9.0 mEq/L) or ECG derangements (bradycardia, spiked T waves, flattened to absent P wave, widened QRS complexes) are present.

**ECG derangements/severe hyperkalemia**

- Calcium gluconate, 10% solution: 0.5 to 1.5 mL/kg over 10 to 15 minutes. Watch ECG for worsening bradycardia as a side effect. Will stabilize the heart but does not treat hyperkalemia directly.
- Dextrose, 1 mL/kg 50% dextrose, diluted 1:3 with balanced crystalloids<sup>28</sup>
- R insulin, 0.2 U/kg, followed by a bolus of 1 to 2 g dextrose/unit of insulin, then dextrose added to balanced crystalloids to make a 2.5% to 5.0% solution of dextrose
- Dogs with life-threatening arrhythmias should receive insulin. Dextrose alone will help decrease the potassium concentration by causing endogenous insulin release, but this takes more time.

- Alpha-2 agonists (e.g., inhaled albuterol or IV terbutaline at 0.01 mg/kg<sup>29</sup>)

■ **Hypoglycemia**

- 1 mL/kg 50% dextrose, diluted 1:2 with balanced crystalloid

■ **Severe anemia from gastrointestinal blood loss**

- Packed red blood cell transfusion

■ **Glucocorticoid deficiency**

- Dexamethasone, 0.2 mg/kg IV initially, then 0.1 mg/kg q12h until oral prednisone is tolerated. CAN be given before obtaining samples for ACTH stimulation test

OR

- Hydrocortisone sodium succinate, 0.5 to 0.625 mg/kg/hr.<sup>30</sup> CANNOT be given before obtaining samples for ACTH stimulation test.

■ **Supportive therapy**

- Warming measures if patient is hypothermic
- Anti-emetics
- Gastroprotectants
- Pain management
- Nutrition (patients are usually eating within 24 hours)

we usually give 0.5 to 1.0 mg/kg/day. As the dog transitions to at-home care, the dose should be gradually lowered over a few weeks. Mineralocorticoid supplementation with DOCP or fludrocortisone is usually postponed until the diagnosis of hypoadrenocorticism is confirmed. Future dosing will need to be based on laboratory results, particularly electrolyte concentrations, and clinical signs.

**PROGNOSIS**

For dogs with properly diagnosed hypoadrenocorticism, the prognosis and quality of life are good (**FIGURE 3**); most of these dogs die of something unrelated to hypoadrenocorticism. One study encompassing 205 dogs revealed a median survival time of 4.7 years with no significant effect resulting from factors such as age, breed, sex, or weight.<sup>35</sup> However, clients must be well aware of subtle signs of illness and committed to daily medication and regular rechecks for the rest of the dog's life. With proper treatment and regular veterinary follow-up, dogs with hypoadrenocorticism can lead a long and healthy life. **TVP**



**FIGURE 3.** This golden retriever exhibited nonspecific lethargy and gastrointestinal signs after a new (human) baby joined the household. He was 2 years old at the time of diagnosis and is thriving 8 years later. He receives 1.3 mg/kg of DOCP q30d and 0.03 mg/kg prednisone/day. Dogs with hypoadrenocorticism typically have a great quality of life as long as the clients are diligent about maintaining an appropriate medication and monitoring schedule.



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### Pamela Galati

Dr. Galati is an internal medicine resident at Mississippi State University College of Veterinary Medicine. She completed her veterinary degree at the Royal Veterinary College in London, followed by a rotating and specialty internship at a private practice in Long Island, New York. Her clinical interests include endocrinology and hematology.



### Patty Lathan

Dr. Lathan received a BA in chemistry from Texas A&M University and a VMD from the University of Pennsylvania. She completed an internship at Mississippi State University and a small animal internal medicine residency at Purdue University in 2007. She is an associate professor of small animal internal medicine at Mississippi State University. Her primary interest is endocrinology, specifically the management of adrenal disease and diabetes mellitus. She has published several articles and book chapters, given lectures throughout the United States and internationally, and is president of the Society for Comparative Endocrinology.