

## Canine hypoadrenocorticism: Part I

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**Abstract** – Hypoadrenocorticism (Addison's disease) has been referred to as "the great pretender," due to its ability to mimic other common diseases in the dog and thereby represent a diagnostic challenge. Naturally occurring hypoadrenocorticism is an uncommon canine disease. Young, female dogs are overrepresented. Hypoadrenocorticism typically results from immune-mediated destruction of all adrenocortical layers, resulting in deficiencies of mineralocorticoids (aldosterone) and glucocorticoids (cortisol). A small number of dogs suffer from glucocorticoid deficiency only. Dogs suffering from hypoadrenocorticism may present in a variety of conditions, from a mildly ill dog to a shocky and recumbent dog. This review discusses etiology, pathophysiology, history, physical examination findings, and diagnostic findings in the Addisonian patient. A follow-up article (Part II) will discuss the definitive diagnosis and management strategies for these patients.

**Résumé** – **Hypoadrénocorticisme canin : Partie I.** L'hypoadrénocorticisme (maladie d'Addison) est une maladie difficile à cerner en raison de sa capacité d'imitation d'autres maladies courantes chez le chien, ce qui complique son diagnostic. L'hypoadrénocorticisme qui se produit naturellement est une maladie canine rare. Les jeunes chiennes sont surreprésentées. L'hypoadrénocorticisme est habituellement le résultat d'une destruction à médiation immunitaire de toutes les couches corticosurrénales qui produit des déficiences au niveau des minéralocorticoïdes (aldostérone) et des glucocorticoïdes (cortisol). Un nombre réduit de chiens souffrent seulement d'une déficience des glucocorticoïdes. Les chiens souffrant d'hypoadrénocorticisme peuvent présenter divers états, allant d'un chien légèrement malade à un chien en choc et en décubitus. Cet article de compte rendu analysera l'étiologie, la pathophysiologie, l'anamnèse, les résultats de l'examen physique et les constatations diagnostiques chez le patient atteint de la maladie d'Addison. Un article de suivi (Partie II) analysera le diagnostic définitif et les stratégies de gestion pour ces patients.

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### Introduction

Naturally occurring hypoadrenocorticism (Addison's disease) is an uncommon illness, with estimates of its incidence ranging from 0.36% to 0.5% (1,2). The clinical syndrome occurs when at least 85% to 90% of the adrenocortical tissue is destroyed, resulting in deficiencies of mineralocorticoids and glucocorticoids. Spontaneous recovery has not been reported.

### Overview of adrenocortical anatomy and physiology

Mammalian adrenal glands consist of an outer cortex and inner medulla (3). Catecholamines from the medulla are not vital for

life, but the adrenocortical hormones are (4). The adrenal cortex consists of 3 layers (5–7). The outermost layer, the zona glomerulosa, synthesizes and secretes mineralocorticoid hormones and supplies precursor cells for the inner 2 cortical layers (4). The middle layer, the zona fasciculata, secretes glucocorticoid hormones. The inner layer, the zona reticularis, secretes androgen sex hormones (5–7).

Aldosterone is the most important naturally occurring mineralocorticoid, while cortisol represents the most important glucocorticoid (5). Both hormones are synthesized from cholesterol (7). Little pre-formed adrenocortical hormone is stored within cells, but cholesterol can be rapidly converted to hormone following stimulation (6). Similar to other steroid hormones, adrenocortical hormones bind to a cytoplasmic receptor in the target cell, and the hormone-receptor complex moves to the nucleus and increases transcription of mRNA's encoded by the genes to which it binds. The net result is an increase in proteins that alter the target cell's function (5,6).

### Aldosterone's actions

Aldosterone has a specific and vital action in the body because it enhances sodium (Na), potassium (K), and body water homeostasis. It plays an important role among the redundant systems

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that regulate renal handling of sodium (8). Aldosterone is the most important hormone affecting renal potassium excretion (9) and its main target organ is the kidney, with lesser actions in the intestinal mucosa, salivary glands, and sweat glands (4).

In the kidney, the primary site of action is the principal cells (P cells) of the cortical collecting duct. Aldosterone stimulates insertion of epithelial sodium channels (ENaCs) in the luminal surface of cortical collecting duct cells (6). It also stimulates the sodium-potassium ATPase pump on the basolateral side of the cortical collecting duct cells. Aldosterone increases the number of open K<sup>+</sup> channels in the luminal membrane, which enhances K<sup>+</sup> egress into the renal tubular fluid. Aldosterone's net effects include reabsorption of Na and chloride (Cl), with concomitant excretion of K<sup>+</sup> and hydrogen (H<sup>+</sup>). Water absorption and expansion of the extracellular fluid volume (ECFV) occur secondary to retention of Na (6).

### Regulation of aldosterone secretion

The most important direct stimulus for aldosterone secretion is angiotensin II (4), a product of the renin-angiotensin system (RAS). The main role of RAS is defense of the ECFV via Na balance (8). Several stimuli activate RAS, including reduced extracellular fluid volume, systemic blood pressure, or Na concentration in renal filtrate (8). Increased K<sup>+</sup> concentration in the extracellular fluid also represents a direct and potent stimulus for aldosterone secretion (1,4,7,9). Extracellular K<sup>+</sup> concentration is tightly regulated by the body, and small changes (1 mmol/L) in plasma K<sup>+</sup> concentration can stimulate or suppress aldosterone secretion (4). Finally, adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland exerts a necessary and permissive effect for aldosterone release (6), as do hyponatremia and decreased extracellular pH (8). Dopamine and atrial natriuretic peptide — both released in response to ECFV expansion — inhibit secretion of aldosterone (8).

### Cortisol's actions

Cortisol affects almost every tissue in the body, its biological effects varying with the dose (4,6,7). Cortisol aids in maintaining blood pressure, water balance, and vascular volume, particularly in the canine species (4), and it increases vascular sensitivity to catecholamines (4). Cortisol helps to maintain vascular tone, vascular permeability, and endothelial integrity (1,4). In the fasting animal, glucocorticoids help to preserve normoglycemia by increasing lipolysis and gluconeogenesis while decreasing peripheral glucose utilization (4,6,7). Cortisol suppresses inflammatory responses and has catabolic effects on connective tissue, muscle, and bone (4). Finally, cortisol stimulates erythrocytosis and counteracts stress (1,4).

### Regulation of cortisol secretion

Almost no stimuli can directly impel the zona fasciculata cells to secrete cortisol. Rather, glucocorticoid secretion depends entirely on ACTH secreted from the anterior pituitary gland (4–6). Secretion of ACTH is, in turn, controlled by corticotrophin-releasing hormone (CRH) from the hypothalamus (6,7). Following stimulation by ACTH, cortisol is released by the zona fasciculata cells (6,7). Together, these glands comprise the

hypothalamic pituitary axis (HPA), which operates by a simple feedback inhibition loop (1,4,6,7). Cortisol exerts a strong inhibitory feedback on the pituitary gland as well as on the hypothalamus (1,4). The hypothalamic-pituitary axis becomes more active as dogs age (4). Under normal resting conditions, ACTH is secreted in an episodic, pulsatile, but non-circadian rhythm (4,6,7). The hypothalamus receives signals including pain and mental stress stimulus from parts of the nervous system (6,7). Stress therefore represents a potent stimulus for CRH release, followed by ACTH and then cortisol release, above the normal basal secretions (4).

### Etiology

Naturally occurring primary adrenocortical failure occurs from atrophy or destruction of all 3 adrenal cortical layers, which results in inadequate secretion of both mineralocorticoids and glucocorticoids (1,10). Primary immune-mediated destruction of the adrenal cortex appears to cause this form of Addison's disease, and is the most common reason for primary hypoadrenocorticism in humans (1,10). Rare causes of primary adrenal cortex destruction include infiltration by fungus (*Histoplasma*, *Blastomyces*, *Coccidioides*, *Cryptococcus*) (5), neoplasia, amyloidosis, trauma, or coagulopathy (1).

Autoimmune polyglandular syndrome has rarely been described in the dog, but it occurs in about 50% of humans with primary hypoadrenocorticism (1,2,11,12). In a series of 187 dogs with primary hypoadrenocorticism, 28 (14.9%) exhibited at least 1 other endocrinopathy (1). Sixteen dogs had hypothyroidism, 14 had insulin-dependent diabetes mellitus, 3 had hypoparathyroidism, and 2 had azoospermia (1). Several dogs had more than 2 concurrent endocrine disorders (1). Although uncommon among dogs with primary hypoadrenocorticism, the clinician should not overlook the possibility of concurrent endocrine disorders.

Atypical hypoadrenocorticism represents a minority (10%) of primary hypoadrenocorticism patients that have normal serum electrolytes at initial diagnosis. This may occur secondary to gradual loss of adrenocortical tissue in which loss of glucocorticoid-secreting portions precedes loss of the mineralocorticoid-secreting layer of the adrenal cortex. These patients may go on to develop electrolyte abnormalities in the days to months following initial diagnosis (1,10).

Iatrogenic primary hypoadrenocorticism can result from drugs that cause destruction of the adrenal cortices. At dosages used to control pituitary-dependent hyperadrenocorticism (Cushing's disease), mitotane (Lysodren, o-p'-DDD; Bristol-Myers-Squibb, Princeton, New Jersey, USA) causes selective, cytotoxic effects on the adrenal cortex. Progressive necrosis and atrophy of the zona fasciculata and the zona reticularis ensue, ideally resulting in resolution of clinical signs from excessive cortisol, without the patient displaying signs of absolute cortisol deficiency (13,14). The zona glomerulosa shows the least sensitivity to mitotane's effects. However, a small number of dogs (< 5%) develop permanent iatrogenic primary Addison's disease, even when carefully dosed and monitored (13,14); this occurs secondary to unintentional, non-selective loss of the entire adrenal cortex. These dogs require lifelong supplementation

with mineralocorticoids and glucocorticoids, as all 3 cortical layers undergo necrosis. Other dogs may develop permanent hypocortisolism from mitotane and require lifelong glucocorticoid supplementation (1).

Trilostane (Veteryl, Dechra Veterinary Products, Overland Park, Kansas, USA) has recently gained popularity in treating pituitary-dependent hyperadrenocorticism. It reversibly and competitively inhibits the enzyme 3 $\beta$ -hydroxysteroid dehydrogenase. This causes a decrease in conversion of progesterone to cortisol, aldosterone, and androstenedione, resulting in decreased mineralocorticoids and glucocorticoids (1,15). Trilostane was initially touted as a medical alternative to mitotane that carried few safety risks; however, there are reports of adrenal necrosis severe enough to lead to clinical and biochemical changes compatible with primary and secondary hypoadrenocorticism in dogs receiving trilostane (16,17). In some dogs, prolonged suppression of the adrenal cortex has occurred with eventual recovery, but in other dogs the loss has remained permanent (18–20). In 1 recent report, approximately 25% of the dogs treated with trilostane experienced at least 1 episode of hypoadrenocorticism during the treatment period (18). In the same study, trilostane was permanently discontinued in 11% of dogs because of prolonged cortisol suppression, although only 2% of the dogs required long-term glucocorticoid and mineralocorticoid supplementation (18). Prolonged hypoadrenocorticism occurs more commonly in dogs receiving trilostane for more than 1 y (18,19). Death of some dogs secondary to adrenocortical loss has been reported as well (16).

An uncommonly used, high-dose mitotane protocol for intentional, non-selective destruction of all 3 adrenocortical layers has been described (21). In theory, these dogs may prove simpler to medically manage as Addisonian rather than Cushingoid patients. The dogs require lifelong supplementation of both mineralocorticoids and glucocorticoids since they are effectively rendered primary Addisonian patients (21).

Naturally occurring secondary hypoadrenocorticism results from failure of the pituitary gland to secrete ACTH (1,10). Lack of ACTH leads to severe atrophy of the adrenal zona fasciculata and the zona reticularis, with an intact zona glomerulosa (5). Serum electrolytes remain normal because aldosterone secretion is preserved (1,4,5,22). Clinical signs result from hypocortisolism and include anorexia, vomiting, diarrhea, weight loss, abdominal pain, weakness, lethargy/dullness, and stress intolerance. Causes of secondary hypoadrenocorticism include destruction of the pituitary gland by neoplasia, inflammation, or head trauma (1,5). This form of Addison's disease is much less common than primary hypoadrenocorticism, although its true incidence is not known. Among all dogs with hypoadrenocorticism, estimates of secondary hypoadrenocorticism range from 4% to 24% (1,10). Secondary hypoadrenocorticism can prove an insidious disease, as the blood work and other diagnostics may be relatively normal. Consequently, clinicians must maintain a high index of suspicion for these patients.

Iatrogenic secondary hypoadrenocorticism usually results from exogenous glucocorticoid administration and is more common than the naturally occurring form. Typically, it results from chronic use and can occur with injectable, oral, ophthalmic,

otic, and topical preparations (1). Feedback inhibition from exogenous glucocorticoids suppresses anterior pituitary secretion of ACTH, which in turn leads to atrophy of the zona fasciculata and the zona reticularis (1,6,7). If the exogenous glucocorticoid is withdrawn too quickly, hypocortisolism results. Individuals show variable susceptibility to this problem, and it is not possible to predict which animals may develop clinical illness. In general, exogenous glucocorticoids should be tapered carefully, particularly if chronic administration has occurred.

Tertiary hypoadrenocorticism — caused by hypothalamic disorders disrupting CRH secretion — is rarely reported in humans (6). In dogs, lack of CRH would result in decreased ACTH production, and so would manifest as secondary hypoadrenocorticism (1). Isolated aldosterone insufficiency is rarely recognized in humans (hyporeninemic hypoaldosteronism) and has been recognized in 1 dog (hyperreninemic hypoaldosteronism) (23).

### Signalment

Hypoadrenocorticism can affect dogs of any age, but it tends to occur in young to middle-aged dogs. The age range of reported cases is 4 wk to 16 y (1,10). The average age at diagnosis is 4 to 5 y (1), although the median age of diagnosis for Nova Scotia duck tolling retrievers is earlier than in the general dog population, at 2.6 y (24). Most studies suggest that female dogs account for the majority of patients with Addison's disease, at 69% (1). In bearded collies (25), Portuguese water dogs (26), and standard poodles (27), the disease appears to affect males and females with equal frequency.

Addison's disease occurs in many breeds, but certain breeds appear to have an increased risk for developing this syndrome. These breeds include great danes, poodles (all types), west highland white terriers, Portuguese water dogs, bearded collies, rottweilers, soft-coated wheaten terriers, springer spaniels, basset hounds, and Nova Scotia duck tolling retrievers (1,11,24). Saint bernards may also be overrepresented (22). There is a possible familial predisposition in the Portuguese water dogs, leonburgers, standard poodles, bearded collies, and Nova Scotia duck tolling retrievers (1,11,24). Recent analysis suggests an autosomal recessive mode of inheritance in Nova Scotia duck tolling retrievers (24), in standard poodles (27), and possibly in Portuguese water dogs (26). It remains unknown for bearded collies (25).

### Clinical signs and physical examination findings

There are no pathognomonic clinical signs for hypoadrenocorticism. Rather, Addison's disease causes vague and nonspecific clinical signs that can be attributed to multiple body systems and diseases, including gastrointestinal disease, renal failure, or neurological disease. Given this, definitive diagnosis and prompt treatment rests a great deal on the clinician's index of suspicion that prompts an ACTH stimulation test. This is particularly true in secondary or atypical hypoadrenocorticism, as there may be few laboratory abnormalities to help guide further diagnostics and therapeutics.

Clinical signs may appear episodic, or "waxing and waning" in 25% to 43% of cases (1,28,29). Other patients show

progressive clinical signs. The number and severity of clinical signs vary from dog to dog, as does the length of illness prior to diagnosis (range: 2 to 52 wk) (1,10,29). The rapidity of progression of disease also varies from patient to patient (1). Most dogs with hypoadrenocorticism have chronic disease, although it may be an acute exacerbation that prompts veterinary evaluation (1). In some dogs that appear to have acute disease, the more chronic signs of illness may have been subtle enough to escape detection. Information from 506 dogs with hypoadrenocorticism suggests that the clinical signs present when the dog is mildly ill do not differ markedly from those that are seen when the dog is profoundly ill; rather, the difference lies in the severity of the clinical signs (1). Acute exacerbation of chronic hypoadrenocorticism may result from stress such as boarding, grooming, lifestyle changes, moving, or even a trip to the veterinarian.

Among dogs with hypoadrenocorticism, the most common clinical signs reported by caregivers include poor appetite/anorexia (88% to 95%), lethargy/depression (85% to 95%), and vomiting/regurgitation (68% to 75%) (1,29). Other clinical signs include weakness (51% to 75%), weight loss (40% to 50%), diarrhea (35%), polyuria/polydipsia (17% to 25%), shaking/shivering/tremors (17% to 27%), collapse (10%), or a painful abdomen (8%) (1,2,11,28,29). Hematemesis, hematochezia, melena, ataxia, seizures, and difficult breathing have also been reported (11), as has prior response to nonspecific fluid or corticosteroid therapy (35%) (28). Hair loss has been rarely reported (5%) (28). Episodic muscle cramps in both the thoracic and pelvic limbs were reported in 2 standard poodles with primary hypoadrenocorticism; these muscle cramps began prior to diagnosis and resolved after electrolyte abnormalities were corrected (30). A recent study comparing dogs with mineralocorticoid deficient hypoadrenocorticism (MGDH, or "classic" hypoadrenocorticism) to dogs with glucocorticoid-deficient hypoadrenocorticism (GDH) suggested that both groups of dogs show clinical signs with similar frequency, although vomiting may be significantly more common in dogs with MGDH than in dogs with GDH (22). This same study found that dogs with GDH were older (mean age: 7 y) and had a longer duration of clinical signs (4.38 mo) than dogs with MGDH (mean age: 4.4 y; mean duration of illness: 1.16 mo) (22).

Physical examination findings depend on the severity of the dog's illness, but may range from a mildly dehydrated but fairly alert dog, to a shocky and recumbent dog with severe dehydration, a prolonged capillary refill time, and weak pulse (1, 2,11,28). The most common findings include depression/lethargy (87%), thin body condition (82%), weakness (66% to 69%), dehydration (42%), shock/collapse (24% to 29%), hypothermia (15% to 34%), bradycardia (22% to 25%), weak femoral pulses (22%), melena/hematochezia (17%), and abdominal pain (7%) (1,2,11,28). Bradycardia in a collapsed or shocky dog should raise the index of suspicion for hyperkalemia and its attendant causes (including hypoadrenocorticism), in addition to cardiac conduction abnormalities that cause bradycardia. Dogs with primary adrenal insufficiency are more likely to present with shock than are dogs with secondary hypoadrenocorticism (1).

## Laboratory abnormalities

Hyperkalemia, hyponatremia, and hypochloremia represent the most consistent serum chemistry abnormalities among dogs with hypoadrenocorticism, particularly primary hypoadrenocorticism (1,2,10,11,28,29). These changes may occur independently or together. Hyperkalemia occurs in up to 95% of dogs with primary hypoadrenocorticism, and none of the dogs with secondary hypoadrenocorticism (1). Hyponatremia occurs in up to 86% of dogs with primary hypoadrenocorticism, and up to 34% of dogs with secondary hypoadrenocorticism (1,10). In 506 dogs with hypoadrenocorticism, serum sodium levels ranged from normal (142–155 mmol/L) to severely decreased at 106 mmol/L; the mean serum sodium was 128 mmol/L (1). Serum potassium in these dogs ranged from normal (4.1–5.5 mmol/L) to severely increased at 10.8 mmol/L; the mean measured 7.0 mmol/L (1). In the same group of dogs, neither hypokalemia nor hypernatremia was reported (1). Hypochloremia occurs frequently (40%) as serum chloride levels often parallel serum sodium levels. Chloride losses occur via renal and gastrointestinal routes (1).

In primary hypoadrenocorticism, hyperkalemia and hyponatremia result primarily from aldosterone deficiency, which causes failure of the kidneys to conserve sodium and to excrete potassium (1,6,7,8). In secondary hypoadrenocorticism, hyponatremia results from gastrointestinal losses and inappetence. The most deleterious effect of hyperkalemia occurs in myocardial tissue, where hyperkalemia causes decreased myocardial excitability, slowed conduction, and cardiac standstill (1,6,7,9). Renal sodium loss is accompanied by renal water loss, although water loss can be exacerbated by gastrointestinal losses. These mechanisms lead to depletion of body sodium stores, with severe decreases in extracellular fluid volume (1,6,7). Progressive hypovolemia, hypotension, decreased cardiac output, decreased tissue perfusion and decreased glomerular filtration rate ensue (1,6,7).

The normal sodium to potassium ratio lies between 27:1 and 40:1 (1,2,11). Dogs with primary hypoadrenocorticism frequently (95%) show ratios < 27:1, and sometimes < 20:1 (1,2,11). Ratios < 15:1 strongly suggest hypoadrenocorticism rather than other disorders that can cause the ratio to decrease, although the diagnosis still must be confirmed with an ACTH stimulation test (31).

Hyperkalemia, hyponatremia, hypochloremia, and decreased sodium to potassium ratio represent the classic electrolyte changes among Addisonian dogs, and so hypoadrenocorticism should be on the differential list in these patients. However, these electrolyte abnormalities are not pathognomonic for hypoadrenocorticism. Differentials for hyponatremia and/or hyperkalemia include increased sodium loss with vomiting, diarrhea, severe gastrointestinal disease (including duodenal perforation and gastric torsion), renal and urinary tract disease (including intrinsic acute renal failure, end-stage renal failure, uroabdomen, post-obstructive diuresis), severe liver failure, parasitism (pseudohypoadrenocorticism from whipworms), congestive heart failure, pleural effusion (chylothorax), severe metabolic acidosis such as diabetic ketoacidosis, severe respiratory acidosis, tissue crush injury or reperfusion injury, pregnancy, or artifact (hemolysis especially in Akitas, thrombocytosis, severe

leukocytosis, lipemia) (1,8,32). History, physical examination findings, and other diagnostics should help decrease the size of this formidable differential list.

Normal electrolytes do not exclude the possibility of hypoadrenocorticism. A few dogs with primary hypoadrenocorticism (atypical hypoadrenocorticism) and more dogs with secondary Addison's disease show normal electrolytes, as hypoaldosteronism leads to most of the electrolyte abnormalities observed. The clinician must maintain an index of suspicion for hypoadrenocorticism among this subset of dogs.

Pre-renal azotemia results from decreased renal perfusion and decreased glomerular filtration rate (GFR) (1,6,7). An increase in BUN can occur secondary to gastrointestinal bleeding, and this can cause an increase in BUN in proportion to creatinine. Pre-renal azotemia is present in most (66% to 95%) dogs with primary hypoadrenocorticism at the time of initial diagnosis (1,2,10,11,28). Hyperphosphatemia is reported in 66–85% of dogs with primary hypoadrenocorticism (2,28). This likely results from decreased GFR and decreased renal excretion of inorganic phosphorous, secondary to hypovolemia.

Ideally, a urine sample should be obtained prior to fluid therapy. In a dog with pre-renal azotemia, the urine specific gravity should be normal or increased ( $> 1.030$ ). A dog with primary renal failure and renal azotemia typically displays a urine specific gravity between 1.008 and 1.020. A substantial (60% to 88%) number of Addisonian dogs show decreased urinary concentrating ability, with urine specific gravity  $< 1.030$  (1,2,10,11). Chronic urinary sodium loss can lead to renal medullary washout, which can result in loss of the normal medullary concentration gradient, thereby diluting the urine (1,6,7). One might expect an Addisonian dog to have a higher urine specific gravity, as azotemia in hypoadrenocorticism is thought to be pre-renal (1,6,7). Azotemia, together with dilute urine specific gravity, suggests intrinsic renal failure, which is an important differential for hypoadrenocorticism and carries a very different prognosis. In Addisonian dogs, BUN and creatinine will often improve readily, rapidly, and completely with appropriate IV fluid support and hormone replacement. If this does not occur, it raises concerns about insufficient fluid support, a concurrent and primary intrinsic renal problem, or renal damage secondary to hypovolemia and renal hypoperfusion.

Lack of aldosterone impairs the ability of the renal tubule to excrete hydrogen ions (1,4,6, 7). This abnormality — together with hypovolemia, hypotension, and hypoperfusion — contributes to metabolic acidosis in slightly fewer than 50% of dogs with hypoadrenocorticism (1,10,28). Most dogs show mild to moderate metabolic acidosis with serum bicarbonate level 13–17 mmol/L. A smaller number ( $< 10\%$ ) show severe metabolic acidosis (serum bicarbonate 9–12 mmol/L) (1). Mild to moderate metabolic acidosis generally resolves with improved circulating volume and perfusion, although in severe cases it may also be necessary to supplement the fluids with bicarbonate. Metabolic acidosis further exacerbates hyperkalemia, as it causes a shift of potassium from the intracellular space to the extracellular space in exchange for hydrogen ions (1,6,7,9). Severe metabolic acidosis can contribute to further problems with cardiovascular function, including decreased

cardiac output, decreased arterial blood pressure, decreased hepatic and renal blood flow, and decreased cardiac contractility (33). Severe metabolic acidosis may predispose the heart to ventricular arrhythmias (33).

Increased total serum calcium occurs in up to 30% of dogs with hypoadrenocorticism (1,2,11,28). Ionized calcium may or may not be increased (1). Development of hypercalcemia appears to be correlated with those dogs that develop hyperkalemia and present with severe dehydration (1,2). The mechanism for hypercalcemia remains incompletely understood, but may result from a combination of factors, including hemoconcentration, decreased glomerular filtration rate, and decreased renal calcium excretion (1,2,11). Hypercalcemia in Addisonian dogs generally does not cause clinical signs, and it resolves quickly after initiation of IV fluid therapy and hormone replacement (1,2,11). Use of specific medications such as furosemide or pamidronate to promote calciuresis is typically not required. Important differential diagnoses for hypercalcemia include neoplasia, primary hyperparathyroidism, renal failure, vitamin D toxicosis, hypercalcemia of growing dogs, and granulomatous disease (1,2,11). Among diseases causing hypercalcemia, hypoadrenocorticism appears to be the second in frequency, after malignancy (1,11). These diseases can have overlapping clinical signs, and so hypoadrenocorticism should be on the differential list in any dog with hypercalcemia.

Estimates of hypoglycemia (blood glucose  $< 3.92$  mmol/L) vary, but it may develop in up to 22% of dogs with primary hypoadrenocorticism and up to 43% of dogs with secondary Addison's disease (1,10,28). Clinical signs attributable to hypoglycemia — such as seizures, or mental obtundation — appear to be rare even in those patients with documented hypoglycemia (1,11). Glucocorticoids increase hepatic glycogen stores and increase glucose production by gluconeogenesis. Important differential diagnoses for hypoglycemia include sepsis, liver disease, starvation or severe maldigestion, puppy hypoglycemia, hunting dog hypoglycemia, insulin-secreting pancreatic tumors, other neoplasia, insulin overdose, and artifact. Dogs with hypoadrenocorticism may experience concurrent sepsis, particularly secondary to severe GI ulceration and bacterial translocation.

Moderate to severe hypoalbuminemia is reported in 17% to 39% of dogs with hypoadrenocorticism (1,2,11). Impaired albumin synthesis, lack of nutrient intake from anorexia, gastrointestinal loss, and impaired nutrient absorption may be contributing factors (11). Other broad categories for hypoalbuminemia include decreased hepatic synthesis, or loss through the kidneys or gastrointestinal tract. A recent study noted that serum albumin levels were significantly lower in dogs with glucocorticoid deficient hypoadrenocorticism than in dogs with mineralocorticoid deficient hypoadrenocorticism (22).

Mild to moderate increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may occur in 30% to 50% of cases (1,2,10,11,28). The underlying cause remains unknown, but it may result from poor cardiac output, hypotension, and poor tissue perfusion (2,10,11,28). Alternatively, these changes may result from a concurrent hepatopathy attributable to immune-mediated disease (1). Concurrent immune-mediated hepatopathy may be suspected if hypoglycemia,

hypoalbuminemia and hypocholesterolemia are present. The latter is present in 17.5% of dogs with hypoadrenocorticism (1). In a dog with renal azotemia and increased liver enzymes, an infectious disease such as leptospirosis would be a consideration.

Mild, normocytic, normochromic nonregenerative anemia is common (21% to 25% cases) (1,2,10,22). Mild anemia may be secondary to bone marrow suppression from lack of glucocorticoids. In some cases, particularly those with abundant gastrointestinal bleeding, anemia may be severe, that is, PCV < 20%. If severe dehydration exists, however, hemoconcentration may mask anemia until circulating volume and hydration status have been restored.

The total white blood cell count generally remains in the normal range, but it may vary from low normal to mildly increased (1). A mildly increased white blood cell count may result from concurrent infection. The eosinophil count may be decreased or normal or increased, as may be the absolute lymphocyte count. Absolute eosinophilia exists in about 10% to 20% of cases (1,2,10,11,28). Absolute lymphocytosis occurs in 10% to 13% of patients (1,2,10,28). A sick and stressed dog without hypoadrenocorticism would be expected to show a stress leukogram (lymphopenia, eosinopenia). Although it is not a consistent feature of Addisonian patients, lack of a stress leukogram provides a valuable clue in identifying these suspects, particularly in glucocorticoid deficient dogs. Normal or increased eosinophils and/or lymphocytes in a sick dog should prompt the clinician to consider Addison's disease.

### Diagnostic imaging

Survey thoracic and abdominal radiographs, and abdominal ultrasound, often comprise part of the diagnostic workup for a chronically or a critically ill dog, particularly in those that are presented with acute collapse. In dogs with hypoadrenocorticism, thoracic radiographs may show microcardia, reduced caudal vena cava size, or decreased pulmonary vessel size (hypoperfusion) (1,2,10,29). These changes are not specific and can occur in any patient with underlying hypovolemia and dehydration. Presence of these changes — particularly with nonspecific clinical signs — should prompt the clinician to consider hypoadrenocorticism. Much less commonly, thoracic radiographs show evidence of megaesophagus (1,10). Although rare, reversible megaesophagus has been reported in dogs with hypoadrenocorticism, and ruling out hypoadrenocorticism would represent part of the workup for a dog with esophageal motility problems (1,2,10,11). Abdominal radiographs may show microhepatica, which may occur with hypovolemia or with primary liver disease (2).

Abdominal ultrasound may show decreased adrenal size (34). A recent study compared right and left adrenal gland sizes in 14 healthy dogs and in 28 dogs with confirmed hypoadrenocorticism (35). The study showed that dogs with mineralocorticoid deficient hypoadrenocorticism have significantly smaller adrenal glands than healthy dogs, and that the same thing could be true for dogs with glucocorticoid deficient adrenal glands (35). This study confirmed the findings of an earlier preliminary study (36).

### Blood pressure

Hypotension is present in approximately 90% of humans with primary hypoadrenocorticism, but it is much less common with secondary hypoadrenocorticism (1,2). Hypotension has certainly been documented in dogs with adrenal insufficiency, and is likely to be common among the severely affected patients (1). Blood pressure measurement represents an important part of the database in critically ill patients. The veterinary literature lacks survey data regarding the incidence of hypotension among primary and secondary Addisonian patients.

### Electrocardiogram

An electrocardiogram (ECG) is warranted in collapsed or shocky patients, particularly in a collapsed patient with bradycardia. In an untreated Addisonian patient, the ECG may be normal or it may show significant, life-threatening changes compatible with severe hyperkalemia and imminent death. Recognizing ECG changes suggestive of hyperkalemia is important, regardless of the underlying cause, as it will enable the clinician to institute rapid and potentially lifesaving medical therapy. Some of the classic changes occur only after moderate to severe hyperkalemia (7.0 to > 8.5 mmol/L). Continuous ECG monitoring allows the clinician to monitor the response to therapy as hyperkalemia resolves. Lack of ECG changes does not exclude the possibility of severe electrolyte and acid-base abnormalities, particularly hyperkalemia. Glucocorticoid-deficient Addisonian dogs generally do not show electrocardiographic changes (37).

Electrocardiographic manifestations of hyperkalemia result from changes in cell membrane excitability and its depressive effects on the conduction system. Although not precisely correlated with serum potassium levels, ECG changes generally worsen as the concentration rises (37,38). The earliest ECG changes are observed when the potassium level is > 5.5 mmol/L, and this includes increased amplitude of the T-waves, which become thin and peaked. This change may be subtle and may not occur in all patients. The T-wave may show a positive or a negative deflection. Bradycardia may be present at this stage as well. When serum potassium exceeds 6.5 mmol/L, a prolonged P-R interval is observed (first-degree heart block), together with a prolonged QRS interval. The amplitude of the R-wave decreases and S-T segment depression may occur. Both the QRS intervals and the P-R intervals progressively lengthen as serum potassium exceeds 7.0 mmol/L. The amplitude of the P-wave decreases and the duration of the P-wave increases. The Q-T interval lengthens. A serum potassium level > 8.5 mmol/L is accompanied by disappearance of the P-wave (atrial standstill) and severe bradycardia. The P-wave disappears because the atrial myocardium is not activated. As the serum potassium level continues to rise and the QRS complexes continue to widen, a sinoventricular rhythm appears. When serum potassium exceeds 10.0 mmol/L, the QRS complex continues to widen and is replaced by a smooth biphasic curve (sine wave). In terminal phases, ventricular flutter, ventricular fibrillation, and ventricular asystole may be observed (37,38).

In addition to hyperkalemia, the ECG may be influenced by concurrent hyponatremia and severe metabolic acidosis. One study identified arrhythmias in 46% of untreated Addison's

disease, including bradyarrhythmias, tachyarrhythmias, conduction disturbances, sinoventricular rhythm, ventricular fibrillation, and asystole (37). In another study that evaluated 122 dogs with untreated Addison's disease, 47% showed atrial standstill, 29% showed bradycardia, 6% showed atrial or ventricular extrasystoles, and 5% showed 2nd or 3rd degree heart block (29). Many of these abnormalities are compatible with hyperkalemia, although some of them, such as tachyarrhythmias, may not be expected in an Addisonian patient. Although rare, one recent report described atrial fibrillation that developed some 40 h after initial evaluation for acute hypoadrenocorticism, and some 30 h after the correction of hyperkalemia in a 9-year-old Doberman pinscher recently diagnosed with primary hypoadrenocorticism (39).

In summary, hypoadrenocorticism is an uncommon disease that can create a variety of clinical presentations, including vague, chronic GI signs to overt shock and acute collapse with severe bradycardia and hyperkalemia. Addison's disease should be considered both in patients with "classic" electrolyte changes (hyponatremia and hyperkalemia) and with normal electrolytes. An ACTH stimulation test should be performed in all patients suspected of having hypoadrenocorticism. A follow-up article will discuss definitive testing and treatment of both the acute Addisonian crisis patient and the chronic patient. CVJ

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