Hypoadrenocorticism in dogs presenting to a tertiary veterinary clinic in Switzerland: overall prevalence, clinical signs, laboratory changes and outcome

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Hypoadrenokortizismus bei Hunden, die in einer tertiären Tierklinik in der Schweiz vorgestellt wurden: Gesamtprävalenz, klinische Symptome, Laborveränderungen und Ergebnis

Hypoadrenokortizismus (HAD) ist eine relativ seltene Endokrinopathie, und Hunde zeigen oft unspezifische klinische Symptome.

Die Labordatenbank eines tertiären Überweisungszentrums wurde für die Überprüfung verblindet und zwischen März 2015 und März 2023 retrospektiv nach Hunden mit Verdacht auf HAD durchsucht und anschliessend anhand der basalen Cortisolmessungen und/oder eines Adrenokortikotrope Hormon Stimulationstests (ACTH-STIM) kategorisiert. Die Diagnose von HAD basierte auf abnormalen Ergebnissen eines ACTH-STIM (Cortisol nach ACTH-STIM < 2 ug/dl).

HAD wurde bei 54 Hunden diagnostiziert, was 9,6 % der untersuchten Population (n = 564) entspricht. Hunde ohne HAD wiesen signifikant höhere Natriumkonzentrationen (p < 0,001), niedrigere Kreatininkonzentrationen (p = 0,007) und niedrigere Phosphatkonzentrationen (p < 0,001) auf als Hunde mit HAD. Zu den häufigsten Rassen, bei denen HAD diagnostiziert wurde, gehörten: Mischlinge (n = 16), Jack Russel Terrier (n = 5) und Berner Sennenhunde (n = 3). Das mittlere Alter bei der Diagnose betrug 5 Jahre (IQR: 3–8,75, Bereich: 1–14). Neunundzwanzig Hunde waren männlich und 26 Hunde weiblich. Die häufigsten klinischen Symptome waren Kombinationen aus Hypo-/Anorexie (n = 37, 68,5 %), Lethargie (n = 35, 64,8 %) und Erbrechen (n = 31, 57,4 %). Zwei von 54 Hunden (3,7 %) hatten Ruhe-Cortisolwerte > 0,5 µg/dl (> 13,79 nmol/l) (max. 0,63 µg/dl [17,38 nmol/l]), und sechs Hunde (11,1 %) Post-ACTH-STIM-Cortisolwerte > 0,5 µg/dl (Median: 0,82 µg/dl [22,62 nmol/l], IQR 0,51–0,96 [14,07–26,48]). Hunde mit eunatreischem, eukalemischem Hypoadrenokortizismus (EEH) wiesen häufiger eine Anämie auf (OR:

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Abstract

Hypoadrenocorticism (HAD) is a relatively uncommon endocrinopathy and dogs often present with non-specific clinical signs.

The laboratory database of a tertiary referral center was blinded for review and retrospectively searched between March 2015 and March 2023, for dogs with suspected HAD and then categorized according to basal cortisol measurements and/or an adrenocorticotropic hormone stimulation test (ACTH-STIM). Diagnosis of HAD was based on abnormal results of an ACTH-STIM (post-ACTH-STIM cortisol < 2ug/dl).

HAD was diagnosed in 54 dogs, representing 9,6 % of the screened population (n = 564). Dogs without HAD had significantly higher sodium (p < 0,001), lower creatinine (p = 0,007), and lower phosphates (p < 0,001) concentrations than dogs with HAD. Most common breeds diagnosed with HAD included: mix breed (n = 16), Jack Russel Terrier (n = 5) and Bernese Mountain Dog (n = 3). Median age at diagnosis was 5 years (IQR: 3–8,75, range: 1–14). Twenty-nine dogs were male and 26 dogs were female. Most common clinical signs were combinations of hypo-/anorexia (n = 37, 68,5 %), lethargy (n = 35, 64,8 %), and vomiting (n = 31, 57,4 %). Only two of 54 dogs (3,7 %) had resting cortisol values > 0,5 µg/dl (> 13,79 nmol/l) (max. 0,63 µg/dl [17,38 nmol/l]) whereas six dogs (11,1 %) had post-ACTH-STIM cortisol values > 0,5 µg/dl (median: 0,82 µg/dl [22,62 nmol/l], IQR 0,51–0,96 [14,07–26,48]). Dogs with eunatremic, eukalemic hypoadrenocorticism (EEH) were more likely to present with anemia (OR: 14,19, 95 % CI, 2,71–74,22), whereas dogs with typical HAD were more likely to present with hyperphosphatemia (OR: 23,33, 95 % CI, 2,68–203,14). Forty-three dogs (79,6 %) had hyponatremic and/or hyperkalemic HAD and the remaining 11 dogs had EEH. In-house mortality was 5 % (3/55). One dog with EEH developed typical HAD seven weeks after initial diagnosis. Among dogs with HAD, the proportion diagnosed with EEH was similar to previous studies. In contrast

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14,19, 95 % KI, 2,71–74,22), während Hunde mit typischem HAD häufiger eine Hyperphosphatämie aufwiesen (OR: 23,33, 95 % KI, 2,68–203,14). Dreiundvierzig Hunde (79,6 %) hatten einen hyponatriämischen und/oder hyperkaliämischen HAD, die übrigen 11 Hunde hatten einen EEH. Die Mortalität in der Klinik betrug 5 % (3/55). Ein Hund mit EEH entwickelte sieben Wochen nach der Erstdiagnose eine typische HAD. Unter den Hunden mit HAD war der Anteil der mit EEH diagnostizierten Hunde ähnlich wie in früheren Studien. Im Gegensatz zu früheren Berichten, in denen weibliche Tiere überrepräsentiert waren, waren in dieser Kohorte mehr männliche als weibliche Tiere betroffen. Es wurde kein signifikanter Altersunterschied bei der Vorstellung zwischen Hunden mit typischer HAD und EEH beobachtet.

Schlüsselwörter: Hund, Addison, eukalämisch-eunatriämisch, klinisch-pathologische Veränderungen, Mortalität

to previous reports in which females were overrepresented, more males than females were affected in this cohort. No significant difference in age at presentation was observed between dogs with typical HAD and EEH.

Keywords: dog, addison, eukalemic eunatremic, clinicopathological changes, mortality

Introduction

Hypoadrenocorticism (HAD), also known as Addison's disease, is a well described but relatively uncommon endocrinopathy, with a reported prevalence of 0,06–0,09 % in the general dog population in Europe.[16,8,32] Two clinical forms of HAD are typically recognized, based on the presence (typical HAD) or absence (atypical HAD) of electrolytes imbalances.[35,43] This distinction must be differentiated from the pathophysiological origin of the disease that include primary or secondary HAD. Primary HAD is the most common form of HAD and results from the auto-immune destruction of the adrenal cortex.[37,3,4,39,33,34] Secondary HAD occurs following pituitary or hypothalamic failure leading to impaired secretion of adrenocorticotropic hormone (ACTH) or hypothalamic corticotropin-releasing hormone (CRH) respectively.[37,36,4,39]

Classically, primary HAD results in both mineralocorticoids (aldosterone) and glucocorticoids (cortisol) deficiencies whereas only the latter is deficient in secondary HAD.[5,35,36,4,39,22] Cortisol deficiency causes non-specific clinical signs such as chronic gastrointestinal issues (e.g. vomiting, diarrhea, inappetence) as well as lethargy.[37,15] Clinicopathologic changes associated with cortisol deficiency include absence of a stress leukogram, mild aregenerative anemia and hypoglycemia.[37,15] Aldosterone-deficiency causes a decreased reuptake of sodium in exchange for potassium in the distal renal tubule, which can lead to hyponatremia and/or hyperkalemia, along with diluted urine, dehydration, and potentially hypovolemia.[35,2,43,33] However, up to 30 % of dogs with primary HAD present without electrolyte imbalance, which is termed as atypical HAD or eunatremic eukalemic hypoadrenocorticism (EEH).[1,40,32,42] As the renin-angiotensin-aldosterone system (RAAS) is largely independent of pituitary and hypothalamic control, mineralocorticoid production is typically preserved in secondary HAD, and electrolyte disturbances are not expected.[5,37,35,36,4] Dogs suffering from secondary HAD and dogs with atypical HAD will both present as EEH.[5,35] From a clinical perspective, distinguishing EEH from secondary HAD is important: dogs with secondary HAD have a very low risk of developing electrolyte disturbances, whereas dogs with EEH may progress to typical HAD over time.[5,35] Differentiation requires measurement of endogenous adrenocorticotropic hormone (ACTH), which is markedly increased in EEH but low in secondary HAD[5,36,4,39]

Diagnostic screening for HAD often begins with measurement of basal serum cortisol (BSC) in dogs with chronic gastrointestinal symptoms and values > 2 µg/dl (> 55,2 nmol/l) are frequently used to exclude HAD.[41,8,9] If BSC is ≤ 2 µg/dl, or clinical suspicion remains high, an ACTH stimulation test (ACTH-STIM) is performed to diagnose HAD. Historically, a few studies proposed using urinary cortisol-to-creatinine ratio (UCCR) to screen for HAD with excellent sensitivities and specificities.[3,25] However, changes in assay antibodies used in the chemiluminescent immunoassay (CLIA; Immulite 2000cortisol; Siemens Health Care Diagnostics Ltd) revealed that cortisol values measured with the new antibody were lower than previously described.[44] One recent study however showed non-inferiority of UCCR < 1 µg/dl compared to BSC.[10] However, ACTH-STIM remains the gold standard for HAD diagnosis.

There is compelling evidence of genetic basis for HAD in some specific breeds,[11,13,24,38,2] with familial HAD described in the Leonberger and Pomeranian.[24,38] Some breeds have been shown to have a higher risk to develop HAD, including Portuguese Water Dogs, Standard Poodles, Cocker Spaniels and Bearded Collies.[7,16,27,26] In previous studies,

dogs are typically presented at 2–6 years of age.[27,8] Additionally, some studies have suggested a higher risk of HAD in females dogs,[16,27] but this sex predisposition is not consistently reported in other studies.[5,21]

The main objectives of this study were to: (1) describe the hospital prevalence, demographics, clinical signs, clinicopathological features and short-term outcome of dogs diagnosed with HAD in a tertiary veterinary clinic in Switzerland, and (2) describe clinical and clinicopathological features which might help differentiate between EEH and typical HAD.

Materials and Methods

Case selection and data collection (Figure 1)

In this retrospective single center study, the database of the central laboratory was blinded for review and was searched for dogs that had either a single BSC measurement or paired serum cortisol measurements when ACTH-STIM[21] was performed, between February 2015 and May 2023. As a tertiary referral clinic, dogs presenting with chronic gastrointestinal signs (e.g. vomiting, diarrhea, weight loss, hyporexia, borborygmi) are routinely screened for HAD by measuring BSC. When HAD cannot be excluded (BSC < 2 µg/dl), further screening with ACTH-STIM is recommended to all owners. For ACTH-STIM, 5µg/kg Tetracosactid (Synacthen 0,25 mg/1 ml, Curatis AG, Liestal, Switzerland) is injected intravenously after a first blood sample (T0), followed by a second blood sample (T1) 60 minutes post-injection. All serum cortisol concentrations were measured at an external reference laboratory (IDEXX Diavet AG Laboratories, Freienbach, Switzerland) using a competitive chemiluminescence immunoassay (IMMULITE 2000XPi; Siemens Healthcare Diagnostics, Deerfield, IL), previously validated for canine serum.

Dogs were classified as having HAD if post-ACTH-STIM cortisol concentrations remained < 2 µg/dl and no corticosteroid treatment had been administered in the 12 weeks prior to testing. Dogs with BSC or post-ACTH cortisol values ≥ 2 ug/dl were classified as not having HAD, based on previous literature. [1] They were named as dogs without adrenal insufficiency. Dogs were excluded if cortisol measurements were performed as part of the diagnostic or monitoring of hyperadrenocorticism.

Medical records, blinded for review, of the Small Animal Hospital were searched and complete blood count (CBC) and serum biochemistry were retrieved where available for all included dogs. Results were compared between dogs with and without adrenal insufficiency. Further analyses were only performed on dogs with HAD, and data were retrieved from medical records of the Small Animal Hospital of the University of Bern, and were analyzed including: signalment, body weight, clinical signs, presence of Addisonian crisis, BSC and post-ACTH-STIM cortisol values, and survival.

Dogs with HAD were further categorized as having typical HAD and EEH if they had respectively concurrent hyponatremia and/or hyperkaliemia or both sodium and potassium within reference ranges (RR) at admission.

Statistical Analysis

Statistical analyses were performed using commercially available software (DATAtab Team (2024). DATAtab: Online Statistics Calculator. DATAtab e.U. Graz, Austria. URL https://datatab.de) and Microsoft Excel (Microsoft Corporation. Microsoft Excel (Internet)).

Data distributions were analyzed for normality using histograms and the Shapiro-Wilk test. Variables with a normal distribution are presented as mean (standard deviation

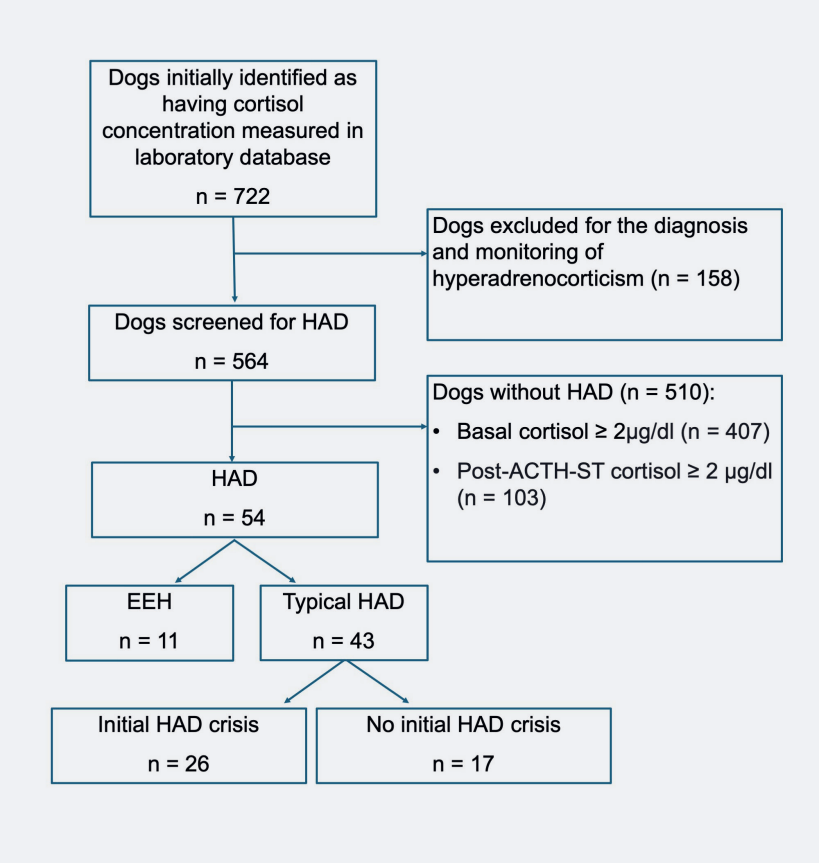

Figure 1: Flowchart illustrating the exclusion of dogs from the initial case selection to form the final study population, with proportions of dogs diagnosed with eunatremic, eukalemic hypoadrenocorticism (EEH) and typical hypoadrenocorticism (HAD). Initial HAD crisis was diagnosed based on cardiovascular instability.

[SD]), while non-normally distributed variables are presented as median (interquartile range [IQR]). The lower limit of detection of cortisol concentrations was 0,5 µg/dl. For statistical analysis of adrenal testing, values < 0,5 µg/dl were recorded as 0 µg/dl when calculating means (SD).

Clinicopathological parameters were compared between dogs with and without adrenal insufficiency and between dogs with typical HAD and EEH (including adrenal testing), using a two-sample t-test. To assess the equality of variances for a laboratory parameter Levene's test was used. If variance could be confirmed, two-sample t-test for equal variance was used, if variance could not be confirmed, two-sample t-test for unequal variance was used. Laboratory parameters of select CBC and biochemistry falling above or below RR were compared between dogs with and without HAD using a Fisher's Exact test. To assess the odds of having values outside of RR, odds ratio (OR) was calculated.

Receiver operator characteristics (ROC) analysis was used to evaluate laboratory analytes yielding significant difference between dogs with and without adrenal insufficiency, including serum sodium and phosphate concentrations, as predictors of adrenal insufficiency. The maximal point of the Youden's index (Sens-[1-Spec]) was used as the optimal cut-off value for ROC analyses. Statistical significance was set at $p < 0,05$, except in cases of multiple comparisons, for which the Bonferroni correction was applied.

Results

Population characteristics

A total of 722 dogs were identified as having serum cortisol concentrations measured during the initial data collection. Of these, 158 were subsequently excluded for having blood tests (pre-pill, ACTH-STIM or low dose dexamethasone suppression test) performed for diagnosis or monitoring of hyperadrenocorticism. This resulted in 564 dogs that were screened for HAD and of which 54 (9,6 %) were diagnosed with HAD (Figure 1).

Among them, 29 (53,7 %) were males and 26 (46,3 %) females. Median age at diagnosis was 5 years (IQR: 3–8,75, range: 1 – 14). Most common breeds were mixed breed (n = 16), Jack Russel Terrier (n = 5), Bernese Mountain Dog (n = 3), followed by Cairn Terrier, Poodle, Chihuahua, Brittany, Irish Soft Coated Wheaten Terrier, and West Highland White Terrier (n = 2 each).

Table 1: Percentages and number of dogs with various clinical signs among dogs with typical hypoadrenocorticism (HAD) and eunatremic, eukalemic hypoadrenocorticism (EEH) and p-values for comparison of clinical signs between the 2 groups.

Clinical Sign	Typical HAD	EEH	p-value
Hypo-/anorexia			0,002
%	79 %	27 %	
n	34/43	3/11	
Apathy			0,03
%	72 %	36 %	
n	32/43	4/11	
Vomiting			0,04
%	65 %	27 %	
n	28/43	3/11	
Diarrhea			0,24
%	19 %	36 %	
n	8/43	4/11	
Weight loss			1
%	18 %	18 %	
n	8/43	2/11	
PU/PD			0,37
%	14 %	27 %	
n	6/43	3/11	
Various neurological signs			0,72
%	35 %	45 %	
n	15/43	5/11	

Note: Data are presented as percentages and counts. The p-values in bold correspond to statistically significant findings after Bonferroni-correction ($p < 0,007$).

Most dogs (79,6 %, 43/54) were diagnosed with typical HAD and the remaining 11 dogs (20,4 %) with EEH. At admission, 24/54 dogs (44,4 %) were presented with HAD crisis (Figure 1). One dog that was initially diagnosed with EEH developed subsequent typical HAD seven weeks after initial diagnosis, which corresponds to a prevalence of 9 % (1/11) of dogs with EEH developing typical HAD after diagnosis (median follow up time 5,5 months, range: 0,5–34 months)

Clinical signs

Most common clinical signs included a combination of hypo-/anorexia (n = 37, 68,5 %), lethargy (n = 35, 64,8 %), vomiting (n = 31, 57,4 %), followed by diarrhea (n = 12, 22,2 %), weight loss (n = 10, 18,5 %) and polyuria and polydipsia (n = 9, 16,7 %). Neurological signs were reported in 20 dogs (37 %) and included shaking, reluctance to walk, hind limb weakness, and seizures (Figure 2).

Dogs with typical HAD were significantly more likely to present with hypo-/anorexia (p = 0,002). No significant difference between groups was found for the remaining clinical signs: lethargy, vomiting, diarrhea, weight loss, polyuria and/polydipsia and neurological signs (Table 1).

Clinicopathological differences between dogs with and without adrenal insufficiency

Dogs without HAD had significantly higher median sodium (p < 0,001), and lower phosphate (p < 0,001) concentrations than dogs with HAD. No significant differences were observed for the other tested parameters (hematocrit (Htc), hemoglobin (Hb), white blood cell (WBC), eosinophil, lymphocyte count, phosphate, glucose, total bilirubin, creatinine, urea) between dogs with and without HAD.

The area under the ROC curve (AUROCC) for serum sodium concentration as a predictor for adrenal insufficiency in the population of dogs tested for HAD was 0,8327 (95 % CI, 0,7471–0,8911) with an optimal cut-off point of ≤ 140,0 mmol/l yielding a sensitivity of 76,47 % (95 % CI 0,63–0,87) and a specificity of 86,12 % (95 % CI, 0,83–0,89) (Figure 3A). The AUROCC for serum phosphate concentration as a predictor for adrenal insufficiency in the same population was 0,7551 (95 % CI, 0,6785–0,8154) with an optimal cut-off point of ≥ 1,56 mmol/l yielding a sensitivity of 67,35 % (95 % CI 0,53–0,8) and a specificity of 78,9 % (95 % CI, 0,75–0,83) (Figure 3B).

Clinicopathological findings

Dogs with EEH were more likely to have anemia, as assessed through Htc (OR: 14,19, C.I. 2,71–74,22) and Hb concentration (OR: 14,19, C.I. 2,71–74,22), compared to dogs with typical HAD (p = 0,0048). There was no significant difference between EEH and HAD dogs for the frequency of leukocytosis (p = 0,27), lymphocytosis (p = 0,18) or eosinophilia (p = 0,28) (Table 2).

Dogs with typical HAD were more likely to present with hyperphosphatemia (OR: 23,33, C.I. 2,68–203,14) than dogs with EEH (p < 0,0002). There was no difference in frequency of hypoglycemia (EEH: 18,2 %, HAD: 17,1 %), nor hyperbilirubinemia (EEH: 28,6 % vs. 24 %) between groups (p = 1,0 each). Although median serum urea concentration in dogs with HAD was significantly higher than in dogs with EEH (p < 0,001), statistically no difference in number of dogs with serum urea concentrations above RR was found (p = 0,04). There was neither a significant difference in median serum creatinine concentration (p = 0,039), nor in number of dogs with values above the RR between the two groups (p = 0,04) (Table 2). Mean (SD) serum cholesterol and albumin concentrations were below the RR for both EEH (cholesterol: 3,51noml/l [1,54]; albumin: 22,55 g/l [6,78]) and typical HAD dogs (cholesterol: 3,46noml/l [1,33]; albumin: 29,68 g/l [5,88]), respectively. There was no significant difference between the two groups for serum cholesterol (p = 0,919) and albumin (p = 0,002) concentrations.

Only 2/54 dogs (3,7 %) had BSC concentrations > 0,5 µg/dl (max. 0,63 µg/dl) and only 6/54 dogs (11,1 %) had post-ACTH-STIM cortisol values > 0,5 µg/dl (median: 0,82 µg/dl, IQR: 0,705–0,83 µg/dl). There was no significant difference in BSC and post-ACTH-STIM cortisol concentrations between dogs with typical HAD and EEH (Table 3).

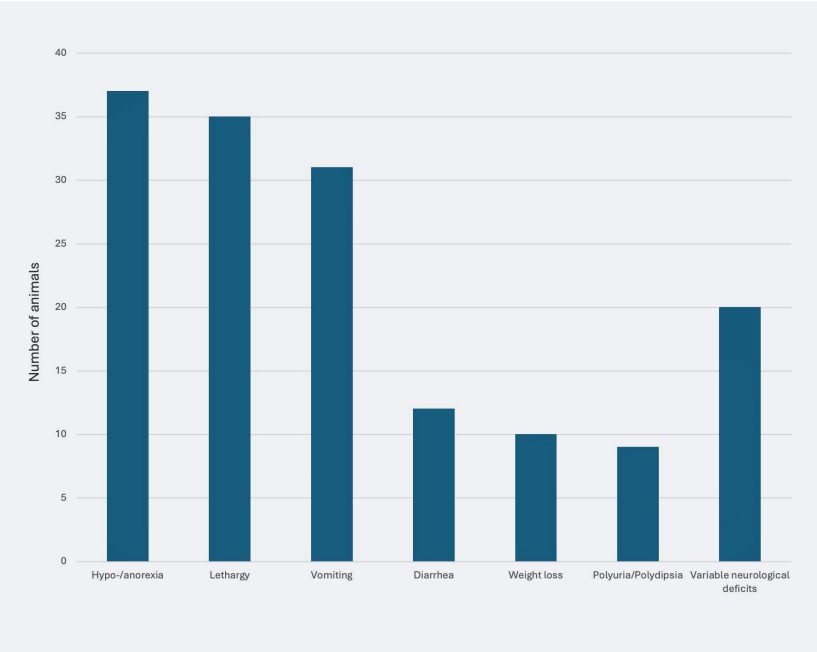

Figure 2: Most common clinical signs in 54 dogs diagnosed with hypoadrenocorticism at a tertiary veterinary referral hospital.

Treatment

Almost all dogs were treated with intravenous infusion (88,9 %, 48/54), most commonly with NaCl 0,9 % (75 %, 36/48), followed by PlasmaLyte (16,7 %, 8/48) and Ringer's Acetate (8,3 %, 4/48). Most dogs (72,2 % 39/54) did not receive potassium-lowering drugs. When administered, most common potassium-lowering drugs were included: 5 % glucose-supplementation (16,7 %, 9/54), isotonic sodium bicarbonate infusion (11,1 %, 6/54), and terbutaline (1/54). Calcium gluconate boli were administered to help address cardiac abnormalities such as missing P-waves on electrocardiography in 7,4 % of cases (4/54),

All dogs diagnosed with HAD were treated with glucocorticoids, either directly with oral prednisolone (median dosage: 0,67 mg/kg, IQR: 0,5–1) or with intravenous dexa-

Table 2: Results of clinicopathological variables in dogs with typical hypoadrenocorticism (HAD), and dogs with eunatremic, eukalemic hypoadrenocorticism (EEH).

Variable (unit)		Typical HAD	EEH	
	Reference	Result	Result	p-value
	Range			
Hematocrit (%)				
Mean (Standard deviation)	40–60	45 (11)	39 (11)	0,135
Below reference range		31,7 % (13/41)	81,8 % (9/11)	0,0048
Hemoglobin (g/l)				
Mean (Standard deviation)	138–197	155,54 (39,56)	127,45 (37,72)	0,004
Below reference range		31,7 % (13/41)	81,8 % (9/11)	0,0048
WBC count (x109/l)				
Mean (Standard deviation)	4,3–12,89	14,53 (6,9)	17,69 (6,54)	0,179
Above reference range		43,9 % (18/41)	81,8 % (9/11)	0,04
Lymphocyte count (x109/l)				
Mean (Standard deviation)	0,8–4,4	2,54 (1,94)	3,4 (2,63)	0,233
Above reference range		11,9 % (5/42)	11,1 % (1/9)	1,0
Eosinophil count (x109/l)				
Mean (Standard deviation)	0–1,3	0,52 (0,7)	0,78 (0,82)	0,305
Above reference range		7,3 % (3/41)	18,2 % (2/11)	0,28
Phosphate (mmol/l)				
Mean (Standard deviation)	0,74–1,7	1,95 (0,54)	1,27 (0,28)	< 0,001
Above reference range		10 % (1/11)	67,6 % (28/40)	< 0,0002
Glucose (mmol/l)				
Mean (Standard deviation)	4,23–6,7	5,92 (2,96)	5,23 (1,44)	0,465
Below reference range		17,1 % (6/41)	18,2 % (2/11)	1,0
Bilirubin (mg/l)				
Mean (Standard deviation)	0,4–3,0	2,41 (2,15)	4,55 (7,41)	0,366
Above reference range		24 % (6/26)	28,6 % (1/7)	1,0
Creatinine (µmol/l)				
Mean (Standard deviation)	47–123	151,93 (115,05)	79,02 (38,46)	0,039
Above reference range		40,5 % (15/37)	0 % (0/11)	0,04
Urea (mmol/l)				
Mean (Standard deviation)	3,3–10,1	17,01 (11,32)	6,06 (2,86)	< 0,001
Above reference range		53,9 % (14/26)	0 % (0/7)	0,04

Note: Data are presented as mean and standard deviation (SD). The p-values in bold correspond to statistically significant findings, p values > 0,005 were considered statistically significant after Bonferroni correction for multiple comparisons. Values in italic correspond to values outside of the reference range.

Abbreviations: RR, reference range; WBC; white blood cells.

methasone (median dosage: 0,14 mg/kg, IQR: 0,14–0,25) before subsequent switch to oral prednisolone. Of the 11 dogs with EEH, three were initially treated with dexamethasone until subsequent switch to oral prednisolone, seven were treated with prednisolone from the beginning on, and one dog was treated with hydrocortisone. Although no aldosterone concentrations were assessed, two dogs were treated with mineralocorticoids: one with deoxycorticosterone pivalate (DOCP), one with fludrocortisone.

Of the 43 dogs with typical HAD, 15 were initially treated with hydrocortisone continuous rate infusion[13] until subsequent switch to fludrocortisone (33,3 %, 5/15) or DOCP (66,7 %, 10/15). Ten dogs (23,2 %) were directly treated with DOCP and 16 (37,2 %) were treated directly with fludrocortisone. In the long-term management 21 dogs (51,2 %) were treated with fludrocortisone and 20 dogs (48,8 %) were treated with DOCP. At our institution, prescription habits for DOCP and fludrocortisone showed a gradual shift over time, although the difference was not statistically significant (Chi-square test, p = 0,218). Early in the study period, fludrocortisone was more commonly prescribed (2015/16: 77 % vs. 23 % DOCP), but by 2021/22, DOCP prescriptions had become more frequent (29 % vs. 71 % fludrocortisone). Intermediate years showed a more balanced distribution (2017/18: 56 % vs. 44 %; 2019/20: 57 % vs. 43 %).

Outcome

Fifty-four dogs (95 %) survived to discharge. One dog with EEH and two dogs with typical HAD died (1) or were euthanized (2) because of severe extra-adrenal comorbidities. Dog 1, diagnosed with EEH, presented in cardiorespiratory arrest due to atrial fibrillation and severe dyspnea from laryngeal swelling. Despite initial stabilization, the dog was euthanized on day 3 of hospitalization due to the need for mechanical ventilation. Dog 2, with typical HAD and a concurrent splenic mass, developed tricavitary effusion by day 3 and signs of sepsis by day 6 of hospitalization. The dog was euthanized on day 10 due to insufficient response to treatment. Dog 3, also with typical HAD, showed no improvement with initial therapy but responded briefly to hydrocortisone infusion and red blood cell transfusion before dying peracutely on day 3 from an unknown cause.

Discussion

In this cohort screened for HAD, 10 % were ultimately diagnosed with the disease. The prevalence is substantially higher than that reported in the general canine population, where prevalence is estimated at 0,06–0,09 %.[16,20] Recent studies investigating selected populations of dogs, such as those presenting with chronic gastrointestinal signs or collapse episodes, have also reported increased prevalence, ranging from 0,3–4 %[12,17] and 1,7 %[9], respectively. However, even in these targeted populations, the incidence of hypoadrenocorticism remains below that observed in the current cohort. This discrepancy likely reflects the specific nature of the population seen at this referral center, which primarily operates as a tertiary referral clinic. Dogs presented at referral institutions are likely representing more complex or diagnostically challenging cases. Although this study is likely representing a geographically restricted population, investigating the prevalence of HAD in other referral centers would be of interest. This would help clarify whether this population of dogs has a genuinely higher incidence of HAD, or if the observed prevalence is simply a selective effect related to the referral status of the clinic. Overall, the unspecific clinical signs combined with the high prevalence of HAD, highlight the nonspecific presentation of the disease.[6] This highlight that exclusion of HAD is a major step in the work up of dogs with nonspecific clinical signs such as unexplained lethargy, weakness, or gastrointestinal signs.[1]

Demographic analysis of the HAD dogs in this cohort showed that slightly more males were affected than females. In some, but not all, previous studies, females were found to be at higher risk of HAD compared to males.[7,16,27,26,34] Median age at diagnosis was similar to previous reports.[16,27,29,30,15,26,32,42,23,34] However, the age range was very wide and even dogs younger than one year and dogs older than ten years of age were diagnosed with HAD, which is also similar to age-range that have been previously described in older studies.[27,34] The most common pure breed in this population was the Jack Russel Terrier, which has not previously been reported as being predisposed to HAD. Other breeds identified in this study including Bernese Mountain

Table 3: Results of adrenal testing in dogs with typical hypoadrenocorticism (HAD) and eunatremic, eukalemic hypoadrenocorticism (EEH).

	Typical HAD (n = 43)		EEH (n = 11)		
Variable (unit)	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Basal cortisol (µg/dl)	0,01	0,1	0,06	0,19	0,35
Post-ACTH (µg/dl)	0,05	0,18	0,24	0,41	0,16

Dog, Poodle, Soft-coated Wheaten Terrier, and West Highland White Terrier have been overrepresented in other HAD studies.[8,18,32,21] However, as this study did not include comparison to the general population, definitive conclusions about breed or sex predispositions cannot be drawn. Breed prevalence may also vary by country, as popular breeds in Switzerland might differ from those elsewhere.[1,13,18,21]

The most common clinical signs were hypo-/anorexia, lethargy, and vomiting, followed by neurological symptoms, diarrhea, and weight loss. Unlike in previous studies where diarrhea was common,[32,42] less than 25 % of dogs in this cohort showed diarrhea. In a recent study, neurological signs in a cohort with HAD was uncommon, with only 7 % being affected by neurological signs.[31] Dogs with typical HAD were significantly more likely to present with hypo-/anorexia compared to those with EEH. Dogs with typical HAD showed more frequently lethargy and vomiting, but after applying the Bonferroni correction for multiple comparisons, no statistically significant differences were found. A similar study at Purdue University Teaching Hospital found vomiting as the only significantly different sign between the two groups.[32]

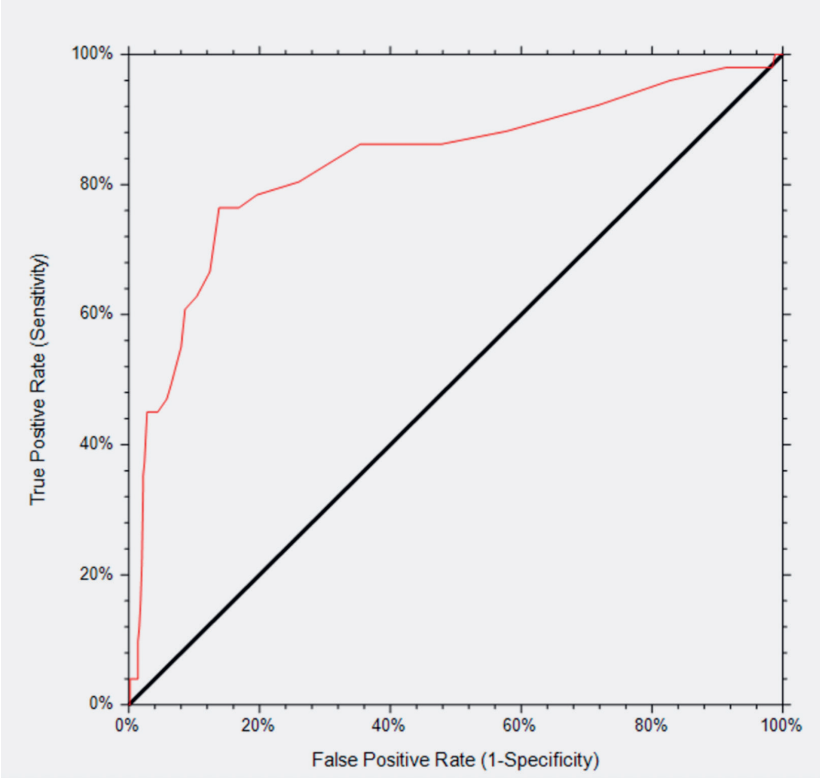

Figure 3A: Receiver operating characteristic (ROC) curve illustrating the diagnostic performance of serum sodium levels in differentiating between dogs with and without hypoadrenocorticism.

Serum phosphate and sodium concentrations demonstrated acceptable and good discriminatory value to distinguish between dog with and without adrenal insufficiency in this population of dogs screened for HAD. A serum sodium level of ≤ 140,0 mmol/l yielded 76 % sensitivity and 86 % specificity, whereas a serum phosphate level of ≥ 1,56 mmol/l yielded 67 % sensitivity and 79 % specificity. Although not discriminatory, low sodium or high phosphate levels should raise clinical suspicion in a cohort of dogs that is screened for HAD, but beyond this clinical utility of these clinicopathological parameters alone remain questionable. A recent study proposed that multiple variables were associated with increased likelihood of HA diagnosis in dogs with BSC ≤ 2 µg/dl (> 55,2 nmol/l), particularly the presence of lethargy, anorexia, low sodium and albumin.[31] Unfortunately, phosphate concentrations were not evaluated in this study. Assessing clinicopathological variables in combination with clinical signs and low BSC likely will help clinicians identify dogs with HAD in clinical practice.

Several clinicopathological variables were significantly different between the two disease groups. Dogs with EEH were more likely to be anemic, while dogs with typical HAD were more likely to present with hyperphosphatemia. There was no difference in likelihood of being azotemic between dogs with typical HAD and EEH. While the median serum urea concentration was significantly higher in dogs with typical HAD, there was no significant difference in the proportion of dogs with urea concentrations above RR. Elevated urea in dogs with typical HAD may be of pre-renal origin, secondary to mineralocorticoid deficiency and the resulting dehydration and/or hypovolemia. However, it could reflect a degree of gastrointestinal bleeding, which might explain its occurrence in both dogs with typical HAD and those EEH. A combination of both origin in case of typical HAD could explain the higher magnitude of elevated urea. However, the lack of an observed difference in proportions could also reflect limitations in sample size. It is possible that hyperphosphatemia is a more sensitive marker for dehydration in dogs with HAD than azotemia, which could reflect the statistical difference between the two groups. It was previously reported that dogs with EEH were more commonly hypocholesterolemic,[42] and dogs with typical HAD were more commonly hypoalbuminemic,[42] but there was only a trend towards higher albumin concentration in dogs with typical HAD, as the difference was not significant after Bonferroni correction. The reason for the discrepancies between these studies remains unknown, but it is possible that the cohort analyzed in this study was too small, leading to type II error. The exact mechanism for the development of hypocholesterolemia is unclear, however multiple pathophysiological mechanisms have been described.[19] In humans with Addison's disease and adrenalectomized rats a glucocorticoid-responsive steatorrhea has been reported which raised the suspicion of a decreased gastrointestinal lipid absorption in dogs with HAD.[14] Additionally, a decreased

fatty acid mobilization due to cortisol deficiency and an increased fatty acid utilization because of high ACTH-concentrations has been described.[19,6] Given that all of these pathophysiological mechanisms are based on a glucocorticoid deficiency and aldosterone concentration does not appear to have an influence on cholesterol concentrations, no difference between the two groups appears coherent.

In this study, half of the dogs that received mineralocorticoids were prescribed fludrocortisone and half the dogs were prescribed DOCP. Currently, primarily DOCP is prescribed as a first-line treatment for typical HAD at our clinic, which is in line with regulations for drug prescription. A recent survey distributed in six European countries (but not including Switzerland) showed that almost 80 % of veterinarians prescribe DOCP and not fludrocortisone as first-line treatment.[28] Twenty percent of survey respondents indicated that their first-line treatment preference was prescription of only DOCP without additional glucocorticoid supplementation.[28] DOCP however has exclusive mineralocorticoid properties, and single-agent therapy is strongly discouraged in HAD. In our cohort, all dogs were initially treated with both mineralo- and glucocorticoids supplementation, and no dog that was treated with DOCP was weaned off glucocorticoids completely. It is unknown what are the prescription habits concerning Addison's disease among Swiss veterinarians.

The prevalence of EEH in this cohort among dogs with spontaneous HAD was similar to what has been previously described.[1,42,34] In-house mortality was similarly low to previously reported mortality and overall short-term survival is good.[42]

This study has some limitations, mainly due to its retrospective nature. As a restricted population were included in this study, findings are primarily valuable within a restricted geographic area and may not be directly generalizable to other populations. Nevertheless, it contributes to the documentation of the disease by describing a cohort of dogs that were comprehensively diagnosed with HAD. Unfortunately, dogs diagnosed with EEH were not differentiated as suffering primary or secondary HAD through assessment of endogenous ACTH concentration. This is likely explained in part by the technical constraints of the assay, as EDTA samples must be immediately cooled and rapidly frozen, a requirement that is often difficult to meet in emergency settings (e.g. dogs presented on emergency setting in the night or the weekend). In addition, the financial cost may also limit its systematic measurement. Aldosterone measurements (pre and post-ACTH-STIM) were not performed for the diagnosis of dogs categorized as having EEH, likely because of the same reasons. Therefore, an overestimation of the number of dogs with EEH is possible. A longer-term follow-up might have allowed for the observation of whether some of these dogs developed a mineralocorticoid deficiency. Additionally, only a small number of dogs were categorized with EEH, which questions the generalizability of the results.

Conclusion

This study provides valuable information regarding a specific population of dogs referred to a tertiary referral center in Switzerland. HAD can occur in a wide range of breeds and ages, and in both sexes. Because of its unspecific clinical presentation, screening of dogs with vague clinical signs via BSC and ACTH-STIM remains crucial to identify affected dogs and promptly provide appropriate treatment. Describing this referral population is relevant as it helps practicians to have an overview of the presented and treated population, as well as insights into the overall management of the disease.

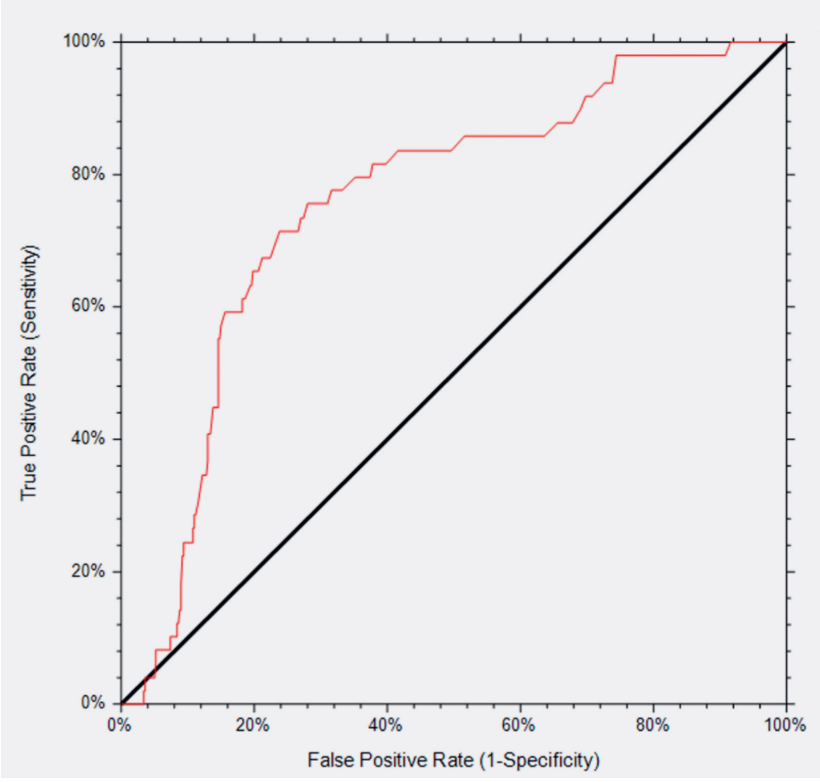

Figure 3B: Receiver operating characteristic (ROC) curve illustrating the diagnostic performance of serum phosphate levels in differentiating between dogs with and without hypoadrenocorticism.

Hypoadrenocorticism in dogs presenting to a tertiary veterinary clinic in Switzerland: overall prevalence, clinical signs, laboratory changes and outcome

J. Eiermann, A. Schlachet, S. Schuller, B. Lutz

Hypoadrenocorticisme chez les chiens présentés dans une clinique vétérinaire tertiaire en Suisse: prévalence globale, signes cliniques, modifications biologiques et issue

L'hypoadrénocorticisme (HAD) est une endocrinopathie relativement rare et les chiens présentent souvent des signes cliniques non spécifiques.

La base de données de laboratoire d'un centre de référence tertiaire a été consultée en aveugle et examinée rétrospectivement sur la période comprise entre mars 2015 et mars 2023 ausnt aux chiens suspectés d'être atteints d'HAD puis classés en fonction des mesures de cortisol basal et/ou d'un test de stimulation de l'hormone adrénocorticotrope (ACTH-STIM). Le diagnostic d'HAD était basé sur des résultats anormaux d'un ACTH-STIM (cortisol post-ACTH-STIM < 2 ug/dl).

Une HAD a été diagnostiquée chez 54 chiens, soit 9,6 % de la population examinée (n = 564). Les chiens sans HAD présentaient des concentrations de sodium significativement plus élevées (p < 0,001), de créatinine plus faibles (p = 0,007) et de phosphates plus faibles (p < 0,001) que les chiens atteints d'HAD. Les races les plus fréquemment diagnostiquées avec une HAD étaient les suivantes : croisés (n = 16), Jack Russel Terrier (n = 5) et Bouvier bernois (n = 3). L'âge médian au moment du diagnostic était de 5 ans (IQR : 3–8,75, intervalle : 1–14). Vingt-neuf chiens étaient des mâles et 26 des femelles. Les signes cliniques les plus courants étaient des combinaisons d'hypo-/anorexie (n = 37, 68,5 %), de léthargie (n = 35, 64,8 %) et de vomissements (n = 31, 57,4 %). Seuls deux des 54 chiens (3,7 %) présentaient des valeurs de cortisol au repos > 0,5 µg/dl (> 13,79 nmol/l) (max. 0,63 µg/dl [17,38 nmol/l]), tandis que six chiens (11,1 %) présentaient des valeurs de cortisol post-ACTH-STIM > 0,5 µg/dl (médiane: 0,82 µg/dl [22,62 nmol/l], IQR 0,51-0,96 [14,07-26,48]). Les chiens atteints d'hypoadrénocorticisme eunatremique et eukalémique (EEH) étaient plus susceptibles de présenter une anémie (OR : 14,19, IC à 95 %, 2,71–74,22), tandis que les chiens atteints d'HAD typique étaient plus susceptibles de présenter une hyperphosphatémie (OR : 23,33, IC à 95 %, 2,68–203,14). Quarante-trois chiens (79,6 %) présentaient une HAD hyponatrémique et/ou hyperkaliémique et les 11 chiens restants présentaient un EEH. La mortalité interne était de 5 % (3/55). Un chien atteint d'EEH a développé une HAD typique sept semaines après le diagnostic initial. Parmi les chiens atteints d'HAD, la proportion diagnostiquée avec une EEH était similaire à celle des études précédentes. Contrairement aux rapports précédents dans lesquels les femelles étaient surreprésentées, cette cohorte comptait plus de mâles que de femelles. Aucune différence significative n'a été observée

Ipoadrenocorticismo in cani presentati a una clinica veterinaria terziaria in Svizzera: prevalenza complessiva, segni clinici, alterazioni di laboratorio ed esito

I cani affetti da ipoadrenocorticismo (HAD), un'endocrinopatia relativamente rara, spesso presentano segni clinici aspecifici.

Il database di laboratorio di un centro di riferimento terziario è stato reso cieco per la revisione e la ricerca retrospettiva, tra marzo 2015 e marzo 2023, per cani con sospetto HAD e successivamente categorizzati in base alle misurazioni del cortisolo basale e/o a un test di stimolazione con ormone adrenocorticotropo (ACTH-STIM). La diagnosi di HAD si basava su risultati anomali dell'ACTH-STIM (cortisolo post-ACTH-STIM < 2 µg/dl).

L'HAD è stato diagnosticato in 54 cani, pari al 9,6 % della popolazione esaminata (n = 564). I cani senza HAD presentavano concentrazioni significativamente più alte di sodio (p < 0,001), più basse di creatinina (p = 0,007) e più basse di fosfati (p < 0,001) rispetto ai cani con HAD. Le razze più frequentemente diagnosticate con HAD includevano: razze miste (n = 16), il Jack Russel Terrier (n = 5) e il Bovaro Bernese (n = 3). L'età mediana alla diagnosi era di 5 anni (IQR: 3-8,75, range: 1-14). Ventinove cani erano maschi e ventisei femmine. I segni clinici più comuni erano combinazioni di ipo-/anoressia (n = 37, 68,5 %), letargia (n = 35, 64,8 %) e vomito (n = 31, 57,4 %). Solo due dei 54 cani (3,7 %) presentavano valori di cortisolo a riposo > 0,5 µg/dl (> 13,79 nmol/l) (max. 0,63 µg/dl [17,38 nmol/l]), mentre sei cani (11,1 %) presentavano valori di cortisolo post-ACTH-STIM > 0,5 µg/dl (mediana: 0,82 µg/dl [22,62 nmol/l], IQR 0,51-0,96 [14,07-26,48]). I cani con ipoadrenocorticismo eunatremico, eucalemico (EEH) avevano maggiori probabilità di presentare anemia (OR: 14,19, IC 95 %, 2,71-74,22), mentre i cani con HAD tipico avevano maggiori probabilità di presentare iperfosfatemia (OR: 23,33, IC 95 %, 2,68-203,14). Quarantatré cani (79,6 %) avevano HAD iponatremico e/o ipercalemico e i restanti 11 cani presentavano EEH. La mortalità intraospedaliera era del 5 % (3/55). Un cane con EEH ha sviluppato un HAD tipico sette settimane dopo la diagnosi iniziale. Tra i cani con HAD, la proporzione diagnosticata con EEH era simile a quella di studi precedenti. A differenza di quanto riportato in precedenza, in cui le femmine erano sovrarappresentate, in questa coorte i maschi erano più colpiti delle femmine. Non è stata osservata alcuna differenza significativa nell'età di presentazione tra i cani con HAD tipico ed EEH.

Parole chiave: cane, Addison, eucalemico eunatremico, alterazioni clinico-patologiche, mortalità

entre les chiens atteints d'HAD typique et ceux atteints d'EEH en termes d'âge au moment de la présentation.

Mots-clés: chien, Addison, eukalémique eunatremique, changements clinico-pathologiques, mortalité

Hypoadrenocorticism in dogs presenting to a tertiary veterinary clinic in Switzerland: overall prevalence, clinical signs, laboratory changes and outcome

J. Eiermann, A. Schlachet, S. Schuller, B. Lutz

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