Introduction

Atypical hypoadrenocorticism (AHOC) is the term used for patients with inadequate cortisol production. It is also referred to as atypical Addison’s disease or glucocorticoid deficient hypoadrenocorticism. Unlike patients with classic hypoadrenocorticism, those with AHOC are still able to produce adequate mineralocorticoids (i.e., aldosterone). Consequently, they do not manifest many of the clinical signs associated with complete adrenal failure and are often misdiagnosed with gastrointestinal or hepatic problems.

Adrenal Gland Physiology

The adrenal gland consists of a capsule, an outer cortex, and an inner medulla. The cortex is subdivided into three sections, based primarily on physiologic function. These sections are the zona glomerulosa, the zona fasciculata, and the zona reticularis; they secrete mineralocorticoids (aldosterone), glucocorticoids (cortisol), and sex hormones (androgens and estrogens), respectively.

The function of the adrenal gland is complex, and various hormonal influences play an important role in the release of the various steroid hormones. Adrenocortical trophic hormone (ACTH) is needed for the release of glucocorticoids, while angiotensin is the primary trigger for the release of aldosterone.

There are three main mechanisms for adrenal insufficiency. The most important is the primary type, in which an immune-mediated process results in destruction of the adrenal cortex. Over 90% of the tissue must be lost before clinical signs are noted. In some patients, the attack is initially directed against the zona fasciculata; the glomerulosa is spared, and the ability to secrete aldosterone is preserved. Secondary hypoadrenocorticism describes patients with compromised ACTH release. In this disorder, the adrenal glands are not destroyed and continue to make mineralocorticoids. Iatrogenic hypoadrenocorticism occurs in patients on adrenolytic therapy (such as mitotane) and adrenal hormone inhibitors (such as trilostane). It also occurs following the abrupt withdrawal of long-term exogenous glucocorticoids.

Clinical Signs and Findings

AHOC can affect any age or breed of dog, but the classic signalment is a middle-aged female. Certain breeds (e.g., Portuguese water dog, West Highland white terrier, black standard poodle) are genetically predisposed.

Cortisol is a remarkably important hormone: it influences most body systems and has a profound effect on many metabolic processes. Glucocorticoid receptors are expressed by most tissues, and the full effects of cortisol are still unclear. Under normal circumstances, secretion is increased at times of physical or psychological stress, in response to increased ACTH release by the pituitary. Adequate amounts of cortisol are needed for gluconeogenesis, smooth muscle function, GI health, and food intake.

The signs of hypocortisolemia are vague and nonspecific, which is why so many patients with AHOC are initially misdiagnosed. In addition, the manifestations often wax and wane, and owners may report periods of apparent improvement. The most prevalent complaints include hyporexia or complete anorexia, along with changes in stool consistency. Some patients will vomit or manifest abdominal discomfort. Lethargy and depression are also frequently noted.

Occasionally, more severe signs are reported. Hypoglycemia may result in exercise-induced collapse or seizures, a reversible megaesophagus may cause regurgitation, and gastrointestinal hemorrhage with melena and hematemesis may occur.

The signs of hypocortisolemia are often exacerbated by stressful events, such as boarding, grooming, or surgery. Any patient with an episodic illness that appears to be triggered by stress should be evaluated carefully for AHOC. In addition, dramatic improvements are noted if glucocorticoids are administered, followed by a quick decline when therapy is discontinued.
Laboratory Evaluation

Complete blood count is usually within normal limits. The “normal” CBC is in fact a useful clue, as dogs with AHOC are unable to mount a stress response with the expected white cell pattern. Some patients may be mildly anemic, due to gastrointestinal (GI) loss and depressed erythropoiesis. An eosinophilia is commonly noted and is a very useful flag for HOC.

The serum biochemical profile often shows some changes, but they are generally mild. It is often helpful to look back to previous lab work for the patient, as “normal” parameters may still be substantially different. For example, the serum albumin and cholesterol may have dropped 30% but still be within the published ranges. Hypoalbuminemia, hypocholesterolemia, and hypoglycemia may be present and may cause concerns about hepatic dysfunction.

GI hemorrhage is a common problem in dogs with AHOC and can be severe. This will increase the BUN concentration, as the blood becomes a high protein “meal.” Serum creatinine levels are unchanged, so the BUN: creatinine ratio is often > 20.

As aldosterone synthesis is unaffected, serum electrolytes are within normal limits. The urine analysis is also usually within normal limits.

Imaging Studies

Megaesophagus is a rare complication of hypocortisolemia and may be noted on survey radiographic images. A skilled ultrasonographer may note small adrenal glands or a change in echogenicity.

Diagnosis

The gold standard test for evaluating patients with suspected hypoadrenocorticism is the adrenocorticotrophic hormone (ACTH) stimulation test. A baseline serum cortisol concentration is determined, and then the patient is injected with a dose of ACTH. Synthetic ACTH (Cortrosyn®) is recommended, as the compounded gels may have unpredictable activity. The dose with Cortrosyn is 5 ug/kg IV or IM. The maximum dose is 250 ug, even in dogs > 50 kg. A second serum sample is collected 60 minutes later. Patients with healthy adrenal glands will respond robustly, with a post-ACTH stim cortisol concentration > 5 ug/dl. Most dogs with AHOC have a “flat-line” response, with both pre- and post-cortisol concentrations < 1.0 ug/dl. If a subnormal response is noted (i.e., a low baseline with an inadequate response to ACTH), the possibility of iatrogenic HOC should be considered. The patient history usually identifies dogs with this disorder, but occasionally topical medications are overlooked and can confuse the issue.

A recent study showed that a single baseline cortisol concentration can be used to exclude the possibility of HOC. Dogs with confirmed HOC always have a resting cortisol concentration below 2.0 ug/dl, so the diagnosis can be confidently discounted if the resting cortisol is > 2.0 ug/dl. This is an inexpensive and useful screening test and can be performed in minutes on in-house blood chemistry machines.

The ratio of serum cortisol to endogenous ACTH can also be used to confirm the diagnosis. However, this test only identifies dogs with primary HOC, which is a substantial drawback. In addition, careful handling (special tubes, shipment on ice, etc.) is necessary to ensure an accurate determination of ACTH levels.

It is important to remember that many synthetic glucocorticoids will cross-react with assay methods for serum cortisol. This means that products given before an ACTH stim test may affect the results. Dexamethasone does not cross-react with the cortisol assay, so this can be safely administered in an emergency situation without affecting test results. Ideally, all steroids should be withheld for 24 hours before any adrenal function tests are performed.

Therapy

Glucocorticoids should be provided as soon as all adrenal testing is completed. If the patient is unwilling to eat, parenteral steroids should be provided. Prednisolone sodium succinate (10-20 mg/kg IV) is an ideal choice. Dexamethasone (0.5 mg/kg) is also acceptable and may be less expensive. Some publications suggest much higher doses, but there is no supporting data, and side effects are more likely.
As soon as the patient is eating, oral glucocorticoids can be started. In general, it is assumed that physiologic replacement doses of prednisone are around 0.1 mg/kg, once daily. However, patients are under substantial stress at the time of diagnosis, so higher doses (up to 0.5 mg/kg twice daily) are warranted. The dose can then be slowly tapered down over the next few weeks. Higher doses should be given before, during, and after any perceived stress, such as boarding or surgery.

Additional therapies may be necessary at the time of diagnosis. Fluid support is rarely needed, but may improve well-being in severely compromised patients or those with hypoglycemia. GI protectants and antacids may be necessary, and occasionally dogs need transfusion support following severe GI hemorrhage.

**Monitoring**

Many dogs with AHOC eventually lose the ability to secrete aldosterone. Consequently, regular (q3 months) checks of serum electrolytes and renal parameters are indicated. If routine lab work shows patterns associated with cortisol excess, such as elevated ALP activity or hypercholesterolemia, the prednisone dose should be reduced. Similarly, excessively dilute urine may be a sign of over-supplementation.

There is no need to repeat an ACTH stim test in a dog with AHOC, as the results will never change. The only exception to this rule would be a dog with iatrogenic AHOC following therapy for hyperadrenocorticism.

**Summary**

AHOC is an uncommon but interesting disorder. A high index of suspicion is necessary for a timely diagnosis, but the response to therapy is rapid and gratifying. Many patients are initially treated for GI or hepatic problems as the disease may mimic other disorders. A baseline serum cortisol concentration should be performed in any patient with a history or laboratory data suggesting hypocortisolemia.

**Further Reading**


