Hypoadrenocorticism in dogs – the Mad Hatter of veterinary internal medicine

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Abstract

Hypoadrenocorticism arises from insufficient adrenal gland function and is also known as Addison's disease, a rarely occurring disease (0.1%) in dogs. Due to its oscillatory course and overall nonspecific symptoms, it is a diagnostic challenge for clinicians, and is often misdiagnosed or unattended among other differentials. There are two forms of hypoadrenocorticism: primary and secondary. The aim of this study was to analyse the data of dogs suffering from Addison's disease, treated at the Clinic for Internal Medicine, Faculty of Veterinary Medicine, University of Zagreb, Croatia and to compare them with data from similar institutions worldwide. The archive of Clinic for Internal Medicine, Faculty of Veterinary Medicine, Zagreb, Croatia was searched to investigate and statistically analyse signalment, clinical and laboratory data, and the duration of symptoms, treatment protocols and outcome of canine hypoadrenocorticism. The study group included 14 dogs (36% male and 64% female) diagnosed with hypoadrenocorticism. All dogs had a history of gastrointestinal symptoms, *i.e.* vomiting in 100%, diarrhoea in 64% and melena in 7%. Hypovolemic shock was noted in 57%, hypothermia in 64% and bradycardia in 29% of cases. The most frequently observed laboratory abnormalities were an increase in BUN (86%), creatinine (57%) and potassium concentration (79%), and a decrease in sodium (71%), Na/K ratio (86%), cholesterol (21%) and glucose concentration (21%). Duration of symptoms (till ACTH-stimulation test performance) was broad, from 2 – 2190 days (median 90±1195.5 days). The outcome was favourable in 100% cases after initiation of adequate treatment.

Key words: *Addison's disease; adrenal gland; mineralocorticoid deficiency; glucocorticoid deficiency; dog*

Introduction

Canine hypoadrenocorticism is a rare disease (with prevalence around 0.1%) characterised by hypofunction of the adrenal cortex. Since first being described by Thomas Addison in 1917, it has also been known as Addison's disease. Due

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to the non-specificity of clinical signs and their waxing and waning nature, hypoadrenocorticism is among the most underdiagnosed (if not the most underdiagnosed) diseases in veterinary medicine.

Regarding the pathophysiological mechanism, there are two main forms of hypoadrenocorticism: primary (lack of glucocorticoids and/or mineralocorticoids due to adrenal cortex destruction) and secondary (lack of adrenocorticotropic hormone (ACTH) due to abnormalities in the hypothalamic-pituitary axis). Furthermore, primary hypoadrenocorticism can manifest as typical (lack of both mineralocorticoids and glucocorticoids, thus resulting in disturbances of Na and K concentrations and lowering of their ratio) or atypical (lack of glucocorticoids, characterized with normal Na and K concentration and their ratio) (Hess, 2017). Usually, at the time of presentation, the adrenal cortex, including the zona glomerulosa (mineralocorticoid production) and *zonae fasciculata* and reticularis (cortisol production) are destroyed at similar rates, resulting in a lack of both cortisol and aldosterone, thus causing primary typical hypoadrenocorticism (in 90–95% of cases) (Scott-Moncrieff, 2010; Scott Moncrieff, 2015; Klein and Peterson, 2010a). However, the atypical form can convert into the typical form in due course, when the destruction of the zona glomerulosa catches up with the destruction of the *zonae fasciculata*. The aetiology may include immune-mediated destruction of the adrenal cortex, drug-induced adrenocortical necrosis (mitotane), enzyme inhibition (trilostane) or infiltrative processes such as neoplastic or fungal disease (Klein and Peterson, 2010a). Central (anterior pituitary) deficiency of ACTH causes secondary hypoadrenocorticism (in 5–10% cases), resulting in isolated glucocorticoid insufficiency in which

mineralocorticoids are spared as ACTH does not directly influence their release (Peterson et al., 1996).

Hypoadrenocorticism is a disease of dogs of all ages (reported in animals from 4 months to 14 years old) and afflicts more female than male dogs (64% and 69% of reported cases being females) (Peterson et al., 1996; Adler et al., 2007; Seth et al., 2011; Hanson et al., 2016). There are several overrepresented breeds and inheritance has been proven in some breeds (e.g. Standard Poodles, Nova Scotia Duck Tolling Retrievers, Portuguese Water Dogs and Bearded Collies) (Oberbauer et al., 2002; Famula et al., 2003; Hughes et al., 2007; Treeful et al., 2019). Other breeds commonly afflicted with hypoadrenocorticism where inheritance has not been proven are mixed breed dogs, Poodles (other than Standard Poodles), Golden Retrievers, Cairn Terriers, Rottweilers, Great Danes and West Highland White Terriers (Lathan and Thompson, 2018).

Due to the multisystemic effects of both glucocorticoids and mineralocorticoids, clinical signs are non-specific and can include signs that can be attributed to almost all body systems with poor appetite/anorexia (88% to 95%), lethargy/depression (85% to 95%), vomiting/regurgitation (68% to 75%), weakness (51% to 75%), weight loss (40% to 50%), diarrhoea (35%), polyuria/polydipsia (17% to 25%), shaking/shivering/tremors (17% to 27%), collapse (10%), and/or a painful abdomen (8%) as most commonly reported (Scott-Moncrieff, 2010). Since hypoadrenocorticism can mimic a large number of other diseases (*i.e.* kidney failure, inflammatory bowel disease) it has been nicknamed "the great pretender". Clinical examination findings may range from a mildly dehydrated but alert dog, to a "shocked" and recumbent dog with a prolonged capillary refill time. Shock, bradycardia and atrial standstill with tall pointed T-waves in electrocardiogram

are common in critically ill patients in Addisonian crisis (Scott-Moncrieff, 2015).

Patients with hypoadrenocorticism may present with a myriad of laboratory abnormalities related to glucocorticoid and/or mineralocorticoid insufficiency, such as non-regenerative anaemia, leukocytosis, hypoglycaemia, elevated blood urea nitrogen (BUN) and creatinine, hyperkalemia, hyponatremia, hypercalcemia, hypocholesterolaemia, hyperphosphatemia, hypochloraemia, and elevated liver enzymes (Peterson et al., 1996).

The gold standard for diagnosing hypoadrenocorticism is the ACTH stimulation test that assesses the ability of adrenal gland to produce cortisol in response to a maximal stimulus (Scott-Moncrieff, 2015; Botsford et al., 2018).

Since Addisonian crisis represents a real medical emergency, treatment is directed towards correcting hypovolemia, hypotension, electrolyte imbalances and providing corticosteroid and mineralocorticoid supplementation. Long-term management of stabilized hypoadrenocorticism is based on supplementation of corticosteroids and/or mineralocorticoids (desoxycorticosterone pivalate or fludrocortisone) (Scott-Moncrieff, 2015; Jaffey et al., 2017). The routine monitoring of patients with hypoadrenocorticism is regular control via ACTH stimulation testing, although some authors recommend the measurement of endogenous ACTH as the best means of treatment surveillance (Zeugswetter and Haninger, 2018). Prognosis of canine hypoadrenocorticism is excellent with regular treatment.

The aim of this study was to analyse the data collected from dogs with hypoadrenocorticism admitted to the Clinic for Internal Medicine, Faculty of Veterinary Medicine, University of Zagreb, Croatia, and to compare them with the data collected in similar institutions worldwide.

Materials and methods

No ethical approval was required as this study did not involve laboratory animals, as only patient archive data from the system "Vef. Protokol 1.1.1.28" were used with signed owner's consent. Among 22,979 canine records (first admission data) at the Clinic for Internal Medicine, Faculty of Veterinary Medicine, University of Zagreb, Croatia in the period between November 2005 and August 2018, 14 dogs were diagnosed with hypoadrenocorticism. The inclusion criterion was owner-signed informed consent for diagnostic and treatment procedures.

The following data were investigated and statistically analysed: breed, gender, age, body weight, duration of clinical signs until the time of diagnosis (by performing the ACTH-stimulation test), as well as the time frame between the onset of clinical signs and establishing the provisional diagnosis of hypoadrenocorticism (based on history, clinical signs, clinical examination findings, standard laboratory workup and diagnostic imaging). Furthermore, complete blood count (CBC), biochemistry, urinalysis, and diagnostic imaging were performed for each patient. Haematology was performed using Horriba ABX Haematology Analyser Diagnostics, Montpellier, France and biochemistry using the Olympus Diagnostica GMBH, Hamburg, Germany. The following biochemical parameters were analysed: BUN-blood urea nitrogen, (mmol/L), Cre-creatinine (μmol/L), ALT-alanine aminotransferase (U/L), AST-aspartate aminotransferase (U/L), AP-alkaline phosphatase (U/L), Chol-cholesterol (mmol/L), CRP-canine-C-reactive protein (mg/L), TP-total proteins (g/L), Alb-albumins (g/L), BG- blood glucose (mmol/L), Ca-calcium (mmol/L), Na-sodium (mmol/L), K-potassium (mmol/L) and Na/K ratio. Patients with elevated concentrations of BUN (with or without elevated creatinine concentration) were

classified as azotaemic, either pre-renal (urine specific gravity>1030) or renal (urine specific gravity<1030).

Radiographic imaging was performed using Eichermeyer EDR HP (IMD Generators s.r.l., Italy) with digital data processing and image distribution with Agfa CR 30-X (Agfa, Japan), while ultrasound was performed using MyLabTM 40 (Esaote, Italy).

The maximum length and thickness of each adrenal gland was measured in the longitudinal plane using electronic callipers. The maximum thickness was defined as the greatest dorsoventral dimension and was assessed as a single measurement made perpendicular to the long axis. The criterion that was assessed was thickness of the left adrenal gland less than 0.32 cm according to Wenger et al. (2010).

The diagnosis of hypoadrenocorticism was established by the ACTH stimulation test. This test was performed in all 14 dogs by measuring basal cortisol concentration (prior to intravenous administration of 0.25 mg synthetic ACTH) and stimulated cortisol concentrations (one hour after administration of ACTH) in veterinary accredited laboratories (either *SYNLAB*, München, Germany or LABOKLIN, Bad Kissingen, Germany) while the concentration of endogenous ACTH (SYNLAB, München, Germany) was measured in one dog. The sample for measuring endogenous ACTH concentration was taken into a precooled siliconized tube with an EDTA anticoagulant and after centrifugation in precooled (4 °C) centrifuge, the plasma was immediately separated and frozen. Furthermore, the frozen plasma was handled on dry ice until analysis. The therapy protocols, and time required for stabilisation of each patient and their outcomes were also investigated.

The treatment protocol during stabilization consisted of:
- **Fluid therapy**
  - 20–40 mL/kg/h intravenous fluids (0.9% saline) during the first several hours, followed by 2–4 mL/kg/h of fluids (0.9% saline until electrolyte balance achieved, then substituted with Plasmalyte or Ringer-lactate at the same rate)

- **Glucocorticoids**
  - intravenous dexamethasone (0.5–2 mg/kg/day on the first day, then 0.01–0.05 mg/kg/day until ACTH stimulation testing)
  - intravenous prednisolone: 1–2 mg/kg/day

- **Mineralocorticoids:**
  - desoxycorticosterone pivalate (DOCP) – 2.2 mg/kg subcutaneously the first day
  - fludrocortisone acetate perorally 0.01– 0.03 mg/kg/day (divided into two doses)

- **Treatment for hypoglycaemia:**
  - 0.5 g/kg 25% dextrose intravenously

After stabilization, prednisone was subscribed perorally (0.2–0.4 mg/kg/day) in all 14 dogs. Mineralocorticoid supplementation was accomplished by peroral administration of fludrocortisone (0.01–0.03 mg/kg/day, divided into two doses) in 50% and by subcutaneous application of DOCP (2.2 mg/kg approximately every 25 days) in 43% of dogs while one dog (7%) with secondary hypoadrenocorticism did not receive mineralocorticoid supplementation.

Statistical analysis

Descriptive statistics was performed using the Statistica 8 for Windows program (StatSoft Inc.) with numerical values shown as range and median ± 2 standard deviations.

Results

Investigated population

The investigated population consisted of 14 dogs with hypoadreno-

corticism, representing 0.14% of the "first admission" patient population. There were 5/14 (36%) males, (1/5 (20%) neutered) and 9/14 (64%) females (8/9 (88%) spayed). Among them, 4/14 (29%) were cross-breeds and 10/14 (71%) were pure breed dogs (three Standard Poodles and one representative of each of the following breeds: Chihuahua, Miniature Poodle, Irish Setter, German Shepherd, White Swiss Shepherd, American Hairless Dog and St. Bernard) with overrepresentation of Standard Poodles: 3/10 (30%) of pure breeds; 3/14 (21%) of ca-

Table 1. Frequency of symptoms and clinical signs in dogs with hypoadrenocorticism

Symptoms and clinical signs	Prevalence (%)
Recurrent gastrointestinal signs	100
Vomiting	100
Anorexia	86
Weakness	79
Diarrhoea	64
Hypothermia	64
Polyuria/polydipsia	29
Melena	7
Shivering	7

Table 2. Vital signs in dogs with hypoadrenocorticism

	Reference range	Range	Median ± 2sd[1]	↑ (%)	↓ (%)	√ (%)
T (°C)	38.0–39.2	35.6 - 39.4	37.9±2.6	14	64	22
P (b/min)	60–160	30 - 140	100±66.7	0	29	71
R (i/min)	10–40	8 - 38	25±18.1	0	7	93

T-body temperature, P-pulse: heart rate (beats per minute), R-respiratory rate (inspiration per minute)
↑- portion of dogs with increased values, ↓ - portion of dogs with decreased values.
√ - portion of dogs with normal values, [1]2sd-2 standard deviation.

Table 3. Haematology parameters in dogs with hypoadrenocorticism

Parameter		Reference range[1]	Range	Median ± 2sd[2]	↑ (%)	↓ (%)	√ (%)
E [x 10^{12}/L]		5.5 – 8.5	5.0 – 8.8	7.1±2.9			
Hb [g/L]		120 - 180	108 – 207	169.5±70.2	21	21	58
PCV [%]		37 – 55	31 – 61	47±20.4			
L [x 10^9/L]		6 -17	5.1 – 24.8	8.7±10.6	7	7	86
PLT [x 10^9/L]		200 - 700	114 - 471	339.5±228.1	0	14	86
DBCC	Sg [%]	60 – 77	42 - 84	66.5±28.8	14	36	50
	Nsg [%]	- 1	1 - 4	3±3.1	14	-	86
	Lym [%]	12 – 33	6 - 46	27±25.3	36	7	57
	Mono [%]	3 – 10	1 – 10	4±6.4	0	21	79
	Eo %	0-10	0-10	4±2.6	0	0	100

↑ - portion of dogs with increased values, ↓ - portion of dogs with decreased values, √ - portion of dogs with normal values,
E-number of erythrocytes, Hb-haemoglobin concentration, PCV-packed cell volume, L-total leukocyte number, T-platelet number, DBCC-differential blood count, Sg-portion of segmented neutrophils, Nsg-portion of non-segmented neutrophils, Lym-portion of lymphocytes, Mono-portion of monocytes, Eo-portion of eosinophils.
[1]Reference range: Centre for Clinical Pathology, Clinic for Internal Medicine, Faculty of Veterinary medicine, University of Zagreb, Croatia
[2]2sd-2 standard deviations.

Table 4. Biochemistry in dogs with hypoadrenocorticism

Parameter	Reference range[1]	Range	Median ± 2sd[2]	↑ (%)	↓ (%)	√ (%)
BUN [mmol/L]	3.3 - 8.3	4.3 - 51.3	29.5±29.9	86	0	14
Cre [µmol/L]	44 - 140	73 - 675	168±402.4	57	0	43
Chol [mmol/L]	3.7 - 7.1	1.6 - 8.3	4,4±4,5	14	21	65
BG [mmol/L]	3.6 - 6.5	1.7 – 5.9	4,8±2,8	0	21	79
AST [U/L]	- 82	23 - 1195	83±794.8	29	-	71
ALT [U/L]	- 88	28 - 185	47.0±89.6	14	-	86
AP [U/L]	30 - 156	10 - 241	26.5±109.3	7	14	79
TP [g/L]	55 - 75	51 - 76	68±16,8	7	7	86
Alb [g/L]	26 - 33	17 - 36	30±12.7	29	29	42
CRP [mg/L]	0 - 10.7	0 - 96.8	0±54.54	21	0	79
Ca [mmol/L]	2.1 - 3.1	2.1 - 2.9	2.35±0.62	0	0	100
Na [mmol/L]	140 – 155	117 - 154	128±21.7	0	71	29
K [mmol/L]	3.6 - 5.8	4 - 10.5	7.2±3.7	79	0	21
Na/K	27:1 - 40:1	12.3 - 38.5	18.1±14.3	0	86	14

BUN-blood urea nitrogen, Cre-creatinine, Chol-cholesterol, BG-blood glucose, AST-aspartate aminotransferase, ALT-alanine aminotransferase, Ap-alkaline phosphatase, TP-total proteins, Alb-albumins, CRP-canine C-reactive protein, Ca-calcium, Na-sodium,
K-potassium, Na/K-ratio, ↑-portion of dogs with increased values, ↓-portion of dogs with decreased values, √-portion of dogs with normal values.
[1]Reference range: Centre for Clinical Pathology, Clinic for Internal Medicine, Faculty of Veterinary medicine, University of Zagreb, Croatia
[2]2sd-2 standard deviations.

nine hypoadrenocortism. Patient age (12–144 months; 36±79.6 months) and body weight (2.7–56 kg; 21.4±31.8 kg) varied markedly. The most common symptoms were of gastrointestinal origin (Table 1). Hypothermia (Tables 1 and 2) was present in 9/14 (64%) whilst bradycardia was noted in 4/14 (29%) of the investigated dogs (Table 2, Figs. 1 and 2). Eight dogs (57%) were admitted in hypovolemic decompensated shock (Figs. 1 and 2). The clinical examination data, and haematology and biochemistry results are shown in Tables 3 and 4. Twelve of 14 dogs (86%) were azotaemic. Among those, 7/12 (58%) were diagnosed with prerenal and 5/12 (42%) with renal azotaemia.

Figure 1. Addisonian crisis in a St. Bernard bitch with a diagnosis of hypoadrenocorticism
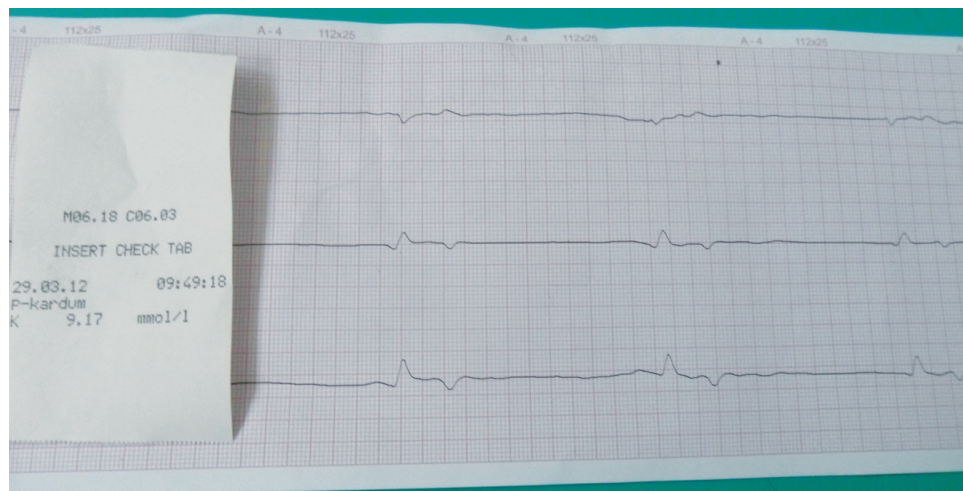
Figure 2. ECG tracing showing severe bradycardia (sinoventricular rhythm) due to severe hyperkalaemia in a St. Bernard bitch with a diagnosis of hypoadrenocorticism (leads I, II and III, 50 mm/s, 10 mm/mV), heart rate 46/min

Diagnostic imaging

Eight of 14 (57%) radiographic findings were unremarkable while microcardia and circulatory collapse were detected in 4/14 cases (29%) and gastroenteritis in 2/14 (14%). In 9/14 (64%) of dogs, "thinned and elongated" adrenals were detected by ultrasonography. All patients had a thickness of the left adrenal gland of less than 0.32 cm.

Endocrinology testing

In all 14 dogs, ACTH stimulation testing showed extremely low cortisol concentrations, both basal and stimulated (<8.3 nmol/L). Concentration of endogenous ACTH was measured in 1/14 (7%) dog and was undetectably low (<1.10 pmol/L). On the basis of these results, a diagnosis of primary hypoadrenocorticism was established in 13/14 (93%) dogs and of secondary hypoadrenocorticism in 1/14 (7%). Twelve (92%) of 13 dogs with primary hypoadrenocorticism were diagnosed as typical, while 1/13 (8%) had atypical hypoadrenocorticism.

Symptom duration and the outcome

The timeframe between the onset of clinical signs and performance of ACTH stimulation test ranged from 2 – 2190 (90±1195.5) days while the timeframe between objective presumption of hypoadrenocorticism and performing ACTH stimulation test was from 0 – 11 (3.5±8.3) days. Upon initiation of treatment, the outcome was favourable in all 14 dogs.

Discussion

This study confirmed the literature data for canine hypoadrenocorticism regarding the wide age range (12 – 144 months), predominance of females (64%) and increased prevalence of Standard Poodles (21%) (Peterson et al., 1996; Scott-Moncrieff, 2015). Since mineralocorticoid deficiency results in a disturbance of the Na/K ratio, dehydration and hypovolemic shock, whereas deficiency in glucocorticoids results in lethargy, weakness, shaking and numerous different gastrointestinal

signs (*i.e.* vomiting, diarrhoea, abdominal pain, etc.), the clinical presentation of individual patient will depend on the combination of signs resulting from the prevailing deficiency at the moment. Recurrent gastrointestinal signs were noted in 100% of patients, among which vomiting was present in 100%, diarrhoea in 64% and melena in 7% of patients. Considering that these symptoms are common and unspecific, it is not unusual that the diagnosis of hypoadrenocorticism is often overlooked. Therefore, the success in reaching the diagnosis is primarily based on the clinician's index of suspicion to initiate ACTH stimulation testing. In the case of recurring episodic gastrointestinal signs, hypoadrenocorticism should be included on the list of possible differentials, especially if patients are highly responsive to fluid treatment (Klein and Peterson, 2010b).

The results of this study showed that the majority of patients were in hypovolemic shock when admitted (57%), which was also supported by the presence of hypothermia (64%) and radiographically proven circulatory collapse and microcardia (29%). Bradycardia, although often associated with hypoadrenocorticism (due to hyperkalaemia often declared as the hallmark of Addison's disease), is still relatively rare (29% in this study; 22-25% reported by Klein and Peterson (2010a)), especially compared to incidence of hyperkalaemia (79%). This is not surprising considering that not all hyperkaliaemic patients develop bradycardia, but only those with extremely high serum potassium concentrations. However, the presence of bradycardia in any collapsed dog should alert the clinician to put Addison's disease at the top of the list of differentials, while the absence of bradycardia (71% in this study) does not exclude hypoadrenocorticism.

As in previous studies (Thompson et al., 2007; Scott-Moncrieff, 2015), some similar abnormalities in haematology such as anaemia (21%), mature neutrophilia (14%), left-shift (14%) and lymphocytosis (36%) were also noted in this study, though due to their non-specificity, most of these findings were of no diagnostic importance. However, the lack of stress leukogram in two severely sick hypovolemic dogs with no electrolyte abnormalities directed us to perform ACTH stimulation testing. Both of these patients were initially treated with only glucocorticoid supplementation, and electrolyte imbalance occurred later, so mineralocorticoid supplementation was subsequently added to the therapy protocol.

The most commonly observed biochemistry discrepancies in canine hypoadrenocorticism included azotaemia (86%), hyperkalaemia (79%) and hyponatremia (79%), which can occur either independently or in combination (Kintzer and Peterson, 1997; Greco, 2007; Scott-Moncrieff, 2010; Scott-Moncrieff, 2015). Azotaemia with or without increased creatinine concentration is the consequence of hypovolemia, hypotension and decreased renal perfusion, though it can also indicate kidney injury or even renal failure due to delayed treatment of hypovolemia (Scott-Moncrieff, 2015). In this study, 58% of patients had pre-renal azotaemia as a consequence of hypovolemia, hypotension and shock (decreased renal perfusion). However, prolonged renal hypoperfusion due to delayed shock therapy will ultimately result in renal azotaemia, which was also noted in this study as the remaining 42% of azotaemic patients had urine specific gravity less than 1030. It is important to understand that renal azotaemia is not a synonym for renal failure, as some patients may have renal dysfunction without having structural renal disease. They may have

a functional problem and in patients with hypoadrenocorticism, this is most often due to hyponatremia. It is a well-established fact that sodium is the osmotic fundament of plasma, thus the loss of sodium reduces total body water, which in turn reduces the glomerular filtration rate and therefore results in azotaemia. Moreover, low sodium impairs osmotic stimuli for antidiuretic hormone secretion and promotes urine dilution (Maddison, 2008). In patients with Addison's disease, aldosterone deficiency is the main cause of the inability of kidney to retain sodium and to excrete potassium and hydrogen ions, resulting in hyponatremia and hyperkalaemia, which in some cases is combined with metabolic acidosis (Kemppainen and Behrend, 1997; Scott-Moncrieff, 2015). The Na/K ratio has been used for many years but its diagnostic value has proven controversial. Namely, the reference range of the physiological Na/K ratio varies from 27:1 to 40:1, and the previous recommendations for suspicion of canine hypoadrenocorticism was a ratio below 27:1. Different studies were conducted to test the Na/K ratio in dogs with various systemic conditions (<15-24:1 Roth and Tyler, 1999; <24:1 Adler et al., 2007) and they found that different diseases may cause a lowering of the Na/K ratio, *i.e.* abdominal or thoracic effusions, sepsis, kidney diseases, cardiorespiratory diseases, parvovirus infection and trichuris invasion (Roth and Tyler, 1999; Nielsen et al., 2008). Nielsen et al. (2008) showed that only 16.7% of cases of Na/K ratio <27:1 were caused by Addison's disease, while the vast majority (83.3%) of Na/K ratios <27:1 (previously proposed as a diagnostic for Addison's disease) were caused by other diseases.

The vast majority of patients in the present study had a Na/K ratio below 27:1; however, since we did not investigate the Na/K ratio in other diseases, we cannot conclude about the share of patients with low Na/K ratios due to other causes. Roth and Tyler (1999) found that all dogs in their study with a Na/K ratio <15:1 had Addison's disease, which can be considered as too strict a cut-off point when analysing results of this study. In other words, with such a low cut-off point, we would not have tested 10 of the 14 dogs in this study (with ACTH stimulation test). Therefore, the presumption that Addison's disease is diagnosed only on the basis of electrolyte disturbance is misleading. Therefore, despite substantial evidence of the usefulness of electrolyte disturbances in presuming Addison's disease, the evidence for a direct link between serum sodium and potassium in relation to a specific disease are very limited. Hence, despite the Na/K ratios previously recommended as a diagnostic for hypoadrenocorticism, the only objective diagnosis of canine hypoadrenocorticism can be established via ACTH-stimulation testing. It is important to emphasise that some dogs with Addison's disease may have both normal potassium and sodium concentrations and therefore a normal ratio due to either secondary or early primary (atypical) hypoadrenocorticism. The golden standard for differentiating between primary and secondary hypoadrenocorticism is measurement of the endogenous ACTH concentration. There is no better way to deal with atypical hypoadrenocorticism than regular checks of electrolyte concentrations to detect the development of Na/K ratio disturbances, and to initiate mineralocorticoid supplementation as needed.

One of the features of canine hypoadrenocorticism is also hypoglycaemia due to the lack of glucocorticoids, which was present in up to 30% of dogs and in some cases can cause seizures (Levy, 1994; Lifton et al., 1996; Syme and Scott-Moncrieff, 1998). One of the pitfalls of canine Addison's disease is that hypoglycaemia is more common in

toy breeds which are already predisposed to hypoglycaemia. This is in concordance with the results of this study, in which among 21% of hypoglycaemic patients the only one to developed seizures was a toy breed patient.

The number of dogs with hypocholesterolaemia observed in this study was significantly higher (21%) than in other studies (7%) (Scott-Moncrieff, 2015). It is assumed that hypocholesterolaemia accompanied with hypoalbuminemia can be caused by acute ischemia of the gastrointestinal (GI) system (Peterson et al., 1996; Adler et al., 2007), and therefore the significantly higher portion of hypocholesterolaemic patients in this study can be explained by the fact that all dogs in this study were admitted with acute gastroenteritis (causing acute ischemia of the GI tract) after several previously treated GI episodes. This is also supported with a significantly higher portion of recurring GI signs in this study (100%) compared to similar studies (50%; Seth et al., 2011).

The duration of symptoms was extremely variable but still quite long (2 – 2190 days, mean 90±1195.5 days) supporting the premise that Addison's disease is still too often unattended or even overlooked in Croatian veterinary practice. Of course, we cannot claim that all previous episodes of gastrointestinal (and other) signs were due to undiscovered hypoadrenocorticism, though similarly, we cannot be certain that this was not the case in some or all of the patients, particularly since the vast majority of patients were treated symptomatically for some time. Following treatment, all patients were doing better for a while, but never stopped relapsing and coming back to the same or different veterinary practice until their admission to the emergency service of our clinic due to severe hypovolemic shock. The aim of this study was to emphasize the "tricky" nature of this disease, making diagnosis difficult in patients for which Addison's disease was not included on the list of differentials. Moreover, the recurrent signs did not return in any patient after initialization of proper treatment (i.e. glucocorticoid and mineralocorticoid supplementation).

Accordingly, the golden rule in diagnosing canine hypoadrenocorticism should combine measurement of electrolyte concentration and performing ACTH stimulation test in any dog presented with recurring GI symptoms. Although not crucial, diagnostic imaging can also be a very helpful tool in the diagnostic workup of hypoadrenocorticism. As most dogs with hypoadrenocorticism have a measurable reduction in the size of the adrenal glands on ultrasound examination, they appear thinner than healthy adrenal glands for the dog of determined size and body weight. As they become thinner, to the ultra-sonographer they appear wormlike, explained by the words "thin and elongated" in contrary to their normal shape (peanut shaped left and arrow tip shaped right adrenal gland).

All patients were treated in line with the current therapy protocols (fluids, glucocorticoids, mineralocorticoids) and the outcome was favourable in all patients, which is in concordance to other studies. Discovery and usage of DOCP greatly facilitated, improved and simplified treatment protocols, since it is an injectable medication given on monthly basis (in comparison with fludrocortisone which should be given perorally twice per day). Moreover, Baumstark et al. (2014) demonstrated that DOCP suppresses plasma renin activity more effectively than fludrocortisone, suggesting that DOCP is more effective than fludrocortisone at replacing aldosterone in Addisonians. In this study, the dose of DOCP was 2.2 mg/kg as recommended, though a recent study recommended a starting dosage of 1.5

mg/kg of DOCP as effective in controlling clinical signs and serum electrolyte concentrations in the majority of dogs with hypoadrenocorticism (Sieber-Ruckstuhl et al., 2018).

In conclusion, Addison's disease can have numerous different presentations and the difficulty of diagnosis does not lie in performing complicated diagnostics, but in considering it as a possibility. The combination of prolonged history (previous episodes of similar unspecific signs), clinical signs (especially hypovolemia and bradycardia), laboratory results (especially electrolyte disturbances and azotaemia) and diagnostic imaging ("thin and elongated" adrenal glands) should be sufficient in pursuing with the diagnostics of hypoadrenocorticism. Although hypoadrenocorticism is often described as a diagnostic challenge, it should actually be termed a "remembrance challenge" since once awoken, the likelihood of detection of hypoadrenocorticism with ACTH stimulation test (as easy to perform as to interpret) is in fact certain.

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Hipoadrenokorticizam u pasa – „Ludi Šeširdžija veterinarske medicine"

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Pod pojmom hipoadrenokorticizam podrazumijevamo smanjenu funkciju nadbubrežne žlijezde, a sama bolest je poznata i pod nazivom Addisonova bolest. Hipoadrenorticizam je bolest koja se u pasa rijetko javlja s učestalošću od oko 0,1 %. Zbog kombinacije nespecifičnih simptoma i njihova osciliranja predstavlja dijagnostički izazov te se smatra bolešću čija se u veterinarskoj medicini dijagnoza najčešće previdi. Postoji primarni i sekundarni oblik bolesti. Cilj je ovog istraživanja bio detaljno analizirati podatke pasa s Addisonovom bolešću zaprimljenih u Kliniku za unutarnje bolesti Veterinarskog fakulteta Sveučilišta u Zagrebu te ih usporediti s podatcima iz sličnih institucija u svijetu. Detaljno su pretraženi podatci arhive klinike, a analizirani su i statistički obrađeni klinički i laboratorijski parametri, vrijeme trajanja simptoma te terapijski protokoli i ishod u pasa s hipoadrenokorticizmom. Istraživanu skupinu činilo je 14 pasa s hipoadrenokorticizmom od kojih 36 % mužjaka i 64 % ženki. U svih pasa zabilježeni su recidivirajući simptomi od strane probavnog sustava, od kojih se u 100 % slučajeva javljalo povraćanje, u 64 % proljev, a u 7 % melena. Klinički je u 57 % pasa uočen hipovolemični šok, u 64 % pasa hipotermija, a u 29 % bradikardija. Od laboratorijskih pretraga najčešća odstupanja bila su povećanje koncentracije ureje (86 %), kreatinina (57 %), hiperkalemija (79 %), hiponatremija (71 %), smanjeni Na/K omjer (86 %), hipoholesterolemija (21 %) te hipoglikemija (21 %). Trajanje simptoma do provedbe ACTH-stimulacijskog testa iznosilo je 2 - 2190 dana (prosječno 90±1195 dana), a nakon uvođenja adekvatne terapije ishod je u svih pasa bio povoljan.

Ključne riječi: *Addisonova bolest, deficit mineralokortikoida, deficit glukokortikoida, nadbubrežna žlijezda, pas*