The Syndrome of Inappropriate Secretion of AntiDiuretic Hormone in Patients With Brucellosis

Ahmet Cumhuri Dulger,¹ Mehmet Aslan,^{2*} Mehmet Resat Ceylan,³ Sehmus Olmez,¹ Sevdegi Karadas,⁴ and Hayrettin Akdeniz³

¹Department of Gastroenterology, Medical Faculty, Yuzuncu Yil University, Van, Turkey

²Department of Internal Medicine, Medical Faculty, Yuzuncu Yil University, Van, Turkey

³Department of Infectious Disease and Clinical Microbiology, Medical Faculty, Yuzuncu Yil University, Van, Turkey

⁴Department of Emergency Medicine, Medical Faculty, Yuzuncu Yil University, Van, Turkey

Objective: Various studies have shown that a number of infectious disease causes syndrome of inappropriate antidiuretic hormone (SIADH). However, the relationship between infectious disease and SIADH is not yet fully known. In this prospective study, we aimed to assess the presence of SIADH in patients with brucellosis. **Patients and methods:** Thirty-five patients with acute brucellosis were retrospectively reviewed. The diagnosis of brucellosis was performed using the Wright test in connection with blood culture. SIADH was defined by euvoletic hyponatremia (serum sodium level lower than 135 mEq/l) with increased urinary sodium excretion (uri-

nary sodium higher than 40 mmol/l). **Results:** Of the 35 patients, 19 (54%) had SIADH; 20 (57%) also had hypouricemia (uric acid level lower than 4 mg/dl). Additionally, all of the studied patients had a high mean urinary sodium excretion rate (mean 132 mmol/l; range 40–224). Most importantly, the hyponatremic patients were more likely to have a lower albumin level ($P < 0.01$). **Conclusions:** SIADH is a major complication of brucellosis. The presence of SIADH could be a diagnostic tool for diagnosing brucellosis. Further larger randomized studies may confirm these findings. J. Clin. Lab. Anal. 29:366–369, 2015. © 2014 Wiley Periodicals, Inc.

Key words: SIADH; brucellosis; hyponatremia; urinary sodium

INTRODUCTION

Human brucellosis is a zoonosis caused by a facultative, nonmotile, rod-shaped intracellular Gram-negative bacterium of the genus *Brucella* (1). Brucellosis is also one of the most common zoonotic diseases worldwide, and it continues to pose a major public health problem in the Mediterranean basin and in Turkey (2). Eastern Turkey has been considered a hyperendemic area for human brucellosis (3). Brucellosis is becoming a major global health burden, particularly in developing countries. However, the current therapies are associated with significant side effects.

Hyponatremia is typically defined as a serum sodium concentration lower than 135 mmol/l and is considered to be a frequent complication of many clinical conditions (4). Hyponatremia may occur in the presence of an increase (hypervolemic), a decrease (hypovolemic), or near-normal (euvoletic) total body sodium. Hypona-

tremia with impaired urinary dilution can be related to primary disorders in the regulation of AVP secretion or can be secondary to nonosmotic stimuli such as hypovolemia or glucocorticoid and thyroid hormone deficiency. Euvoletic hyponatremia due to water retention in the presence of essentially normal sodium stores has been termed syndrome of inappropriate antidiuretic hormone (SIADH) (5).

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*Correspondence to: Dr. Mehmet Aslan, Department of Internal Medicine, Medical Faculty, Yuzuncu Yil University, 65000, Van, Turkey. E-mail: m.aslan301@mynet.com

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Alterations of the osmoregulatory system (reset osmostat) are believed to play a central pathogenic role in the development of SIADH, which is characterized by appropriate antidiuretic hormone (ADH) release at lower (inappropriate) serum osmolalities. The ectopic production of arginine vasopressin (AVP) by neoplasms such as lung cancer, the release of AVP by many drugs, and the exogenous administration of AVP could contribute to the development of SIADH by impairing osmoregulation (6).

Currently, the diagnosis of SIADH can only be established accurately by laboratory examinations and is considered a diagnosis of exclusion. In a patient with euvolemic hyponatremia, the possibility of diabetes mellitus, hypothyroidism, or Addison's disease should be excluded by measuring plasma glucose, TSH, and cortisol levels. If these tests are in normal ranges and there is no medical history of excessive vomiting or lung cancer, a diagnosis of SIADH can be made. Fluid restriction remains the cornerstone of the treatment for primary SIADH (7).

To our knowledge, there is limited information in the literature about SIADH and brucellosis (8, 9). Therefore, as a part of a broad evaluation of hyponatremia in brucellosis, we aimed to assess SIADH among patients with brucellosis in a single center.

PATIENTS AND METHODS

This prospective study was conducted between August 2011 and October 2011 in Yuzuncu Yil University, Faculty of Medical, Department of Internal Medicine and Infectious Disease and Clinical Microbiology. Our clinic is in a tertiary-care hospital that is located in the eastern part of Turkey, near the Iranian border of the country.

Thirty-five patients (mean age 38 years, range 16–73; 11 female and 24 male) with acute brucellosis were included. The diagnosis of brucellosis was confirmed by blood culturing using the standard Bactec method or serologic testing for *Brucella* agglutinins using the standard agglutinin test (Wright test). Any titer higher than 1:320 was considered positive for acute infection in connection with the clinical picture (10). At the time of admission, a compatible clinical picture, including arthralgia, nocturnal fever, sweating, chills, headache, and malaise, was also used to support the diagnosis of acute brucellosis.

SIADH was defined as follows: increased urinary sodium (>40 mmol/l with a normal dietary salt intake), decreased effective plasma osmolality (<275 mOsm/kg of water), clinical euvolemia, the absence of renal, thyroid, and adrenal disease, and no recent use of diuretic agents. Low plasma uric acid (<4 mg/dl) and low blood urea nitrogen (<10 mg/dl) levels were also used as supplemental tests to diagnose SIADH (11).

Following a 12-h fasting period, upon initial admission, blood samples for biochemical and hormonal anal-

yses prior to treatment were obtained. A venous blood gas analysis was performed to exclude patients with metabolic acidosis or alkalosis. The anion gap was calculated by the difference between the plasma concentrations of the major cations (sodium and potassium) and the major measured anions (chloride and bicarbonate). A 24-h urinary collection was also performed to establish urinary sodium excretion.

Patients with malignancy and pregnant women were also excluded from the study. Radiologic examinations such as chest X-ray and abdominal ultrasonography were performed on all the study patients. All patients were treated with combination rifampicin and doxycycline, according to current guidelines (doxycycline 100 mg PO twice daily for 45 days plus rifampicin 600–900 mg PO daily for 45 days) (1).

The study protocol was carried out in accordance with the Helsinki Declaration, as revised in 2000, and was approved by the local ethics committee. All subjects were informed about the study, and written consent was obtained from each subject.

STATISTICAL ANALYSIS

The data were recorded using Microsoft Excel, and SPSS 16.0 version was used for the statistical analysis. Nonparametric analyses were performed to compare the obtained data and used to calculate Pearson's correlations.

RESULTS

The age range for the 35 patients was 16–73 (mean: 38 years); there were 11 females, and 24 males. All patients also had a seropositive Wright test (a titer higher than 1:320), and 11 of the 35 patients (31.4%) also had a positive blood culture for brucellosis.

All of the study patients were euvolemic, and all of them had increased urinary sodium excretion. Nineteen (54%) also had SIADH-associated hyponatremia (serum sodium <134 mmol/l) with low plasma osmolality (<275 mOsm/kg). Twenty patients (57%) also had hypouricemia (plasma uric acid <4 mg/dl). There was no detected acid-base disturbance among the study population. Additionally, 16 (45%) patients had an elevated anion gap (anion gap value >10 mEq/l).

The statistical analysis showed that low albumin levels ($P = 0.014$), high LDH levels ($P = 0.005$), and high globulin levels ($P = 0.013$) were significantly associated with hyponatremia. Urinary sodium excretion was inversely associated with the blood urea nitrogen (BUN) levels ($P = 0.011$).

The patients were also followed for two months to assess whether any neurologic complications arose due to the hyponatremia. Of note, there were no documented

neurologic findings or deaths as a result of hyponatremia during the follow-up period.

DISCUSSION

No data on the prognostic impact of SIADH among patients with brucellosis have been published in the last two decades. This may be the first study to address an association between SIADH and the severity of brucellosis.

In the current study, 35 consecutive patients with acute brucellosis were prospectively evaluated with biochemical testing to determine the presence of SIADH. The results of this study highlight several risk factors for the development of SIADH in patients with brucellosis. The first key finding is that SIADH is highly prevalent among patients with brucellosis. The second key finding is that decreased plasma albumin and elevated plasma globulin levels are significantly associated with SIADH in brucellosis. Although increased urine sodium excretion has not yet been fully established as evidence of severe brucellosis, these findings suggested that the presence of SIADH correlates with hypoalbuminemia as well as hyperglobulinemia.

Hyponatremia in the absence of extracellular fluid (ECF) volume depletion is mostly due to increased persistent AVP secretion, resulting in a defect in water excretion. Hyperosmolality and volume depletion are the major causes of ADH secretion. Plasma sodium is the primary extracellular solute and is the major osmotic factor determining plasma osmolality as well as ADH release. The effective plasma osmolality is usually equal to $2\times$ the plasma sodium concentration, and the normal osmolality of the body water is between 280 and 290 mOsm/kg. Pseudohyponatremia refers to disorders in which marked elevations of substances, such as glucose, lipids, and plasma proteins, result in fictive hyponatremia. SIADH is characterized by euvolemic hyponatremia (hypoosmolar plasma) associated with inappropriate hyperosmolar urine (a urine sodium concentration usually above 40 mmol/l). A diagnosis of SIADH is required in the presence of normal renal, adrenal, and thyroid functions. Patients typically have hypouricemia due to the uricosuric state induced by volume expansion (4).

Alterations in serum sodium levels are rarely observed in patients with infectious diseases and are easily overlooked by clinicians. However, the presence of long-lasting hyponatremia in the case of acute infection may be a significant source of morbidity and extended hospitalization (12).

The basic mechanism of infectious disease-related SIADH is not well defined and has been mostly linked to hypoxia and intravascular volume depletion (11). In general, it is known that infections of the central nervous system (CNS) (meningitis, encephalitis, and abscess)

and pulmonary infections (pneumonia, tuberculosis) may cause SIADH (12). It has been hypothesized that ectopic ADH production triggered by a non-neoplastic inflammatory condition is responsible for SIADH (13). However, the exact mechanisms are still unclear.

Brucella-associated SIADH was reported once in Kuwait two decades ago. However, signs of severe disease such as hypoalbuminemia and hyperglobulinemia also playing a role were not mentioned in those first 14 documented cases (8). A case report of Brucella-related SIADH was described in a recent report from Italy (14); however, this report described a patient with neurobrucellosis-associated SIADH. It is also known that SIADH is commonly found in CNS infections. A recent case report from Turkey also suggested that acute brucellosis without neurologic involvement may be associated with SIADH (9).

Hypouricemia is a harbinger of increased tubular excretion of uric acid and is commonly detected in SIADH patients (15). The results of our study indicate that hypouricemia is a frequent biochemical finding in patients with brucellosis. However, there was no association between uric acid levels and the severity of the disease. We also concluded that plasma uric acid, which is a simple biochemical test, can be used as a diagnostic tool for disease detection in brucellosis patients.

The present study also shows that lower blood urea nitrogen levels are significantly correlated with higher urine sodium levels. Indeed, it is known that the ECF volume is increased in SIADH (15). In SIADH, the serum sodium and chloride concentrations are decreased by dilution, but the serum bicarbonate and potassium levels are usually in normal ranges (16). As patients with neurobrucellosis were excluded from our study, our data revealed the clinical evidence of pure SIADH among patients who did not have neurobrucellosis.

Our study showed that increased urine sodium excretion is a likely predictor of severe infection, which was determined by both hypoalbuminemia and hyperglobulinemia. In addition, SIADH was found to be highly prevalent in patients with brucellosis. It may be concluded that each of these findings increases in parallel with the severity of the brucellosis infection. Hyper- or hypopotassemic patients were excluded from our study, and the serum bicarbonate concentrations of the study patients were also in normal ranges.

However, approximately half of the patients had an increased anion gap. As a rule, a significant increase in the anion gap is typically due to an elevation in the concentration of unmeasured anions, which can be induced by hypovolemia-related hemoconcentration or concurrent lactic acidosis (17). We postulate that this phenomenon may be the result of hemoconcentration in our Brucella-infected patients.

This study has several limitations. First, few patients were enrolled in the current study. Second, the study sample was mostly limited to patients with acute brucellosis. Moreover, we did not determine urinary osmolality, which is an adjunctive method for diagnosing SIADH.

SIADH is a major complication of brucellosis. Our study showed that increased urine sodium excretion is a likely predictor of severe infection, which was determined by both hypoalbuminemia and hyperglobulinemia. In addition, SIADH was found to be highly prevalent in patients with brucellosis. The presence of SIADH could be a diagnostic tool for diagnosing brucellosis in the future. Further, larger randomized studies may confirm the findings.

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest regarding the publication of this article.

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