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Canine Hypoadrenocorticism: A Bibliographic Review

Cinthia Peres Camilo[1], Mauro José Lahm Cardoso[1,2], Paula Nassar De Marchi[2,3], Fernando Galdino Ricci[4], Murilo Sousa Romeiro[3]

[1]Department of Veterinary Clinics, Veterinary Hospital, Londrina State University, Londrina, Brazil
[2]Qualittas College, São Paulo, Brazil
[3]Universidade de Sorocaba, Campus Cidade Universitária, Sorocaba, Brazil
[4]Department of Microbiology, Center of Biological Sciences, Londrina State University, Londrina, Brazil
Email: maurolahm@gmail.com

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Abstract

Canine hypoadrenocorticism may be characterized by insufficiency of adrenocortical hormonal secretion of glucocorticoids and mineralocorticoids. Clinical signs are nonspecific such as dehydration, hypovolemic shock, bradycardia, hypotension, emesis, diarrhea, among other clinical and laboratory changes, and can mimic other diseases, and because of this, the disease can go unnoticed by the veterinarian, increasing the mortality and morbidity of patients seen in emergency consultations. Despite being of low occurrence, hypoadrenocorticism is often underdiagnosed, and should be considered in the differential diagnosis in the presence of gastrointestinal clinical signs or hypovolemic shock, and low Sodium:Potassium ratio. The definitive diagnosis is based on the dosage of cortisol before and after the application of the adrenocorticotrophic hormone. Acute treatment consists of patient stabilization, and chronic includes replacement of glucocorticoids and mineralocorticoids. Prognosis is usually favorable if the diagnosis is early and the correct treatment is performed. This article is a review focusing on clinical signs, laboratory findings, diagnosis and treatment on canine hypoadrenocorticism, to increase the knowledge about the disease to veterinarians.

Keywords

Addison, Aldosterone, Cortisol, Hyperkalemia, ACTH

1. Introduction

Hypoadrenocorticism is an uncommon but underdiagnosed hormonal disease as it presents findings similar to other diseases [1], and therefore it is important

that the clinician knows it, to diagnose it early and promote a better prognosis for patients. The aim of this study was to conduct a review on canine hypoadrenocorticism.

2. Physiology

The adrenal gland is divided into medullary and cortex (**Figure 1**), which is subdivided into fasciculated, glomerulosa and reticulated zone [2]. Cortisol production occurs in fasciculated and reticulated zones, stimulated by the corticotropin releasing hormone by the hypothalamus, which stimulates pituitary and releases adrenocorticotrophic hormone (ACTH), which acts on the adrenal cortex and releases cortisol [2] [3]. Aldosterone production occurs in the glomerulosa zone, through the aldosterone angiotensin renin system [2] [4].

3. Etiology and Pathogenesis

Hypoadrenocorticism is divided etiologically into primary and secondary. The primary has pathogenesis centered on the gland itself and occurs when there is atrophy or destruction of the adrenal cortex, mainly by immunomediated reactions, such as autoimmune polyglandular syndromes [5] [6]. It can also be caused by inflammatory diseases, infections [4], granulomatous diseases, neoplasms, traumas, coagulopathies [2], and iatrogenic by treatment with trilostan or mitotane in dogs with hyperadrenocorticism [7], or by adrenalectomy [8]. In these cases, there is deficiency of glucocorticoids and mineralocorticoids, because the adrenal cortex is responsible for the production of theses hormones [4].

Secondary hypoadrenocorticism occurs when there is injury to the hypothalamus or pituitary gland [2] [7], with consequent decrease in adrenocorticotrophic hormone (ACTH) secretion [1], and may be caused by neoplasms [2], trauma, or iatrogenic by the use of glucocorticoids without gradual withdrawal [5]. Some authors add a division, atypical hypoadrenocorticism, whose pathogenesis is centered on the adrenal gland, equal to the primary, but there is no electrolytic alteration, because in atypical there is only glucocorticoid deficiency [1] [9]. However, this terminology is questionable, as aldosterone secretion remains at low levels and does not differ in dogs with and without electrolytic alteration [10] [11].

Cortisol deficiency produces various effects on the body, such as hypovolemia, hypotension, absence of intestinal anti-inflammatory effect and inability to respond to stress situation, by decreasing vascular sensitivity to catecholamines [2] [3]. In addition, glucocorticoids contribute to glycogenesis and lipolysis in stressful situations and, in their deficiency hypoglycemia may occur. Meanwhile, aldosterone is important in maintaining pressure, as it acts in renal potassium excretion (K) and distal tubular renal reabsorption of Sodium (Na), chlorine and water, and if aldosterone deficiency occurs may be dehydration, hypotension, electrolytic disequilibrium and cardiac alterations [3] [12] (**Figure 2**).

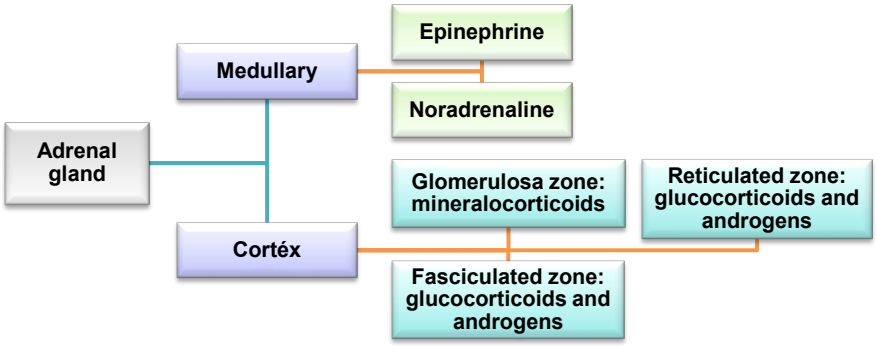

Figure 1. Anatomy and functions of the adrenal gland. Source: Adapted from Van Lanen and Sande, 2014 [2].

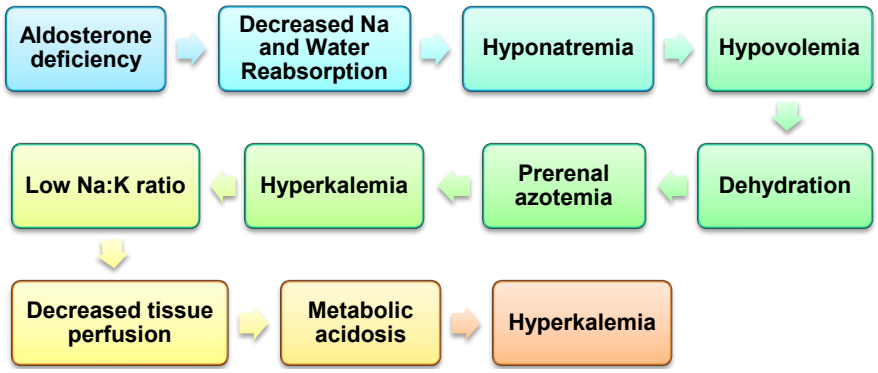

Figure 2. Decrease of aldosterone in the organism and consequences. Source: Adapted from Adler *et al.*, 2007 [13]; Boysen, 2008 [12]; Klein and Peterson, 2010a [3]; Scott-Moncrieff, 2015 [1].

4. Clinical and Laboratory Characteristics

The disease can affect dogs of many ages [13], and as for sex females represent 46% [6] to 70% of cases, and males 30% [14] to 54% of cases [6]. Among the predisposed breeds are Poodle, Portuguese Water Dog [5] [6], Border Collie [5], Rottweiler, Basset Hound, West Highlander White Terrier, Great Dane, Labrador Retriever [6] and Springer Spaniel English [7].

Clinical signs may be acute or chronic and nonspecific [2] [15] as lethargy, anorexia, emesis, diarrhea, melena, abdominal pain, weight loss, weakness, polyuria and polydipsia, tremors and hair drop [3] [14]. Clinical findings and physical examination are associated with severity of disease and may range from mild dehydration to hypovolemic shock, such as weak pulse, bradycardia and hypothermia [3] [14].

In the blood count there may be anemia, usually classified as regenerative, normocytic and normochromic [16], due to bone marrow suppression due to cortisol deficiency, in addition to loss of red blood cells by gastrointestinal bleeding [1] [3]. Leukogram may evidence lymphocytosis and eosinophilia due to cortisol deficiency (**Table 1**), with regulates the distribution of peripheral leukocytes released under various physical, emotional and chemical stressors [16].

Table 1. Frequency of laboratory changes in the blood count in dogs with hypoadrenocorticism (2007-2017).

Laboratory Alteration	Authors and Relative Frequencies (%)				
	Greco 2007	Klein; Peterson 2010	Gunn *et al.* 2016	Haviland *et al.* 2016	Wakayama *et al.* 2017
Anemia	25	21 - 25	25	16	28
Hemoconcentration			7	26	
Eosinophilia	13 - 20	10 - 20	3	18	21
Lymphocytosis	10	10 - 13	2	12	33
Neutrophilia				3	26
Lymphopenia			7	3	5
Neutropenia				6	
Total dogs (n˚)	225	Ni	30	82	40

Legend: Ni = Not informed by the authors. Source: Adapted from Adler *et al.*, 2007 [13]; Greco, 2007 [14]; Klein and Peterson, 2010a [3]; Gunn *et al.*, 2016 [22]; Haviland *et al.*, 2016 [6]; Wakayama *et al.*, 2017 [10].

In biochemical tests (**Table 2**), there may be hypoglycemia due to cortisol deficiency, and decreased glyconeogenesis, hepatic glycogenolysis, lipolysis and glycogen storage [2] [3]. Hypoalbuminemia may occur due to low albumin synthesis by decreased nutrient intake, deficiency in absorption, liver disease or loss via gastrointestinal bleeding [1] [3]. There may also be increase in alanine aminotransferase activity (ALT) due immunomediated disease, poor perfusion and hepatic hypoxia [2] [3]. Prerenal azotemia due to poor perfusion and decreased glomerular filtration rate (GFR), dehydration and hypovolemia, and increased urea may also occur due to gastrointestinal bleeding and liver alterations [3] [7]. While hypocholesterolemia may occur due to fat absorption deficiency, low activity of the enzyme cholesterol synthase and the deficiency of the sensitive hormone lipase enzyme (LHS) in secondary hypoadrenocorticism [1].

In hemogasometry there may be acidosis, due to decreased tissue perfusion and impaired renal function, with causes increased acidic compounds in the blood, hypochloremia due to aldosterone deficiency with consequent decrease in distal tubular renal reabsorption of chorine renal and gastrointestinal losses [2] [3]. There may be Hypercalcemia due to renal excretion decreased by decreased GFR, excess intestinal and bone absorption and hemoconcentration [1] [2]. Hyperphosphatemia may occur due to dehydration and hypovolemia that cause poor renal perfusion, decreased GFR and renal phosphorus excretion [3].

Among the laboratory findings are hyponatremia and hyperkalemia, which occur due to aldosterone deficiency, with leads to decreased distal renal resorption of Na and renal excretion of the K and consequently decreased Na:K ratio (<30) [12] [13], but some dogs do not have these electrolytic changes [10] [14] [15], also called atypical hypoadrenocorticism. The normal Na:K ratio ranges from 27:1 to 40:1 [12], and in [13] the probability of diagnosis was evidenced to be confirmed in dogs with Na:K ratio less than or equal to 24, with 100% specificity

Table 2. Frequency of biochemical changes and hemogasometry in dogs with hypoadrenocorticism (2007-2019).

Laboratory Alteration	Authors and Relative Frequencies (%)					
	Adler *et al.* 2007	Greco 2007	Klein; Peterson 2010a	Gunn *et al.* 2016	Haviland *et al.* 2016	Wakayama *et al.* 2017
Hyponatremia	82	80	86	85	63	
Hyperkalemia	85	95	95	59	76	
Hypochloremia	68	40	40	81	35	
Hyperphosphatemia		85	66 - 85	55	57	
Hypercalcemia	18	30	30	16	36	
Acidosis	60	40	50	50		
Increased creatinine		85	66 - 95	59	71	
Increased urea				66	83	10
Hypoglycemia	10	17	22		9	35
Hypoalbuminemia			17 - 39	7	26	87
Hypocholesterolemia			17.5	22	29	76
Increased ALT		30	30 - 50			
Total dogs (n°)	76	225	Ni	27	78	40

Legend: Ni = Not informed by the authors. Source: Adapted from Adler *et al.*, 2007 [13]; Greco, 2007 [14]; Klein and Peterson, 2010a [3]; Gunn *et al.*, 2016 [22]; Haviland *et al.*, 2016 [6]; Wakayama *et al.*, 2017 [10].

and 79% sensitivity. However, in [15] a sensitivity of only 56% and specificity of 99% for the same value was detected.

5. Diagnosis

The diagnosis is made through history, clinical, laboratory findings and images tests, however, it is confirmed only with hormonal tests [16] [17] and ACTH stimulation test [10]. To perform the stimulation test with ACTH, the first serum sample should be collected to perform basal cortisol dosage and apply ACTH at the dose of 5 μg/Kg, intravenously (IV) or up to 250 μg per dog [14] [17]. After one hour of ACTH application, another sample is collected for post-ACTH cortisol dosage [14] [17] intramuscular administration (MI) is not indicated, as in dogs with dehydration there is decreased absorption of ACTH, may alter test results [17]. However, one study demonstrate that each deposit formulation can be administered by IM for the diagnosis of hypoadrenocorticism, and the sample can also be obtained one hour after its application [18].

A study was conducted with the dose of 1 μg/Kg of ACTH via IV, in dogs with hypoadrenocorticism, and the results were equivalent with the use of the standard dose of 5 μg/Kg, witch, could reduce the cost of the diagnostic test [19]. Serum cortisol measurement can be performed by two laboratory methods, chemoluminescence immunoassay and radioimmunoassay [2] [17], with no differences between them, except where the cortisol value is less than 0.5 μg/Kg,

which is the detection limit of most commercial tests used for chemoluminescence [1].

The diagnosis is confirmed if the post-ACTH cortisol value is less than 2 μg/dL and some authors suggest that the diagnosis can be excluded by basal cortisol dosage, because if the value is greater than 2 μg/dL, sensitivity is 100% for the dog who not present the disease [9] [20]. However, the opposite is not valid, as there are not enough studies to prove the hypothesis that the diagnosis can be made only with the measurement of basal cortisol, and therefore, the stimulation test with ACTH should be performed to confirm the diagnosis [2] [15] [20] [21]. However, one study observed that the serum concentration of basal cortisol of 0.8 μg/dL would be a better predictive value of the disease (**Table 3**) [21], and requires further studies to analyze the predictive value of basal cortisol [2] [9] [15].

The stimulation test with ACTH does not differentiate primary hypoadrenocorticism from the secondary, and for this the serum dosage of endogenous ACTH is made [11] [12] [14] [15], however, this is a limited examination for their hormonal instability [15]. For the measurement of endogenous ACTH, a plasma sample was required, collected in a vial with the previously refrigerated and rapidly processed ethylenediaminotetraacetic acid [14] [15], and normal values correspond from 20 to 80 pg/ml [14]. The endogenous ACTH value is increased in primary hypoadrenocorticism, and in the case of secondary hypoadrenocorticism is decreased to normal [1].

6. Treatment

In the treatment of acute crisis, the patient is seeking to stabilization with the

Table 3. Frequency of serum basal cortisol changes in dogs with hypoadrenocorticism (2007-2019).

Laboratory Alteration	Authors and Relative Frequencies (%)			
	Lennon *et al.* 2007	Bovens *et al.* 2014	Boretti *et al.* 2015	Gold *et al.* 2016
Basal Cortisol	≤2 μg/dL	≤2 μg/dL	≤2 μg/dL	≤2 μg/dL
Sensitivity %	100	100	100	94
Specificity %	78.2	63.3	20	67
Basal Cortisol	≤1 μg/dL	≤1 μg/dL		≤0.8 μg/dL
Sensitivity %	100	85.7		96.9
Specificity %	98	91.8		95.7
Total dogs with non-adrenal diseases (n˚)	110	450	79	351
Total dogs with hypoadrenocorticism (n˚)	13	14	23	163

Source: Adapted from Lennon *et al.*, 2007 [9]; Bovens *et al.*, 2014 [20]; Boretti *et al.*, 2015 [15]; Gold *et al.*, 2016 [21].

correction of hydroelectrolytic disorders, which involves the performance of fluid therapy with physiological solution [2] [8] [12] [22]. After correction of dehydration it may be necessary blood transfusion, according to the degree of anemia of the patient [1]. In case of hypoglycaemia, 50% glucose replacement should be performed in dose of 0.5 - 1 ml/Kg IV [7] [8] [12], with diluted and low administration [12].

Correction of hyperkalemia can be performed only with fluid therapy, which leads to increased excretion of K by increasing GFR, or with glucose supplementation in fluid therapy [1] [7] [12]. For correction of bradycardia and in severe cases of arrhythmias resulting from hyperkalemia, 10% calcium gluconate can be used at dose of 0.5 - 1 ml/Kg IV slow, but does not correct the cause, which is hyperkalemia [8] [12], and electrocardiography monitoring should be done [1].

Glucocorticoid supplementation assists in improving vascular, gastrointestinal integrity, blood pressure maintenance, blood glucose and volemia [1] [17]. Corticosteroid therapy should be performed in Addisonian crisis only with dexamethasone at a dose of 0.5 - 4 mg/Kg IV once a day (SID) or twice a day (IDB) [12] [17], as it does not cause interference in the result of the ACTH stimulation test [1] [17].

Glucocorticoids can alter the results of the ACTH stimulation test in any formulation, and use of hydrocortisone, prednisone and prednisolone [17] should be avoided. If the test has already been performed, hydrocortisone can be used at dose 5 mg/Kg, IV every 6 hours [17], or in continuous infusion (0.5 - 0.625 mg/Kg/hour) [22].

Chronic treatment is based on the replacement of glucocorticoids and mineralocorticoids, and the replacement of glucocorticoids can be done with prednisone (0.2 mg/Kg SID), which in some cases can be gradually removed, according to the maintenance of the normal Na:K ratio [1] [2]. However, prednisone should be used in stressful situations and the dose can be increased to avoid Addisonian crisis [1] [2]. Mineralocorticoid replacement should be performed with fludrocortisone (0.01 - 0.02 mg/Kg IDB), or with deoxycorticosterone pivalate (2 mg/Kg) [2] [23], IM every 25 or 30 days [12].

The patient must be monitored by measuring electrolytes and the Na:K ratio, and also by performing laboratory tests such as urinalysis, glycemia, triglycerides and fasting cholesterol, to ascertain the presence of hyperlipidemia and diabetes, complications of continuous administrations of glucocorticoids [1] [23]. Prognosis is good when the correct treatment is performed quickly [17], but is of harm to reserved when the disease is caused by neoplasms or granulomatous diseases [1].

7. Concluding Remarks

Hypoadrenocorticism is an uncommon and underdiagnosed disease due to failure to perform laboratory tests to measure electrolytes and calculate the Na:K

ratio, and because the disease is not considered in the differential diagnosis in the clinical routine. Therefore, the electrolyte dosage should be performed, since it is a useful test for the suspicion of the diagnosis of primary hypoadrenocorticism, since the Na:K ratio below the reference value is an important indicator for the diagnosis of the disease in dogs with compatible clinical signs.

Hypoadrenocorticism should be included in the list of differential diagnoses for dogs with clinical signs, such as apathy, emesis, diarrhea, weakness, anorexia, tremor, syncope and seizure, with findings on physical examination like dehydration, hypotension and bradycardia, and laboratory alterations such as hypoglycemia, hypoalbuminemia, hyponatremia, hyperkalemia, Na:K ratio below 27, azotemia, hypocholesterolemia, hypochloremia, lymphocytosis, anemia, eosinophilia and acidosis.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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