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HYPOADRENOCORTICISM IN DOGS

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ABSTRACT

Hypoadrenocorticism (HOC) is an uncommon, but easily overlooked clinical entity in the dog that carries an excellent long-term prognosis, if diagnosed accurately. This review discusses the etiology, physiology, pathology, clinical and, laboratory findings associated with HOC in dogs. It explores diagnostic tests, and the treatment for the acute and the chronic canine patient with HOC in the Indian subcontinent. Early identification and aggressive supportive care, remains the cornerstone of management.

Keywords: CIRCI, HOC, glucocorticoid, mineralocorticoid

INTRODUCTION

One of the central dogmas that we always hear and to some extent practice in medicine is that 'nobody should die without steroids'. Especially when this can be the difference between life and death, in animals that have an absolute or relative deficiency of endogenous cortisol, better known as hypoadrenocorticism (HOC) or Addison's disease. The two most commonly encountered adrenal dysfunctions in the dog and to a lesser extent in cats, are hypoadrenocorticism, and hyperadrenocorticism (HAC). Other non-steroid related adrenal dysfunctions like pheochromocytomas, hyperaldosteronism, or sex-hormone producing tumors, can lead to significant clinical syndromes but they are still uncommon in routine practice.

Hypoadrenocorticism is called the 'great pretender' as it can mimic a multitude of clinical syndromes like protein losing enteropathy, acute kidney injury, waxing and waning gastrointestinal signs, seizures etc. The clinical signs are more protracted during periods of stress. If left untreated, this can be fatal, however, dogs with HOC can have normal lives with medications.

(Klein and Peterson, 2010 and Feldman *et al.,* 2014)

ANATOMY AND PHYSIOLOGY

The canine adrenal glands are flattened, bilobed organs located cranial and medial to the kidneys. The left adrenal gland is larger than the right, but the shape and size vary with body weight, age, and breed. Each gland is divided into a cortex and a medulla. The adrenal cortex is composed of three layers, the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis which produce aldosterone, cortisol, and sex hormones respectively. These are controlled by the hypothalamic—pituitary—adrenal axis. Adrenocorticotropic hormone (ACTH) from the pituitary binds to receptors in the adrenal cortex leading to glucocorticoid synthesis and release. Glucocorticoid/ cortisol concentrations exert a feedback mechanism that stimulates or inhibits their production. Mineralocorticoids, namely aldosterone is released in response to hypovolemia or hyperkalemia. The adrenal medulla produces catecholamines, but these are not considered vital for life (Ettinger and Feldman, 2017).

ETIOLOGY

Primary HOC is characterized by a lack of glucocorticoids and mineralocorticoids, from immune-mediated destruction and necrosis of the adrenal cortical tissue. Other rare causes of HOC include secondary to administration of drugs like mitotane, trilostane, ketoconazole for HAC treatment, or rarely from neoplasia, amyloidosis, infections (systemic mycoses, tuberculosis), or infarction of the adrenal glands. In the atypical form of HOC, there is only isolated glucocorticoid deficiency. This usually represents an early stage of the disease. Secondary HOC is rare and results from a primary deficiency of ACTH. This can be seen when long term steroids are stopped all of a sudden, without proper tapering (Thompson *et al.*, 2007).

CLINICAL SIGNS

Clinical signs are vague and can range from life threatening to mild, some of the most common one being like a chronic "failure to thrive". Mineralocorticoid deficiency leads to low sodium concentrations, high potassium concentrations which present as dehydration, hypovolemic shock, and collapse in most cases. A low sodium to potassium ratio < 27:1, may suggest primary HOC. The hyperkalemia can be life threatening, and other causes like oliguric or anuric renal dysfunction, hemolysis, breed related (Akita, Shiba Inu etc.), thrombocytosis (leading to pseudohyperkalemia), metabolic acidosis due to mineral acids (e.g. NH4Cl, HCl), insulin deficiency

and hyperosmolality, acute tumor lysis syndrome, decreased urinary excretion secondary to urethral obstruction, ruptured bladder, gastrointestinal disease (trichuriosis, salmonellosis, or perforated duodenal ulcer), or potassium sparing drugs like spironolactone should be ruled out (Roth and Tyler, 1999).

Glucocorticoid deficiency results in more vague clinical signs and includes lethargy/weakness, shaking, polyuria, polydipsia, vomiting, diarrhea, abdominal pain, inappetence, and weight loss. Exercise intolerance and seizures, usually secondary to hypoglycemia are less common.

Critical illness related cortico-steroid insufficiency (CIRCI) is also referred to as relative adrenal insufficiency and has been associated with sepsis, shock, or trauma. The syndrome is transient, and adrenal function normalizes following correction of the underlying condition. Critically ill patients exhibiting refractory hypotension despite aggressive fluid therapy and the use of vasopressor agents like norepinephrine, should raise clinical suspicion of CIRCI. This is relatively rare (Martin, 2011).

SIGNALMENT

Any age, breed, and sex of dog can develop HOC, however, the most common presentation is in middle-aged (between 5-7 years) female dogs. Common breeds include Great Danes, Poodles (all types), West Highland White Terriers, Portuguese Water Dogs (PWD), Bearded Collies, Rottweilers, Soft-Coated Wheaten Terriers, Springer Spaniels, Bassett Hounds, and Nova Scotia Duck Tolling Retrievers (NDTR). In some breeds like Standard Poodle, Bearded Collie, PWD, and the NDTRa genetic basis is suspected.

PHYSICAL EXAM, AND ABNORMALITIES OBSERVED ON ROUTINE TESTING

Physical examination findings can vary from almost normal to hypovolemic shock. A variety of clinical and laboratory signs can be suggestive of HOC, but are not unique to HOC. Dogs with HOC are usually sick and 'lack of a stress leukogram', *i.e.* neutropenia, lymphocytosis, and eosinophilia. Normal neutrophil counts, relative eosinophilia(>500/μm) and relative lymphocytosis (>2500/μm), should raise suspicion of hypoadrenocorticism. A mild non-regenerative anaemia is present.

Biochemistry changes include azotemia, hypoglycemia, hypochloremia, hypocholesterolemia, hypoalbuminemia, hypercalcemia, and metabolic acidosis (decreased tCO_2/bicarbonate) and dilute urine with a specific gravity <1.030 (Peterson *et al.*, 1996). Imaging changes include microcardia, microhepatia

secondary to hypovolemia, and megaesophagus on thoracic radiographs. Small adrenal glands (< 4mm width of the caudal pole) secondary to bilateral atrophy of the adrenal glands are noted on ultrasonographic evaluation (Wenger *et al.*, 2010).

Electrocardiogram changes include atrial standstill, ventricular premature contractions, atrial fibrillation, or atrioventricular block and this is secondary to hyperkalemia (> 7 mmol/L) and if left untreated this will progress to ventricular fibrillation or asystole.

DIAGNOSIS

Basal cortisol concentration

Basal cortisol is only used to exclude a diagnosis of HOC. It cannot be used for a confirmation of diagnosis as some dogs have low basal cortisol but have an appropriate response to the ACTH stimulation test. Basal cortisol of >2 mcg/dl is a useful test to exclude a diagnosis of hypoadrenocorticism and should be ideally used as a screening test, in dogs that present with vague clinical signs. In dogs with a basal cortisol of <2 mcg/dl, an ACTH stimulation test is done (Lennon *et al.*, 2007).

ACTH stimulation test

The most widely used product is Cortrosyn™, which contains cosyntropin, which is synthetic ACTH. This is administered at 5mcg/kg IV after a basal serum sample is collected. There are a handful of dogs that have an adverse reaction to this. After the initial injection, a second serum sample is collected after 1 hour. A serum cortisol concentration of >6mcg/dl rules out HOC. Prednisone should have been administered for at least 72 hours before the ACTH stimulation test is done, as it will suppress the test and also cross reacts with the assay providing falsely increased results. However, dexamethasone does not react with the assay, and that is why it is preferred in a crisis situation. Single dose of parenteral prednisone (2.2mg/kg IM), dexamethasone (0.1mg/kg IV), or triamcinolone (0.22mg/kg IM) has not shown to suppress the ACTH stimulation test.

Based on internet searches intravenous ACTH, sold as Acthrel, (ovine corticorelin trifluoroacetate) is not available in India. Other options for ACTH include synthetic ACTH gels (Synacthen) which are given intramuscularly. This is also not readily available for routine clinical use in India.

Another product, called Acton Prolongatum® which is a synthetic corticotrophin carboxymethylcellulose in saline of porcine origin is available for

intramuscular use. This is marketed in India and freely available, and a 60 units/mL,5ml vial is valued at Rs.1,964. Compounded ACTH suspensions have been used in dogs at a dose of 2.2 units/kg for the same purpose in other countries (Ginel *et al.*, 2012). There is published data of this use in humans, both adults, and infants for the same purpose in India (Gundgurthi *et al.*, 2013 and Sharma *et al.*, 2019). While no specific safety studies were available for dogs, this might be a cost economic alternative after some safety trial studies.

Unlike HOC, the diagnosis of CIRCI is difficult. A change in cortisol concentration (delta cortisol) of < 3 mcg/dL or < 5 per cent increase in cortisol following an ACTH stimulation test is often used. CIRCI is usually a clinical diagnosis.

Other tests

Other tests like **Cortisol to endogenous ACTH Ratio or CAR** have been explored. Dogs with HOC, have low cortisol concentrations, and due to the lack of negative feedback, a relatively high ACTH concentration. This is not true for secondary HOC where ACTH is low or absent in these cases. Thus, CAR is expected to be significantly lower in patients with HOC. While, this eliminates use of synthetic ACTH injections, ACTH measurement can be challenging if the sample is not handled properly as it degrades very quickly. Most laboratories recommend freezing the sample immediately after collection and during transport or the addition of a proteinase inhibitor, aprotinin to the sample. While CAR is reliable, their ranges differed significantly in the two studies (Lathan *et al.*, 2014 and Boretti *et al.*, 2015) and more investigations are needed before this can be used reliably. Endogenous ACTH and cortisol testing are available in many human laboratories in Kerala.

Intravenous insulin tolerance tests (ITT)

These tests are used in humans for the determination of pituitary and adrenal insufficiency (Sharma *et al.*, 2019). It requires the administration of regular insulin at 0.01 U/kg IV to induce a 50 per cent reduction in glucose concentrations after an overnight fast. Cortisol and glucose concentrations are measured every 15 minutes for 60 minutes. Blood sugar level decreases (by at least 50 per cent for a valid test), and concurrent rise in serum cortisol concentrations rules out HOC. While ITT have been done in dogs, they have been usually done to evaluate glucose intolerance, rather than for HOC. Risks include hypoglycemic seizures and close monitoring is indicated. In atypical HOC cases, **aldosterone concentrations** are

measured in the samples from the ACTH stimulation test to see if supplementation is warranted (Baumstark *et al.*, 2014).

TREATMENT

Acute treatment

Treatment in the acute crisis includes rapid correction of hypovolemia after blood and ACTH stimulation samples are collected. Aggressive IV fluid therapy with isotonic crystalloid, 0.9 per cent sodium chloride at shock fluid doses (up to 90 mL/kg) until perfusion parameters stabilize. If serum sodium concentration is < 120 mEq/L, this has to be done carefully and with a fluid where the sodium concentration is within +/-10mEq/L of the serum concentration to avoid fatal central pontine myelinolysis. Once hemodynamically stable, fluid therapy is continued to correct ongoing dehydration and losses. Alternatively, 0.9 per cent NaCl at 7·5 to 10 mL/kg/hour for the first 1 to 2 hours, decreasing to 5 mL/kg/hour thereafter, with dextrose supplementation, if hypoglycemia was present (Klein and Peterson, 2010b and Gunn *et al.*, 2016).

If hyperkalemia persists despite fluid therapy (indicated by bradycardia), treatment with beta-adrenergic drugs like IV terbutaline or inhaled albuterol were used as they are quick to work. Concurrent dextrose and regular insulin therapy or measures to correct metabolic acidosis were rarely needed (Schaer 2001, and Lathan and Thompson, 2018).

Pending laboratory results, the administration of glucocorticoids and mineralocorticoids in the acute setting can help improve clinical signs and clinicopathologic abnormalities. Dexamethasone at 0.1—0.2 mg/kg IV Q 24, and desoxycorticosterone pivalate (DOCP) at 2.2 mg/kg IM Q 28 days is usually administered. However, DOCP is not available in India and in some other parts of the world. An alternative option is to use a glucocorticoid with some mineralocorticoid activity like prednisone or hydrocortisone. Hydrocortisone in dogs with HOC at 0·5 or 0·625 mg/kg/hour IV is used (Gunn *et al.*, 2016) and is the treatment in humans. Preparations include Cort-H or Anacort, which costs ~Rs. 60/ for a 100mg vial. Prednisolone at 0.5 -1 mg/kg IM or SC can be used, however, published data is lacking in dogs. The oral and SC route is inefficient in sick and dehydrated animals.

The CIRCI is treated with corticosteroids similar to a HOC crisis, 1–2.5 mg/kg/day of hydrocortisone, or 0.2–0.5 mg/kg/day of prednisolone/ methylprednisolone, and 0.03–0.08 mg/ kg/day of dexamethasone are used. Some authors only recommend using hydrocortisone for CIRCI.

Long-term treatment and management

Once the acute crisis is stabilized, long term maintenance is done with either a combination of oral prednisone (0.1-0.2mg/kg PO SIS) with injectable DOCP (q 25-28 days) or oral fludrocortisone acetate (FLORICOT tab, 0.1mg, 10 tablets cost Rs.138.89) 0.02 mg/kg PO Q 24. Lower initial doses of DOCP are equally efficacious in controlling electrolytes. Salt supplementation by salting the food can help correct hyponatremia and may help to reduce the number of fludrocortisone tablets needed. During times of stress, such as illness, injury, surgery, boarding, visitors etc., additional doses of prednisolone should be administered. The dose is normally 2 or 3 times the basal dose of 0.2mg/kg.

Dogs with HOC require life-long treatment, and periodic follow ups. While HOC can be fatal, early identification and proper treatment does result in excellent long-term prognosis in most patients (Kintzer and Peterson, 1997).

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