Extreme hyponatraemia in a dog

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Specimen

peripheral blood and urine samples

Signalment

2-year-old, female, mix-breed dog

History & physical examination

The dog had been treated with carprofen, pantoprazole and gabapentin due to backpain with transient improvement in a primary care clinic. Weakness, tremor, and vomiting appeared newly.

By physical examination body temperature was 37.7°C, mucosal membranes were slightly pale and lumbar region was sensitive by palpation.

Laboratory alterations

CBC measured by ADVIA®2120i was almost unremarkable except slight **microcytosis with hyperchromasia**, and **decreased neutrophil-to-lymphocyte ratio**: 1.7 (**Table 1.**).

Table 1. Selected numerical data of the complete blood count

Parameters	Results	Reference intervals
Red blood cell	6.86	5.50 - 8.50 10^{12}/L
Hemoglobin	148	120 - 180 g/L
MCV	**59**	61 - 80 f/L
MCH	21.5	20.0 - 26.0 pg
MCHC	**367**	300 - 360 g/L
Platelet	242	150 - 450 10^9/L
White blood cell	9.5	6.0 - 15.0 10^9/L
Neutrophil abs.	5.6	4.3 - 9.0 10^9/L
Lymphocyta abs.	3.23	0.50 - 4.50 10^9/L
Monocyta abs.	0.52	0.25 - 1.00 10^9/L
Eosinophil abs.	0.12	0.10 - 1.20 10^9/L
Basophil abs.	0.02	0.01 - 0.08 10^9/L
Large Unstained Cells abs.	0.01	0.03 - 0.58 10^9/L
Reticulocyte abs.	8.6	<60 10^9/L

The clinical chemistry profile revealed **elevated blood sugar level**, **mild** presumptive prerenal **azotaemia**, slightly **elevated CRP-level** and **severe hyponatraemia and hypochloraemia** with **moderate hyperkalaemia** (electrolyte values were double checked) (**Table 2.**).

Table 2. Results of the biochemistry profile

Parameters	Results	Reference intervals
Total protein	65	55 - 75 g/L
Albumin	35.7	25.0 - 41.0 g/L
Globulin	29.3	20.0 - 45.0 g/L
ALT	54	5 - 60 U/L
AST	46	10 - 50 U/L
GLDH	6	- 10 U/L
ALP	141	- 280 U/L
GGT	2	- 9 U/L
Total bilirubin	4.0	0.1 - 5.1 µmol/L
Amylase	834	100 - 1200 U/L
Lipase (DGGR)	19	8 - 81 U/L
CK	89	20 - 225 U/L
LDH	71	20 - 250 U/L
Triglycerid	0.54	0.30 - 1.20 mmol/L
Cholesterol	5.7	3.2 - 6.2 mmol/L
Glucose (serum)	**12.2**	2.8 - 4.9 mmol/L
Fructosamine	329	187 - 386 µmol/L
Urea	**11.0**	2.5 - 6.7 mmol/L
Creatinine	69	20 - 150 µmol/L
Na^+	**97**	135 - 155 mmol/L
K^+	**6.35**	3.60 - 5.60 mmol/L
Na/K ratio	**15.28**	
Cl^-	**67**	100 - 116 mmol/L
calculated osmolality	**217.2**	290-310 mOsm/kg
Total calcium	2.23	2.50 - 3.10 mmol/L
Total magnesium	0.83	0.70 - 1.00 mmol/L
Phosphate	**1.8**	0.8 - 1.6 mmol/L
C-reactive protein	**17.3**	- 10.0 mg/L

Question1: What are the main mechanisms leading to hyponatraemia in dogs?
Answer1: Proposed mechanisms of hyponatraemia in dogs (Stockham - Scott, 2008)

- increased **loss via kidney** (osmotic diuresis, lack of aldosterone effect, lack or diminished effect of ADH, sodium-wasting nephropathies, Na^+ resorption inhibited by ANP)
- increased **loss via GI-tract** (copious diarrhoea and vomiting, excessive salivation)
- increased **loss via exudative skin lesion** (e.g., burn injury)
- **sequestration to third-space** (e.g., uroperitoneum)

- excessive administration of **Na^+-poor fluid** (e.g., 5% Glucose infusion) or **primary polydipsia** or **isotonic fluid loss compensated by hypotonic fluid intake**
- **compensatory dilution of intravascular volume** (due to presence of intravascular hyperosmotic substances, e.g., glucose, mannitol, ethylene glycol, etc.)

Question2: Which further diagnostic steps are recommended to identify underlying mechanism(s) of hyponatraemia?
Answer2:

1. **Measurement of serum osmolality** to confirm true hypoosmolality and exclude the presence of osmotically active molecules in serum.

Serum osmolality was measured: **232** mOsm/kg (RI: 290 - 310 mOsm/kg).

2. **Urinalysis** to evaluate electrolyte excretion and measurement of urine osmolality (**Table. 3.** and **Table 4.**)

Table 3. Results of fractional excretion of electrolytes

Electrolyte (mmol/L)	**Urine**	**Serum**	**Fractioned value (%)**
Na^+	134.10	**98** (135 - 155)	**0.73** (- 0.70)
K^+	84.78	**5.64** (3.60 - 5.60)	8.03 (-20)
Cl^-	162.28	**73** (100 - 116)	**1.19** (-0.80)
Calcium	2.04	2.28 (2.50 - 3.10)	**0.48** (-0.40)
Phosphate	44.00	1.4 (0.8 - 1.6)	16.80 (-39)

Table 4. Result of urinalysis

Parameters	**Results**
colour	straw
transparency	transparent
USG (refractometry)	1042
pH	6
protein	+/-
Hb/blood	negative
Glucose	normal
Ketone	non-detectable
Bilirubin	negative
Nitrite	negative
urine sediment	inactive
osmolality (mOsmol/L)	**1361.0**

Measured urinary osmolality was **1361** mOsm/kg, when serum osmolality was **232** mOsm/kg (RI: 290 - 310 mOsm/kg). Samples were collected simultaneously. At that point **syndrome of inappropriate ADH secretion** (SIADHS) came to our differential diagnosis list.

3. **Performing ACTH-stimulation test** to assess adrenocortical reserve capacity

ACTH-stimulation test was done after 24 hours of last dose of dexamethasone injection:

- basal cortisol level: < **9.93** nmol/L (RI: 19 - 100)
- stimulated cortisol level: < **9.93** nmol/L (RI: 79 - 429.5)

Cortisol levels were measured with Immulite® 2000XPi Immunoassay system. Based on the ACTH-stimulation test Addison's disease was confirmed.

Question3: How can be differentiated Syndrome of Inappropriate ADH Secretion (SIADHS) from Addison's disease?
Answer3: Discriminating criteria for SIADHS and primary hypoadrenocorticism

Table 5. Discriminating criteria for SIADHS and primary hypoadrenocorticism (based on Hannon - Thompson, 2010; Liamis, Milionis. and Elisaf, 2011)

	SIADHS	**primary hypoadrenocorticism**
serum Na^+ level	low	normal - low
natriuresis	increased	increased
ACTH level	normal - high	high
cortisol level	normal - high	low
aldosterone level	normal - high	low
renin activity	low	high
ADH level	normal - high	normal - high
ketonemia	-	possible

Serum beta-hydroxi-butirate level was 0.01 mmol/L (< 0.3).

Baseline and ACTH-stimulated aldosterone levels:

- basal aldosterone level: < **20** pmol/L (RI: 0 - 393)
- stimulated aldosterone level: < **20** pmol/L (RI: 82 - 859)

Serum aldosterone levels were measured with RIA at IDEXX Laboratories (Kornwestheim, Germany).
To the best of our knowledge, at the time of the examination canine plasma renin activity detection was not commercially available.

Question4: What is the proposed mechanism of ACTH-stimulated aldosterone secretion?
Answer4: Proposed mechanism of ACTH-mediated aldosterone secretion.

According to the traditional approach aldosterone release is quite independent from ACTH secretion and its production is mainly influenced by the renin-angiotensin system and plasma potassium level. Based on recent findings in humans, ACTH-receptors (melanocortin type 2

receptor) not only present in zona fasciculata but also in zona glomerulosa. In addition, ACTH can boost the transcription of CYP11B2 (aldosterone synthase) enzyme and this effect is accomplished at much lower ACTH-concentration compared to the level required for cortisol and DHEAS production (Ghorayeb et al, 2016). Notwithstanding, CYP11B2 has not been detected in dog so far. In canines CYP11B1 is responsible for aldosterone and cortisol production (Sanders et al, 2016).

Interpretation/Diagnosis

Based on the laboratory findings **primary hypoadrenocorticism** was the primary diagnosis. **Inappropriate ADH-secretion** was a secondary diagnosis.

Additional information

Follow up and clinical outcome

15 days after the beginning of gluco- and mineralocorticoid supplementation a follow-up blood sample was sent to the lab. At that time the patient had mild normocytic, hypochromic (RBC: 4.79 10^{12}/L, RI: 5.50 - 8.50), moderately regenerative anaemia (absolute reticulocyte number: 355.9 10^{9}/L, RI: < 60).

Serum electrolyte levels were within the reference intervals:

- Na^{+}: 146 mmol/L (RI: 135 -155)
- K^{+}: 4.54 mmol/L (RI: 3.60 - 5.60)
- Na/K ratio: 32.16
- Chloride: 107 mmol/L (RI: 100 - 116)

Discussion

Hypoosmolar hyponatraemia with increased urinary sodium excretion and urinary hyperosmolality is equally characteristic for the Syndrome of Inappropriate Antidiuretic Hormone Secretion and adrenocortical insufficiency.

In primary hypoadrenocorticism there are several mechanisms which are leading to increased or diminished ADH secretion. Not only hypovolaemia but also the decreased systemic blood pressure and cardiac output, and nausea itself directly increase ADH secretion. Moreover, glucocorticoids influence ADH release and in case of hypocortisolaemia the lack of inhibition leads to an exaggerated vasopressin secretion. Finally, the renal sensitivity to ADH (regulation of aquaporin-2 water channels) might be mediated by glucocorticoids.

Demonstrated by our case severe hyponatraemia in Addison's disease is a consequence of multiple mechanisms. SIADHS should be included in the differential diagnosis list in dogs with hyponatraemia, especially in patients with concurrent normokalaemia.

References

Urinary system and **Monovalent electrolytes and Osmolality** in: Stockham, S.L. - Scott, A.S.: **Fundamentals of Veterinary Clinical Pathology** 2nd Edition (2008) Blackwell Publishing

Hannon, M.J. - Thompson, C.J.: **The syndrome of inappropriate antidiuretic hormone: prevalence, causes and consequences**. European Journal of Endocrinology (2010) 162 S5-S12.

Biewenga W.J., Rijnberk, A. and Mol, J.A.: **Osmoregulation of systemic vasopressin release during long-term glucocorticoid excess**: A study in dogs with hyperadrenocorticism. Acta Endocrinologica (Copenhagen) (1991) 124: 583-588.

Liamis, G., Milionis, H.J. and Elisaf, M.: **Endocrine disorders: Causes of hyponatremia not to neglect**. Annals of Medicine (2011) 43: 179-187. (*)

Javadi, S., Galac, S., Boer, P., Robben, J.H., Teske, E. and Kooistra, H.S.: **Aldosterone-to-Renin and Cortisol-to-Adrenocorticotropic Hormone Ratios in Healthy Dogs and Dogs with Primary Hypoadrenocorticism**. Journal of Veterinary Internal Medicine (2006) 20:556-561.

Baumstark, M.E., Sieber-Ruckstuhl, N.S., Muller, C., Wenger, M., Boretti, F.S. and Reusch, C.E.: **Evaluation of Aldosterone Concentrations in Dogs with Hypoadrenocorticism**. Journal of Veterinary Internal Medicine (2014) 28:154-159.

Ghorayeb, N.E., Bourdeau, I. and Lacroix, A.: **Role of ACTH and Other Hormones in the Regulation of Aldosterone Production in Primary Aldosteronism**. Frontiers in Endocrinology (2016) 7:72.

Sanders, K., Mol, J.A., Kooistra, H.S., Slob, A., Galac, S.: **New Insights in the Functional Zonation of the Canine Adrenal Cortex**. Journal of Veterinary Internal Medicine (2016) 30:741-750.

Acknowledgements

Authors wish to express thanks to Prof. Dr. Hans Kooistra sharing his professional opinion.