Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion in non-azotaemic dogs with babesiosis associated with decreased arterial blood pressure

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Abstract

Introduction: A previous study on canine babesiosis showed low serum tonicity in affected dogs, which may result from syndrome of inappropriate antidiuretic hormone secretion (SIADH). This endocrine disorder was recognised in human malaria which is considered a disease with similar pathogenesis to canine babesiosis. The aim of this study was to investigate the occurrence of SIADH in babesiosis-afflicted dogs. Material and Methods: Serum and urinary sodium and urine specific gravity (USG) were determined in dogs with babesiosis. Mean arterial pressure (MAP) was measured at the beginning of the clinical examination. Serum tonicity and osmolality were calculated. Correlations were calculated between MAP and serum and urinary sodium concentrations, USG, serum tonicity, and calculated serum osmolality. Results: Statistically significant correlations were observed between MAP and tonicity, calculated osmolality, USG, and serum and urinary sodium concentrations in non-azotaemic dogs. In three non-azotaemic dogs SIADH was recognised. Conclusion: SIADH develops in non-azotaemic dogs with babesiosis. It is probably associated with decreased blood pressure in infected dogs. Thus, it seems that in fact it may be appropriate vasopressin secretion in canine babesiosis as a protective mechanism in hypotension which leads to hypoxia and renal failure in affected dogs.

Keywords: dog, canine babesiosis, hyponatraemia, hypotension, SIADH.

Introduction

Canine babesiosis is a tick-borne protozoan disease caused by parasites of the genus Babesia. The disease may be caused by infection with small species of the parasite such as B. gibsoni, B. conradae, or B. vulpes, or large species such as B. canis, B. vogeli, or B. rossi (4, 17, 20). In dogs from Poland, only B. canis has been detected (2, 34, 40). Infection with the parasite may lead to systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and septic shock, and the disease is considered similar to human malaria which is caused by infection with mosquito-borne parasites of the genus Plasmodium (8, 23). Both infections are classified as protozoal sepsis, and pathogenesis in both diseases is associated with overproduction of pro-inflammatory cytokines (8, 12, 37, 38). Moreover, in both diseases hypotension was observed, which is defined in dogs as mean arterial pressure lower than 80 mmHg (8, 23). One study on human malaria showed release of antidiuretic hormone (ADH, also known as vasopressin) leading to hyponatraemia in patients with decreased blood pressure (14). The role of ADH in human malaria is not clear. Studies on vasopressin in human malaria showed both appropriate and inappropriate ADH secretion (14, 15, 16).
Hyponatremia was also observed in dogs infected with *B. rossi* and *B. canis*, and syndrome of inappropriate antidiuretic hormone (SIADH) secretion in infected dogs was suggested in a previous study on canine babesiosis (1, 21, 39). SIADH is a disorder of sodium and water balance. The syndrome leads to hyponatremia, hypotonicity (decreased effective extracellular fluid osmolality), and impaired urinary dilution (9, 11). In humans, the first two cases of SIADH were described in 1957 by Schwartz et al. (28), and SIADH is also known as Schwartz-Barter syndrome or syndrome of inappropriate antidiuresis. Hypersecretion of ADH not being observed in all patients with the syndrome, diagnosis of SIADH does not require vasopressin determination (11). The criteria for SIADH in humans are as follows: hyponatremia, hypotonicity (tonicity lower than 280 mOsm/kg, but according to some authors <275 mOsm/kg means true hyponatremia; strong correlation with serum hypoosmolality), high urine osmolality (strongly correlated with high specific gravity), lack of clinical signs of hypovolaemia, high urinary sodium concentration (higher than 30 mEq/L), no detection of renal insufficiency, hypothryroidism, or hypocorticism, and no recent use of thiazide diuretics (9, 24).

SIADH in humans may result from eutopic or ectopic secretion of ADH, and it has been recognised in neoplastic diseases (e.g. bronchogenic carcinoma or leukaemia), lung diseases (e.g. pneumonia or asthma), cerebral diseases (e.g. meningitis or encephalitis), and infectious diseases (e.g. AIDS, tuberculosis, or malaria). Moreover, SIADH may be iatrogenic (from the use of vasopressin or its analogues), nephrogenic (from mutations of vasopressin receptor genes), or idiopathic. Other causes of SIADH in humans include pain (especially post-operative), severe nausea, and stress (11, 15). In dogs, SIADH has been recognised in only a few animals of various breeds and both sexes, and it was concurrent to aspiration pneumonia, liver disease, granulomatous amoebic meningoecephalitis, congenital hydrocephalus, and histiocytic sarcoma (5, 6, 7, 19, 22, 29). SIADH in dogs may also be idiopathic as in humans and this was diagnosed in two dogs (25).

Owing to the facts that babesiosis and malaria are similar diseases, hyponatremia was noted in both, and SIADH was diagnosed in human malaria, the authors of this study hypothesised that SIADH may also occur in canine babesiosis.

**Material and Methods**

Thirty-six serum, whole blood, and urine samples were collected from dogs of various breeds naturally infected with *Babesia canis* but yet to be treated (Group A). Fifteen healthy dogs of various breeds (seven mixed-breed dogs, two Labradors, one Dachshund, one Beagle, one Golden Retriever, one Jack Russell Terrier, one Siberian Husky, and one German Shepherd) comprising eight males and seven females of one to seven years of age were used as the control group (Group B). Two types of tubes were used for the blood collection: tubes coated with EDTA for whole blood samples and dry tubes for serum samples. Urine samples were collected in dry plastic containers. Initial diagnosis of infection was based on the result of blood smear examinations. Confirmations of the infection with *B. canis* and freedom from infection with *Anaplasma phagocytophilum*, the second most prevalent tick-borne canine pathogen in Poland, were based on the results of the PCR methods described in previous studies (26, 33, 39).

Clinical examination (including blood pressure measurement) was performed during the visit before sample collection. Mean arterial pressure was measured using the oscillometric technique with a Cardell 9405 veterinary monitor (Midmark, USA). Serum and urine sodium concentrations were determined by a Rapidchem 744 clinical chemistry analyser (Siemens Healthcare Diagnostics, Germany).

Before determination of urinary sodium concentration, urine samples were centrifuged (2,000 rpm, 5 min) and then supernatant fluid was diluted tenfold in deionised water. Serum and urine concentrations of creatinine and serum urea and glucose content were assayed by an XL 640 clinical chemistry analyser (Erba Mannheim, Germany). Urine specific gravity (USG) was read using a Reichert VET 360 veterinary refractometer (Reichert, USA). These parameters were used to derive effective extracellular fluid (ECF) osmolality (tonicity), calculated osmolality, and the renal failure index. Effective ECF osmolality was calculated according to Wellman et al. (35) using the formula Eff. ECF Osm. = 2 × SNa⁺ (mEq/L) + glucose (mg/dL)/18, where SNa⁺ is serum sodium concentration and milliequivalent weight is millimolar weight multiplied by the valence (mEq/L = mmol/L × valence). Calculated osmolality was yielded by the formula Calc. Osm. = tonicity (mOsm/kg) + BUN (mg/dL)/2.8, where BUN is concentration of blood urea nitrogen. The calculation of BUN required the serum urea concentration and used the formula BUN = serum urea concentration/2.14 (10). The renal failure index (RFI) was calculated according to Waldrop (32) using the formula RFI = UNa⁺ × SCr/UCr, where UNa⁺ is urinary sodium concentration, SCr is serum creatinine concentration, and UCr is urinary creatinine concentration.

Exclusion criteria were as follows: data supporting the suspicion of hypothyroidism, adrenal disease or renal disease (in group A before infection), and recent use of diuretics. Moreover, all infected dogs with clinical signs such as vomiting, diarrhoea, dehydration, ascites, oedema, and RFI > 2 indicating renal injury were excluded from the study.

Obtained results guided the division of group A into two subgroups: A1, of azotaemic dogs and A2, of non-azotaemic dogs. The results were analysed using the Statistica 13.3 programme (Tibco Software, USA). The Shapiro–Wilk W-test was used for the estimation...
of normality in the distributions of concentrations of urinary and serum sodium, effective ECF osmolality, urine specific gravity, and mean arterial pressure in groups A and B and subgroups A1 and A2. Depending on the normality of distributions, Spearman’s rank correlation coefficient (other than normal distribution) or Pearson’s correlation coefficient (normal distribution) was used to calculate correlations between MAP and serum and urinary sodium concentrations, USG, serum tonicity, and calculated serum osmolality in groups A and B and subgroups A1 and A2.

Results

Among 36 infected animals (group A), 15 dogs had azotaemia (mean serum creatinine concentration 3.51 ± 1.85 mg/dL and mean serum urea concentration 245.5 ± 121.4 mg/dL), and 21 dogs had no azotaemia (subgroup A2: mean serum creatinine concentration 1.09 ± 0.30 mg/dL and mean serum urea concentration 39.7 ± 7.8 mg/dL). However, seven azotaemic dogs were excluded from the study owing to RFI > 2 indicating renal azotaemia and corroborating clinical signs such as vomiting, diarrhoea and dehydration in these animals. Mean serum creatinine and urea concentrations in subgroup A1 (azotaemic dogs after exclusion of the seven dogs with renal azotaemia) were as follows: mean serum creatinine concentration 2.37 ± 0.42 mg/dL and mean serum urea concentration 165.7 ± 55.2 mg/dL. None of the dogs in this study had signs of hypothyroidism, adrenal or renal disease before the infection, and none of them had been treated with diuretics recently. A PCR assay confirmed infection with *B. canis* in all 29 infected dogs included in the study. No dogs were infected with *A. phagocytophilum*.

The Shapiro–Wilk W-test for normality in urinary and serum sodium, effective ECF osmolality, calculated osmolality, urine specific gravity, and mean arterial pressure showed a non-normal distribution in USG and MAP in group A and subgroup A2 (Table 1).

In groups A and B and subgroup A1, there were no statistically significant correlations between MAP and effective ECF osmolality, calculated osmolality, serum and urinary sodium concentrations, or urine specific gravity. Statistically significant positive correlations were observed between MAP and tonicity, calculated osmolality, and serum sodium concentration in subgroup A2. Statistically significant negative correlations were observed between MAP and urinary sodium concentration and USG (Table 2).

In three dogs from subgroup A2, serum tonicity and calculated serum osmolality were below 275 mOsm/kg, and serum sodium concentration was below the reference interval; these dogs had high urine specific gravity and high urinary sodium concentration (Table 3). In these dogs, SIADH was diagnosed.

### Table 1. Results of the Shapiro–Wilk W-test for normality in groups A and B and subgroups A1 and A2 in the distribution of effective ECF osmolality, calculated osmolality, serum sodium concentration, urinary sodium concentration, urine specific gravity, and mean arterial pressure

| Parameter                   | Group | W     | p    |
|-----------------------------|-------|-------|------|
| Effective ECF osmolality    | A     | 0.968 | 0.532|
|                            | B     | 0.964 | 0.769|
|                            | A1    | 0.971 | 0.910|
|                            | A2    | 0.957 | 0.469|
| Calculated osmolality       | A     | 0.954 | 0.243|
|                            | B     | 0.984 | 0.989|
|                            | A1    | 0.891 | 0.239|
|                            | A2    | 0.944 | 0.263|
| Serum Na⁺                   | A     | 0.966 | 0.465|
|                            | B     | 0.959 | 0.690|
|                            | A1    | 0.947 | 0.681|
|                            | A2    | 0.958 | 0.486|
| Urinary Na⁺                 | A     | 0.952 | 0.214|
|                            | B     | 0.988 | 0.998|
|                            | A1    | 0.962 | 0.825|
|                            | A2    | 0.953 | 0.363|
| USG                         | A     | 0.919 | 0.029*|
|                            | B     | 0.934 | 0.309|
|                            | A1    | 0.853 | 0.104|
|                            | A2    | 0.902 | 0.039*|
| MAP                         | A     | 0.849 | 0.001*|
|                            | B     | 0.976 | 0.939|
|                            | A1    | 0.892 | 0.245|
|                            | A2    | 0.856 | 0.005*|

ECF – extracellular fluid, Serum Na⁺ – serum sodium concentration, Urinary Na⁺ – urinary sodium concentration, USG – urine specific gravity, MAP – mean arterial pressure, W – value of W in the Shapiro–Wilk W-test, p – value of p, * – p < 0.05

### Table 2. Statistically significant correlations between mean arterial pressure and effective ECF osmolality (Eff. ECF Osm.), calculated osmolality (Calc. Osm.), serum sodium concentration (Serum Na⁺), urinary sodium concentration (Urinary Na⁺), and urine specific gravity (USG) in subgroup A2

| Correlation          | r     | p    |
|----------------------|-------|------|
| Eff. ECF Osm.        | 0.50  | 0.021*|
| Calc. Osm.           | 0.50  | 0.020**|
| Serum Na⁺            | 0.49  | 0.021*|
| Urinary Na⁺          | −0.52 | 0.015*|
| USG                  | −0.46 | 0.031*|

MAP – mean arterial pressure, r – Spearman’s rank correlation coefficient, p – value of p, * – p < 0.05

### Table 3. Effective extracellular fluid osmolality, calculated serum osmolality serum and urinary sodium concentration, urine specific gravity, and mean arterial pressure in three non-azotaemic dogs (from subgroup A2) infected with *B. canis* and in which SIADH was diagnosed

| Dog no. | Eff. ECF Osm. (mOsm/kg) | Calc. Osm. (mOsm/kg) | Serum Na⁺ (mEq/L) | Urinary Na⁺ (mEq/L) | USG | MAP (mmHg) |
|---------|--------------------------|----------------------|-------------------|---------------------|-----|------------|
| 1       | 255.5                    | 259.8                | 124.8             | 132.9               | 1.052 | 93         |
| 2       | 266.5                    | 272.0                | 130.7             | 136.0               | 1.060 | 69         |
| 3       | 249.8                    | 254.5                | 122.4             | 133.7               | 1.055 | 85         |

*Abbreviations as in Table 2*
Discussion

This study is the first in which SIADH was recognised in canine babesiosis. Three dogs had hyponatraemia with serum toxicity and calculated serum osmolality lower than 275 mOsm/kg, high urinary sodium concentration, and high USG, which is strongly correlated with urine osmolality (3). These dogs had no clinical signs of hypovolaemia. An RFI lower than 2 and lack of azotaemia in these dogs indicated normal renal function. Before infection, these dogs were healthy and had no signs of hypothryroidism or hypocorticism. Changes of cortisol levels, ACTH, thyroid hormones, and TSH were observed in canine babesiosis, and therefore concentrations of these hormones were not determined in this study (27, 38).

Before infection, the dogs had not been treated recently with any drugs (including diuretics). Thus, in the authors’ opinion these three dogs with hyponatraemia, hypotonicity, and hypoosmolality had SIADH. This result confirms observations from the previous studies on electrolyte disorders in canine babesiosis where hyponatraemia was observed in dogs infected with *B. canis* and *B. rossi* (1, 21, 39).

Fluid restriction is also useful in recognition of SIADH (11). However, the owners of these dogs did not heed this recommendation. The authors of this study did not determine urine osmolality. However, as mentioned above, Ayoub et al. (3) showed strong linear correlation between USG and urine osmolality in dogs with various pathological conditions. That study also showed no influence of bilirubinuria, haemoglobinuria, proteinuria, or, surprisingly, glucosuria on the correlation between USG and urine osmolality, and only a small influence of ketonuria on this relationship. According to Ayoub et al. (3), the influence of mild to moderate ketonuria on the correlation between USG and urine osmolality was not clinically relevant. Nevertheless, in this study no dogs had ketonuria. Thus, it seems highly probable that the high USG observed in the three dogs with SIADH reflected high urine osmolality.

In humans, there are three etiological classes of SIADH: endogenous, exogenous, and idiopathic. The exogenous class has aetiology in administration of vasopressin or its analogues, and the endogenous class includes four aetiologies: hypothalamic production of ADH, ectopic secretion of ADH (in neoplastic diseases), a potentiating ADH effect of some drugs, and nephrogenic syndrome of inappropriate antidiuresis (11). It seems probable that the cause of SIADH in canine babesiosis is increased hypothalamic production of vasopressin. This study showed correlations between MAP and serum toxicity, calculated serum osmolality, serum and urinary sodium concentrations, and USG, and it seems probable that increased production of vasopressin may be a response to hypotension which was observed in previous studies on canine babesiosis caused by infection with *B. rossi* and *B. canis* (18, 23, 36). However, in this study only one dog with diagnosed SIADH (dog no. 2) had hypotension (MAP < 80 mmHg).

According to Vantyghem et al. (31), stimulation of vasopressin production may also be potentiated by IL-6. Increased concentration of this pro-inflammatory cytokine was also observed in dogs infected with *B. canis* and *B. rossi* (12, 38). Thus it seems probable that IL-6 may contribute to the stimulation of vasopressin production and secretion in canine babesiosis. Moreover, stress, nausea, hypoglycaemia and hypoxia may be other possible causes of vasopressin secretion in infected dogs (31).

Hyponatraemia and SIADH in canine babesiosis seem contradictory to the hyperaldosteronism recognised in a previous study in dogs infected with *B. canis* (13). In the authors’ opinion it seems probable that increased aldosterone production is stimulated by hyponatraemia, and develops with a delay after SIADH. It was also speculated in the previous study that the delay in aldosterone production results from competition between stimulating factors for aldosterone like hyponatraemia and inhibiting factors like normovolaemia (30). Moreover, the previous study on hyperaldosteronism in canine babesiosis showed increased aldosterone production only in azotaemic dogs, and this study showed SIADH only in non-azotaemic dogs (13). Thus, in canine babesiosis SIADH is an early endocrine disorder (at the beginning of the disease), while hyperaldosteronism is a late endocrine disorder in affected animals.

One limitation of this study is the lack of an osmometer for determination of serum and urinary osmolality. However, serum osmolality and toxicity were calculated using results of serum sodium, glucose, and urea concentrations, and calculated serum osmolality should be very similar to the osmolality which would have been determined by osmometer. Moreover, as previously noted USG is strongly correlated with urine osmolality in dogs (3, 10). Another limitation of the study was the non-adherence by the owners of the dogs to the advice to restrict fluids, which could have led to correction of hyponatraemia (10). This was predicated on the mildness of the hyponatraemia set against their fear of azotaemia and renal complications.

In conclusion, there is a high probability that SIADH develops in non-azotaemic dogs with babesiosis. It is probably associated with lower blood pressure in infected dogs, and hypothalamic production of vasopressin is a possible response to hypotension in canine babesiosis. Thus, it seems that in fact it may be appropriate ADH secretion in dogs with parasites of the genus *Babesia* as a protective mechanism in hypotension which leads to hypoxia and renal failure in canine babesiosis. Hyperaldosteronism observed in azotaemic dogs with babesiosis would then seem to be the second line of defence in hypotensive dogs.
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