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Case Report
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Syndrome of Inappropriate Antidiuretic Hormone in a Bulldog with Aspiration Pneumonia

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Key words: Canine; Hyponatremia; Pneumonia; SIADH.

A 15-week-old, male intact, 9.8 kg English Bulldog presented to the University of Georgia Veterinary Teaching Hospital (VTH) for surgical correction of presumed brachycephalic airway syndrome. For 3 weeks before admission, the dog experienced stertorous breathing that was not responsive to antibiotic treatment, including doxycycline, cefpodoxime, and marbofloxacin, for treatment of presumptive pneumonia. Thoracic radiographs performed a week before presentation disclosed a hypoplastic trachea and tracheal collapse, but no evidence of pneumonia. Baermann testing of feces did not identify parasites.

On presentation, the puppy had loud referred upper airway noise and stertorous breathing on auscultation. The nares were stenotic bilaterally. Preoperative laboratory assessment was normal. Serum electrolyte concentrations were not measured.

An upper airway examination was performed under propofol anesthesia, and disclosed a moderately elongated soft palate and everted laryngeal saccules, indicating grade 1 laryngeal collapse. The dog was intubated and maintained under anesthesia using isoflurane in 100% oxygen. A CO_2 laser was used to perform a staphylectomy and metzenbaum scissors were used to perform laryngeal sacculectomy. A bilateral rhinoplasty was performed with the CO_2 laser.

Upon recovery, the dog was eupneic but its breathing remained stertorous; however, he seemed comfortable and eupneic. The dog was maintained on lactated ringer's solution during anesthesia and surgery at a rate of 10 mL/kg/h, which was discontinued upon extubation. The postoperative course was complicated by several episodes of regurgitation, which were temporally associated with administration of hydromorphone (0.05 mg/kg IV q4h). Overnight, progressive respiratory distress developed and 12 h after surgery, the dog became orthopneic, with dull mentation. The puppy was transferred to an oxygen cage with a fractional inspired oxygen concentration of 40%. Thoracic radiographs identified severe alveolar disease in both the left cranial lung lobe and the right middle lung lobe. Plasma electrolyte concentrations were measured and identified moderate hyponatremia (134 mEq/L; reference interval, 140–152 mEq/L) and mild hypochloremia (106 mEq/L; reference interval, 110–121 mEq/L). Venous blood gas analysis identified hypercapnia (50 mm Hg; reference interval, 22–33 mmHg), consistent with a respiratory acidosis (pH = 7.30; reference interval, 7.42–7.50). All chemistry values were obtained from heparinized blood, thus plasma values are reported. Severe leukopenia was identified on CBC with total white blood cell (WBC) count of $1.5 \times 10^3/\mu L$ (reference interval, 5.5–13.9 $\times 10^3/\mu L$) characterized by neutropenia ($0.375 \times 10^3/\mu L$; reference interval, 2.9–12 $\times 10^3/\mu L$) and a mild left shift (band neutrophils $0.135 \times 10^3/\mu L$; reference interval, 0–0.45 $\times 10^3/\mu L$). A CBC performed several days later had leukocytosis ($22.3 \times 10^3/\mu L$), with an inflammatory leukogram (segmented neutrophils $18.286 \times 10^3/\mu L$, band neutrophils $0.223 \times 10^3/\mu L$ and monocytosis $1.784 \times 10^3/\mu L$; reference interval, 0.1–1.4 $\times 10^3/\mu L$) with slight toxic changes in the neutrophils.

Abbreviations:

SIADH syndrome of inappropriate antidiuretic hormone

Antimicrobial treatment with ampicillin and sulbactam (22 mg/kg IV q8h) and amikacin (15 mg/kg IV q24h × 5 days) was initiated to treat presumed bronchopneumonia. In addition, intermittent (q4h) nebulization using 0.9% saline with gentle thoracic coupage and aminophylline treatment (5 mg/kg IV q8h) were instituted. Postoperative analgesia was provided with buprenorphine (0.01 mg/kg IV q8h), and both famotidine (1 mg/kg IV q12h) and metoclopramide (1 mg/kg/day IV as constant rate infusion) were administered to decrease the effects of or development of reflux esophagitis. Food was withheld for 24 h, and subsequently frequent (q4h) feedings of canned food were offered after an absence of observed regurgitation.[a]

Fluid therapy also was instituted on the first postoperative day using a balanced polyionic crystalloid solution[b] with a sodium concentration of 130 mEq/L, supplemented with 16 mEq KCl/L (for a total of 20 mEq/L of potassium). The initial intravenous fluid

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rate was 32 mL/h (approximately 90 mL/kg/day) to provide supportive care for aspiration pneumonia and to correct his sodium deficit. The dog remained well-hydrated during hospitalization based on physical examination findings. The next day, intravenous fluids were changed to a different isotonic crystalloid[c] with a higher sodium concentration (140 mEq/L) to address worsening hyponatremia. Potassium supplementation using KCl was adjusted as necessary over the next several days, based on serial electrolyte monitoring.[d] On the sixth postoperative day, the rate of intravenous crystalloid was decreased to a maintenance fluid rate of 1.8 mL/kg/h.

Urine output was monitored throughout hospitalization using a subjective scale to indicate the volume of urination. The puppy urinated every 2–4 h. Urine specific gravity (USG) was evaluated several times throughout hospitalization. The USG was 1.014 on the second postoperative day, 3 days before initiation of furosemide treatment. Most USG values were between 1.014 and 1.022. On the fifth day of hospitalization (the day furosemide was initiated), the USG increased to >1.050 12 h after the first dose of furosemide. At this point, intravenous fluids that had been discontinued for a short period of time were reinstituted.

Throughout the course of hospitalization, the plasma sodium concentration decreased progressively, and despite ongoing fluid therapy, on the fifth postoperative day, the plasma sodium concentration reached a nadir of 121 mEq/L. In addition, the puppy's weight had increased to 8.7 kg, compared to 8.4 kg measured immediately postoperatively**.** An initial weight of 9.8 kg was recorded in the medical record, and this discrepancy may have resulted from the use of different scales between admission and hospitalization. Furosemide (0.5 mg/kg intravenous q6h) was administered. Only a modest increase in plasma sodium concentration (123 mEq/L) was seen after 24 h of this treatment, and intravenous fluids were changed to 0.9% NaCl supplemented with 30 mEq KCl/L.

Serial measurements of plasma electrolyte concentrations were performed q4-6h for the next 5 days to adjust fluid therapy. Because the plasma sodium concentration failed to increase above 122 mEq/L with 0.9% NaCl treatment, fluids were changed to 1.75% NaCl administered at the same rate (1.8 ml/kg/h). This fluid regimen was chosen by calculating an estimated change in plasma sodium concentration using the formula: change in plasma sodium = (infusate Na^+ − plasma Na^+)/(total body water + 1). The infusate sodium was estimated at 300 mEq/L, and the total body water was calculated to be 0.6×body weight in kg.[1] Using this formula, the puppy would receive approximately 375 mL of infusate over 24 h, for a total increase in plasma sodium of 29 mEq over 3 days, a conservative estimate toward a goal of increasing the plasma sodium concentration by 0.5 mEq/h. At this time, several diagnostic tests were performed to determine the cause of the persistent hyponatremia. Serum cortisol concentration was 2.4 μg/dL (reference range, 0.5–3.0 μg/dL) and urine osmolality was 877 mOsm/kg (reference range, <100 mOsm/kg),[2] while calculated plasma osmolality was 256 mOsm/kg (reference range, 285–295 mOsm/kg). Urine electrolyte concentrations were measured and urine sodium concentration was 197 mmol/L, urine potassium concentration was 68.4 mmol/L, and urine chloride concentration was >250 mmol/L. Urine specific gravity at the time of urine electrolyte concentration measurement was 1.021. Furosemide administration (0.5 mg/kg intravenous q6h) may have contributed to the urine sodium concentration and low urine osmolality. The dog's plasma sodium concentration increased from 123 to 137 mEq/L over 24 h. At this time, the dog's fluids were changed to 0.9% NaCl at the same rate. Over the next 3 days, minor fluctuations of plasma sodium concentrations occurred (varying between 133 and 139 mEq/L), and the dog was maintained on 0.9% NaCl. On the ninth postoperative day, furosemide administration was discontinued, and the plasma sodium concentration was 136 mEq/L. On the tenth postoperative day, intravenous fluid therapy was discontinued, and plasma sodium concentration was 137 mEq/L.

Throughout hospitalization, the dog's respiratory rate and effort varied, necessitating continued nebulization, aminophylline, and oxygen supplementation as necessary. Fractional inspired oxygen varied between 30 and 60%, depending on the severity of respiratory effort. Oxygenation was assessed with intermittent monitoring of SpO_2. On the first postoperative morning, SpO_2 was 85%. On the fourth postoperative day, respiratory rate and effort began to improve, characterized by intermittent periods of eupnea. On the sixth postoperative day, an SpO_2 after light exercise was 89–91%, which improved to 98% with oxygen supplementation. By the seventh postoperative day, the dog remained eupneic, and oxygen supplementation was gradually decreased and was discontinued on the ninth postoperative day. Despite eupneia, the patient continued to exhibit increased respiratory noise at the time of discharge, 11 days postoperatively. Follow-up thoracic radiography performed by the referring veterinarian indicated improvement of alveolar disease, and follow-up conversations with the owner indicated that the dog had not experienced dyspnea since discharge.

Previous reports of the Syndrome of Inappropriate Antidiuretic Hormone in the veterinary literature have described underlying conditions such as hydrocephalus, amebic meningoencephalitis, immune-mediated liver disease, dirofilariasis, idiopathic origin, vinblastine overdose, and possible anesthetic complications.[3–8] Causes of SIADH in humans include pulmonary disorders (pneumonia, non small cell lung cancer), central nervous system (CNS) disorders (particularly traumatic brain injury and subarachnoid hemorrhage), medications (eg, selective serotonin reuptake inhibitors) and neoplasia. Of particular interest, a causal relationship has been identified in humans between head and neck surgeries (specifically primary brain tumor removal) and development of SIADH.[9–12]

Hyponatremia is common in hospitalized human patients, with higher prevalence rates among the

elderly.[9,13] The causes of hyponatremia are varied, and accurate diagnosis is based on a patient's plasma osmolality and hydration status, in addition to lack of thyroid or ACTH deficiencies.[2] Normovolemic hyponatremia is the most common type of hyponatremia in hospitalized human patients, and includes SIADH. This syndrome is the most common cause of hyponatremia in human patients and is a contributing factor to morbidity and mortality.[9] Its prevalence or impact in veterinary patients has not yet been well defined.

The patient reported here likely developed SIADH secondary to aspiration pneumonia. Because electrolyte concentrations were not measured before surgery, we cannot eliminate the possibility of preexisting hyponatremia. A recent report of 221 elderly human patients with aspiration pneumonia noted hyponatremia in 29%, of which 95% had hypotonic hyponatremia. Of those patients, 32% were euvolemic, and 70% of the euvolemic cases were diagnosed with SIADH.[13] The severity of aspiration pneumonia in children has been associated with the development of SIADH, and in 1 study, approximately one-third of 100 children with aspiration pneumonia had SIADH.[14] In this report, recovery from hyponatremia occurred with resolution of respiratory distress. In our report, respiratory signs were substantially improved on the seventh postoperative day, which was the first day where the plasma sodium concentration was 130 mEq/L.

Although the exact connection between pulmonary pathology and SIADH is unknown, mechanisms have been hypothesized, including decreased left atrial tension from increased pulmonary vascular resistance or compression from hyperinflated lungs.[15] In addition, hypoxemia is a direct stimulus for ADH release by hypothalamic stimulation or arterial baroreceptor activation. In this case, both hypoxemia and decreased left atrial pressure may have precipitated the development of SIADH. Unfortunately, measurements of left atrial pressure were not performed.

Several criteria must be met before a diagnosis of SIADH can be made.[2] Nonnormovolemic hyponatremia caused by concurrent liver or kidney disease, congestive heart failure, gastrointestinal fluid loss, or third-space loss were eliminated. We determined the dog was euvolemic based on physical examination findings and absence of other clinical signs (eg, vomiting, diarrhea) or concurrent multiorgan damage. In human patients, the diagnosis of SIADH must include decreased plasma osmolality (<274 mOsm/kg), increased urinary osmolality (>100 mOsm/kg during hypotonicity), increased urinary sodium concentration (>40 mmol/L), euvolemia, normal thyroid and adrenal function, and no recent use of diuretic agents.[2,16] In this patient, persistent hyponatremia, plasma hypoosmolality, and increased urine osmolality were documented, with normal serum cortisol concentration. Thyroid function was not evaluated but was considered unlikely based on young age, lack of clinical signs, and absence of other laboratory abnormalities associated with decreased thyroid function. In addition, it was shown that with progressive water restriction and hypertonic fluid therapy, the plasma sodium concentration increased.

Our study had some limitations. Patients with SIADH typically have inappropriately concentrated

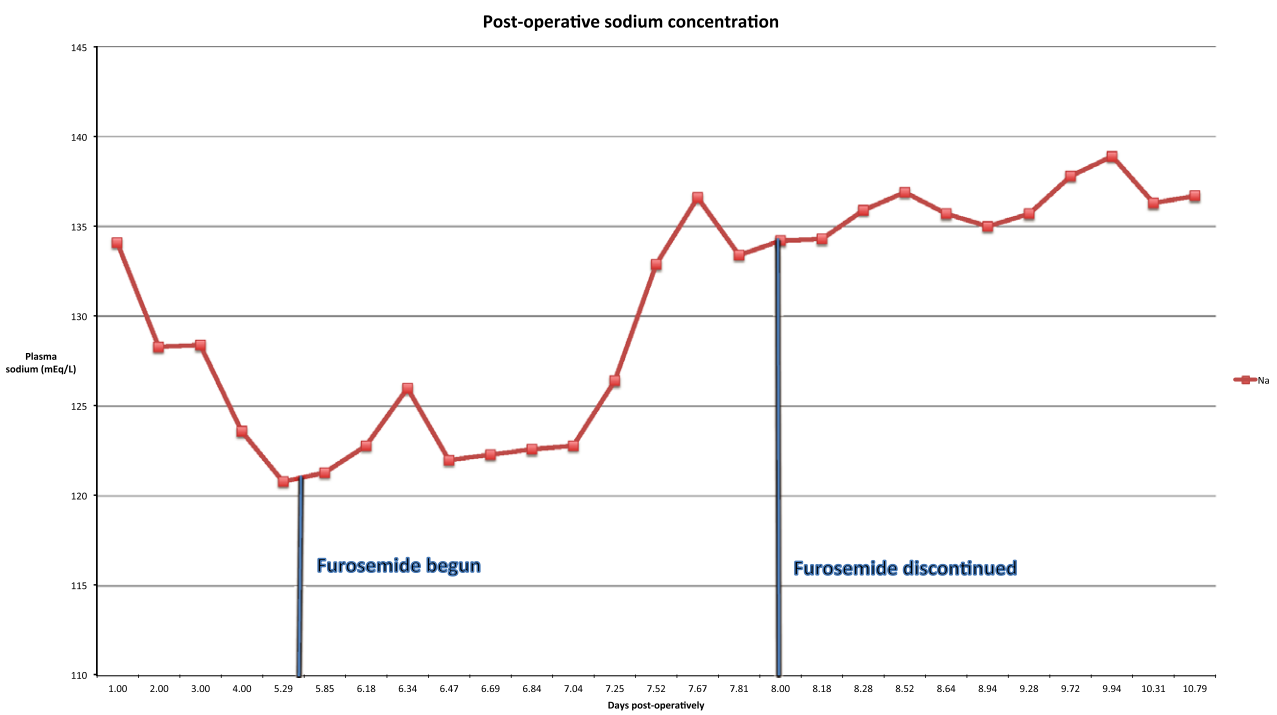

Fig 1. Plasma sodium concentration (mEq/L) measured during hospitalization. Initiation and discontinuation of furosemide depicted with vertical lines. .

urine for the plasma sodium concentration. Only 1 concentrated urine sample (USG >1.050) was documented in this dog. This urine sample was collected on the same day the lowest plasma sodium was recorded (ie, fifth postoperative day). Extremely concentrated urine in the presence of hyponatremia and furosemide treatment indicates that there was a strong response of the body to conserve water at this time. In addition, the frequency of urination (q2-4h) is not consistent with a diagnosis of SIADH. Another confounding factor in this report was the administration of furosemide, which results in diuresis and natriuresis, and which may have prolonged the reestablishment of a normal plasma sodium concentration. Administration of furosemide did not however result in worsening of hyponatremia, as it was initiated at the nadir of the plasma sodium concentration (Fig. 1). Serum ADH concentrations were not measured in this patient, primarily because humans with SIADH have serum ADH concentrations that are increased concentrations to different degrees, and a high ADH concentration is expected in any hyponatremic condition, thus the diagnostic utility of the test is low. Other difficulties in measuring serum ADH concentrations include substantial preanalytical sources of error and a complicated radioimmunoassay procedure.[17] A recent study validating the use of a human enzyme immunoassay for the measurement of canine ADH may make assessment of serum ADH concentration in dogs more convenient in the future.[19] The final limitation with this case report is that the plasma sodium concentration of this patient was not measured preoperatively, thus the actual decrease in plasma sodium concentration after anesthesia and surgery is an assumption based on all the other clinical laboratory findings.

In humans, the use of methyxanthines has been associated with increases in fractional excretion of sodium.[19–23] This effect is thought to be similar to that of thiazide-like diuretics, which promote urine production and inhibit solute reabsorption in the proximal tubule and diluting segment of the nephron. In this case, the temporal association of aminophylline treatment also parallels the worsening of plasma sodium concentrations, and some association with aminophylline treatment cannot be discounted. Aminophylline however was started after initial observation of hyponatremia and aspiration pneumonia was thought to be the driving force for the development of hyponatremia and SIADH.

Footnotes

[a] Unasyn Chicago, IL, USA
[b] Lactated Ringer's Chicago, IL, USA
[c] Plasmalyte Chicago, IL, USA
[d] NOVA biomedical, Waltham, MA

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Conflict of Interest Declaration: Authors disclosed no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Table S1. Fluid type/rate (ml/hr), plasma sodium and chloride values (mEq/L), weight (kg) and USG measurements obtained during hospitalization..