MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 3129-3134
DOI: 10.12659/MSM.899977

Received: 2016.06.08
Accepted: 2016.08.01
Published: 2016.09.03

The Syndrome of Inappropriate Secretion of Anti-Diuretic Hormone (SIADH) and Brucellosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BE 1,2 Keziban Asli Bala
AC 1,2 Murat Doğan
D 1,2 Sultan Kaba
F 1 Sinan Akbayram
B 1 Oktay Aslan
G 1,2 Selami Kocaman
G 1,3 Gülsüm İclal Bayhan
B 1 Lokman Üstyol
F 1 Nihat Demir

1 Department of Pediatrics, Medical School, Yüzüncü Yil University, Van, Turkey
2 Division of Pediatric Endocrinology, Medical School, Yüzüncü Yil University, Van, Turkey
3 Division of Pediatric Infectious Diseases, Medical School, Yüzüncü Yil University, Van, Turkey

Corresponding Author: Keziban Asli Bala, e-mail: kezibanaslibulan@gmail.com
Source of support: Departmental sources

Background: Our study aimed to demonstrate the frequency of the syndrome of inappropriate ADH secretion (SIADH) and associated factors during the course of brucellosis in children and adolescents.

Material/Methods: The study included children and adolescents aged 0–18 years old diagnosed with brucellosis between 2012 and 2014. The data were collected from patient charts. The diagnosis of brucellosis was made based on titrations >1:160 in standard Wright tube agglutination tests and/or positive culture tests. SIADH diagnosis was made based on the following criteria: euvolemic hyponatremia, serum Na^+ <135 mmol/L, presence of serum hypoosmolarity (serum osmolarity <275 mOsm/L), increased urinary sodium (>25 mmol/L with normal dietary salt intake), low uric acid (<2 mg/dL), absence of kidney, thyroid or adrenal disease, and any anti-diuretic use.

Results: The study included 160 children and adolescents with mean age of 9.58±3.95 years (range: 2–18 years) including 70 girls (43.8%) and 90 boys (56.2%). When the patients were stratified based on SIADH, it was found that SIADH was present in 35 patients (21.9%). SIADH was associated with elevated glucose (p<0.001), ALT (p<0.05), AST (p<0.05), LDH (p<0.001), CRP (p<0.001), and MPV (p<0.001); and decreased potassium (p<0.05), chloride (p<0.001), albumin (p<0.001), total protein (p<0.05), and hemoglobin (p<0.05) levels.

Conclusions: Our study reports on the frequency, clinical characteristics, predisposing factors, and management of SIADH that can develop in children and adolescents diagnosed with brucellosis.

MeSH Keywords: Adolescent • Brucellosis • Child • Inappropriate ADH Syndrome

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/899977

2036 4 1 22

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Brucellosis is a zoonotic disease caused by Gram-negative bacteria, namely *Brucella spp*. Humans can be infected by the ingestion of raw dairy products, the consumption of infected meat from sheep, goat, cattle, water buffalo, camel, and pig and close contact with the secretions from infected animals Main symptoms include arthralgia of the large joints, fever, and myalgia. Brucellosis usually causes abortion and sterility in animals; however, it may cause a variety of clinical manifestations in humans including fever and septicemia, and even multiple organ involvement [1]. Currently, brucellosis remains an important public health issue in Turkey. It can affect people at any age, and children may represent 20–25% of all case [2].

Hyponatremia defined as serum sodium level <135 mEq/L is the most commonly seen electrolyte disorder in hospitals. Hyponatremia can result in mortality due to misdiagnosis and mistreatment in some occurrences, although causes of hyponatremia can be readily identify; hyponatremia is seen in 3% of the hospitalized children [3]. The most serious consequences of hyponatremia are cerebral edema and encephalopathy [4]. Before initiating treatment, and immediately after detection of hyponatremia, the presence of accompanying hypoosmolarity should be evaluated. If hyponatremia is accompanied by hypoosmolarity, it should be determined if there is a reduction in free fluid clearance by calculating urinary osmolarity [5,6]. Another marker is urinary Na^+ excretion. In general, urinary sodium concentration <25 mEq/L suggests loss of effective volume, whereas urinary sodium concentration >25 mEq/L suggests renal tubular dysfunction, diuretic use, or syndrome of inappropriate ADH secretion (SIADH). SIADH is a heterogeneous disorder which is among the causes of euvolemic hyponatremia. It is a condition where the ADH level is inappropriately high in terms of normal physiology despite low serum osmolarity. Particularly, it occurs in bronchial carcinoma, pneumonia, acute respiratory failure, hydrocephaly, encephalitis, meningitis, psychosis, spinal cord lesions, and as a result of the use of ACE inhibitors, anticonvulsant, anti-neoplastic agents, anti-Parkinson drugs, lipid lowering agents, tricyclic antidepressants, and oral hypoglycemic agents [7]. When untreated or improperly treated hyponatremia leads to serious consequences [4]. The treatment of hyponatremia also varies depending on the etiological factors related to volume status. For this reason, it is important to determine the frequency and clinical outcome of SIADH with brucellosis diagnosis in the pediatric population, and also one reason euvolemic hyponatremia is an important consideration. In the literature, there are only two articles addressing the development of SIADH during the course of brucellosis and both studies were conducted on adult patients [8,9]. Our study is the first published study demonstrating the frequency of SIADH and associated factors in children and adolescents with brucellosis; thus, we think our study will be an important addition to the literature.

Material and Methods

The study included children and adolescents aged 0–18 years who were diagnosed with brucellosis between 2012 and 2014. The data were gathered from patient charts. The diagnosis of brucellosis was made based on titrations >1:160 in standard Wright tube agglutination tests and/or positive culture tests [10]. SIADH diagnosis was made based on following criteria: euvolemic hyponatremia, serum Na^+ <135 mmol/L, presence of serum hypoosmolarity (serum osmolarity <275 mOsm/L), increased urinary sodium (>25 mmol/L with normal dietary salt intake), low uric acid (<2 mg/dL), absence of kidney, thyroid or adrenal disease or any anti-diuretic use. Plasma osmolarity was calculated by using following formula: 2× (serum Na^+ + K^+) + glucose (mg/dL)/18 + BUN (mg/dL)/2.8 [7].

Our pediatric clinic has extensive experience in the management of patients with brucellosis. Thus, clinicians in our pediatric department are alert for complications that may develop in patients with brucellosis and we closely monitor patients for these complications, especially for hyponatremia. Particularly, all patients are closely monitored during treatment by routine evaluations in order to prevent overlooking hyponatremia, since hyponatremia is more frequently observed in patients with higher disease severity and degree of inflammation. Thus, biochemical evaluations, thyroid functions, ACTH and cortisol values, urinalysis, urinary density, serum glucose levels, and liver and kidney functions are routinely assessed in all hospitalized patient. In our pediatric clinic, overall 560 patients were diagnosed with brucellosis between 2012 and 2014. Of these cases, 400 were excluded from this study due to missing laboratory data. Overall, 160 patients who had all laboratory data needed were included in the study. In addition, patients with chronic diseases, those on drug therapy, or those with neurobrucellosis were excluded. After extracting data from patient charts, demographic characteristics were compared between patients with or without SIADH.

Statistical analyses

Statistical analyses were performed by using SPSS for Windows version 13.0. For comparison between groups, Student's *t*-test was used for parametric variables with normal distribution whereas chi-square test was used for non-parametric variables. $p<0.05$ was considered to be statistically significant. Parametric variables were expressed as mean ±SDS while non-parametric data were expressed as count (%).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

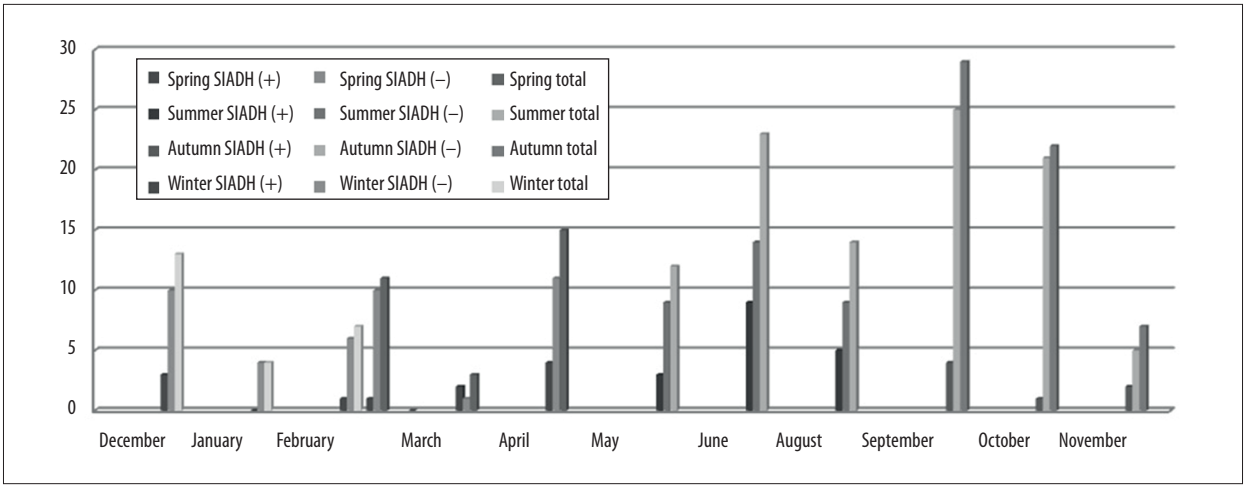

Figure 1. Distribution according to months and seasons at presentation.

Table 1. Comparison according to age and gender.

	Syndrome of Inappropriate ADH Secretion		p
	Present	Absent	
	Mean ±SDS (min–max)	Mean ±SDS (min–max)	
Age (yr)	9.14±3.92 (2–16)	9.7±3.96 (2-18)	>0.05
Gender			
Female (n (%))	17 (48.6)	72 (57.6)	>0.05
Male (n (%))	18 (51.4)	53 (42.4)	

Results

The study included 160 children and adolescents with a mean age of 9.58±3.95 years (range: 2–18 years) including 70 girls (43.8%) and 90 boys (56.2%). Brucella agglutination tests were positive in all patients while only 20% had positive culture tests for brucella bacteria. All patients were euvolemic at presentation and urinary sodium excretion was increased in all patients with SIADH. There was no patient with acid-base disorder. ACTH and cortisol values were within normal ranges. Figure 1 shows time of year at presentation according to months and seasons. There was a significant increase in the number of cases during summer and autumn ($p<0.001$). When the patients were stratified based on SIADH, it was found that SIADH was present in 35 patients (21.9%). Table 1 presents comparison of cases with or without SIADH according to age and gender. No significant difference was found between cases ($p>0.05$). Significant differences were detected when patients were compared for time of presentation ($p<0.05$). The patients with SIADH presented in summer in particular, while those without SIADH were clustered in autumn. No significant differences were seen in physical findings (hepatomegaly, splenomegaly, fever, lymphadenopathy) at presentation ($p>0.05$). Table 2 presents comparison of laboratory data between groups. The SIADH was associated with elevated glucose ($p<0.001$), ALT ($p<0.05$), AST ($p<0.05$), LDH ($p<0.001$), CRP ($p<0.001$), and MPV ($p<0.001$); and decreased potassium ($p<0.05$), chloride ($p<0.001$), albumin ($p<0.001$), total protein ($p<0.05$), and hemoglobin ($p<0.05$) levels. Table 3 presents comparisons of hematological values between groups. There was higher CRP ($p<0.001$) and MPV values ($p<0.001$) and lower hemoglobin levels ($p<0.05$) in the group with SIADH. Table 4 presents comparison of thyroid hormones, ACTH, cortisol, and urinary and plasma osmolarity between groups. There were no significant differences between groups ($p>0.05$). Plasma and urinary osmolarity were found to be significantly lower in the group with SIADH ($p<0.001$ and $p<0.001$, respectively). The uric acid levels were found to be low in 26 (74.3%) of the patients in the group with SIADH and 5% of the patients in the group without SIADH ($p<0.001$).

The patients were treated after stratifying by age (younger or older than 8 years) based on international standards. The patients younger than 8 years of age were treated with

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Comparison of biochemical parameters between groups.

	SIADH		p
	Present	Absent	
	Mean ±SDS	Mean ±SDS	
Serum glucose (mg/dL)	106.6±25.6	93.6±12.6	**<0.001**
Blood urea nitrogen (mg/dL)	11.4±6.1	14.0±6.0	>0.05
Creatinine (mg/dL)	0.4±0.2	0.5±0.1	>0.05
Sodium (mEq/L)	130.8±3.4	141.4±25.9	**<0.05**
Potassium (mEq/L)	4.1±0.6	4.4±0.5	**<0.05**
Chloride (mEq/L)	99.7±5.4	104.2±2.9	**<0.001**
Aspartate amino transferase (U/L)	133.2±341.8	49.6±7.7	**<0.05**
Alanine amino transferase (U/L)	111.5±335.0	44.4±56.4	**<0.05**
Alkaline phosphatase (U/L)	389.2±215.1	463.4±296.3	>0.05
Gama glutamyl transferase	35.6±49.5	38.3±58.5	>0.05
Total Bilirubin (mg/dL)	0.8±1.2	0.4±0.5	>0.05
Direct Bilirubin (mg/dL)	0.5±0.9	0.2±0.4	>0.05
Total Protein (g/dL)	6.7±0.7	7.4±0.9	**<0.05**
Lactic dehydrogenase (U/L)	1110.9±889.2	598.6±239.6	**<0.001**
Albumin (g/dL)	3.7±0.6	4.3±0.4	**<0.001**

Table 3. Comparison of hematological parameters between groups.

	SIADH		p
	Present	Absent	
	Mean ±SDS	Mean ±SDS	
Leukocyte ($\times 10^3 \cdot mm^{-3}$)	6.5±3.4	7.1±2.7	>0.05
Hemoglobin (g/dL)	11.8±1.8	12.5±1.5	**<0.05**
Platelet ($\times 10^3 \cdot mm^{-3}$)	242.4±137.5	284.4±116.5	>0.05
Mean erythrocyte volume (fL)	76.0±17.7	76.7±8.9	>0.05
Mean distribution volume (%)	14.8±2.5	15.7±11.9	>0.05
Mean platelet volume (fL)	8.6±2.3	7.6±1.1	**<0.001**
Platelet distribution volume (%)	13.4±3.9	15.5±2.6	>0.05
Erythrocyte sedimentation rate (mm/h)	25.2±15.5	22.3±13.8	>0.05
C-reactive protein (mg/L)	39.2±49.4	14.1±18.1	**<0.001**

trimethoprim-sulfamethoxazole + rifampicin, and the patients older than 8 years of age were treated with tetracycline + rifampicin. The duration of treatment was 6 week and no complications were observed during treatment. The patients had dramatic responses to fluid restriction during hyponatremia and all patients recovered without complication.

Discussion

In our study, the frequency of SIADH was found to be 21.9% among children and adolescents with brucellosis, representing a rather high frequency. In the comparison of patients with or without SIADH, we found that SIADH was associated with high blood glucose, ALT, AST, LDH, CRP, and MPV levels, and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 4. Comparison of hormonal parameters between groups.

	SIADH		p
	Present	Absent	
	Mean ±SDS	Mean ±SDS	
TSH (mU/mL)	2.18±0.80	2.54±0.77	>0.05
Free T4 (µg/dL)	1.48±0.10	1.37±0.26	>0.05
ACTH (pg/mL)	29.00±10.46	28.75±10.19	>0.05
Cortisol (mg/dL)	12.21±2.48	11.52±2.38	>0.05
Plasma osmolarity (mosm/lt)	274.67±5.50	295.27±6.32	**<0.001**
Urine osmolarity (mosm/kg)	239.44±90.32	498.00±190.31	**<0.001**

decreased potassium, chloride, albumin, total protein, and hemoglobin values. In the literature, there are only two original publications on the frequency of SIADH in patients with brucellosis, while there are a limited number of case reports. In the study by Aysha et al., prospective evaluations were performed in 58 of 270 patients [8]. The study by Dulger et al. prospectively evaluated 35 adult patients with brucellosis and reported SIADH frequency of 57% and SIADH was associated with high LDH, low albumin, and high globulin levels [9]. Our results are in agreement with this study. In addition, our study found that high AST, ALT, CRP, and MPV levels might be associated with the disease, suggesting a potential relationship between severity of inflammation and SIADH.

In the study by Dulger et al., it was suggested that the mechanism underlying SIADH development was not fully understood but it may be associated with hypoxia and intravascular volume depletion in some cases and excessive ADH production in SIADH developing during CNS infections [9]. However, other authors have concluded that the etiology of SIADH remains unclear in patients with brucellosis [11–13].

It should be noted that SIADH is the most frequent cause of hyponatremia, and reflects the severity of the underlying disease and is strongly associated with mortality. In SIADH, hyponatremia is associated with normovolaemia. Clinical features are mainly neurological and can lead to death, but mechanisms of adaptation can limit cerebral edema. Etiologies are classified into six groups: , neurologic disorders, infections (mainly cerebral, meningeal, and pulmonary), drugs (in particular antidepressants), tumors, genetic causes, and idiopathic causes [14]. In particular, infections of the central nervous system (CNS) like meningitis and encephalitis can cause SIADH by releasing excess ADH. In addition, hyponatremia resulting from SIADH can be also a frequent complication during pulmonary infections [15]. In case of pneumonia, hypoxia and intravascular volume depletion are the primary mechanisms resulting in SIADH development. Reset osmostat, a variant of SIADH in which the serum sodium concentration is normally regulated (and is therefore stable) at a lower level (typically between 125 and 135 mmol/L), has been reported in infectious diseases such as tuberculosis and malaria [16,17]. It is noteworthy to mention that pro-inflammatory cytokine interleukin-6 (IL-6) is found to be elevated in several infections (e.g., pneumonia, malaria), suggesting non-osmotic ADH secretion [18,19]. However, anorexia that may develop during the course of infection can also cause SIADH [20]. Hyponatremia in HIV disease is associated with SIADH, volume depletion, and adrenal insufficiency; and patients with acquired immune deficiency syndrome (AIDS) have been reported to have abnormal adrenal cortical function [21]. Madariaga at al. reported a case of an HIV positive patient who presented with hyponatremia and a physical examination suggestive of hypovolemia, and the patient responded well to the administration of a mineralocorticoid hormone [22]. Thus, we think that SIADH may result from non-osmotic stimulation of ADH secretion as a result of excessive amounts of pro-inflammatory cytokines released, such as IL-6, given the fact that SIADH is particularly seen in patients with higher degrees of inflammation and disease severity.

Symptomatic acute hyponatremia is a therapeutic emergency. When hyponatremia is asymptomatic, fluid restriction with salt intake is generally sufficient, but urea can be an alternative therapy, although for chronic SIADH there is currently no specific recommendation. Fluid restriction is not always feasible; and urea has proven efficacy, tolerance, and no associated long-term harm. Vaptans (vasopressin receptor antagonists) are shown to have good tolerance and efficacy for the correction of hyponatremia caused by SIADH in patients with moderate hyponatremia and in asymptomatic patients. In the only study comparing vaptans and urea, efficacy and tolerance were found to be comparable. Currently, urea seems to be the first-line treatment of hyponatremia in SIADH due to its cost although further studies are needed [14]. In our study, the treatment of hyponatremia was resolved with appropriate treatment

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

of brucellosis with antibiotics and fluid restriction. No complications were seen.

Conclusions

In conclusion, this study is important in several respects; it is the first study in the literature demonstrating the frequency of SIADH in children with brucellosis. Second, the study showed that SIADH had a high frequency of 21.9% in patients with brucellosis, and SIADH was more likely to be seen with increasing disease severity. Third, it showed that SIADH in patients with brucellosis had a dramatic response to fluid restriction.

Our study reports on the frequency, clinical characteristics, predisposing factors of SIADH that can develop in children and adolescents diagnosed with brucellosis and can be used as a guide for identifying and managing SIADH in this population.

Conflict of interest

There is no conflict of interest.

Statement

Research funding: None declared.

References:

1. Young EJ: Brucella species. In: Mandell GL, Bennett JE, Dolin R (eds.), Principles and practice of infectious diseases. 6th ed., Philadelphia: Churchill Livingstone; 2005; 2669–72
2. Akbayram S, Dogan M, Peker E et al: Thrombotic thrombocytopenic purpura in a case of brucellosis. Clin Appl Thromb Hemost, 2011; 17(3): 245–47
3. Moritz ML, Ayus JL: Disorders of water metabolism in children: Hyponatremia and hypernatremia. Pediatr Rev, 2002; 23(11): 371–80
4. Fraser CL, Arieff AI: Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med, 1997; 102: 67–77
5. Rose DR: Hypoosmolal states-hyponatremia. Clinical Physiology of Acid-Base and Electrolyte Disorders. 4th ed. New York: McGraw-Hill; 1994; 651–94
6. Weisberg LS: Pseudohyponatremia: A reappraisal. Am J Med, 1989; 86: 315–18
7. Srivatsa A, Majzoub JA: Disorders of water homeostasis. Lifshitz F (ed.), Pediatric Endocrinology, Informa Healthcare, New York: 2007; 651–92
8. Aysha MH, Shayib MA: Syndrome of inappropriate secretion of antidiuretic hormone in brucellosis. J Infect, 1988; 17(1): 29–33
9. Dulger AC, Aslan M, Ceylan MR et al: The syndrome of inappropriate secretion of antidiuretic hormone in patients with brucellosis. J Clin Lab Anal, 2015; 29(5): 366–69
10. Akbayram S, Dogan M, Akgun C et al: An analysis of children with brucellosis associated with isolated thrombocytopenia. Clin Appl Thromb Hemost, 2011; 17(6): E36–38
11. Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med, 2007; 356: 2064–72
12. Liamis G, Milionis HJ, Elisaf M: Hyponatremia in patients with infectious diseases. J Infect, 2011; 63: 327–35
13. Lee P, Ho KK: Hyponatremia in pulmonary TB: Evidence of ectopic antidiuretic hormone production. Chest, 2010; 137: 207–8
14. Frouget T: [The syndrome of inappropriate antidiuresis]. Rev Med Interne, 2012; 33(10): 556–66 [in French]
15. Dixon BS, Anderson RJ: Pneumonia and the syndrome of inappropriate antidiuretic hormone secretion: don't pour water on the fire. Am Rev Respir Dis, 1988; 138: 512–13
16. Hill AR, Uribarri J, Mann J, Berl T: Altered water metabolism in tuberculosis: Role of vasopressin. Am J Med, 1990; 88: 357–64
17. Miller LH, Makaranond P, Sitprija V et al: Hyponatraemia in malaria. Ann Trop Med Parasitol, 1967; 61: 265–79
18. Mastorakos G, Weber JS, Magiakou MA et al: Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: Potential implications for the syndrome of inappropriate vasopressin secretion. J Clin Endocrinol Metab, 1994; 79: 934–39
19. Clemans DL, Bauer RJ, Hanson JA et al: Induction of proinflammatory cytokines from human respiratory epithelial cells after stimulation by non typeable *Haemophilus influenzae*. Infect Immun, 2000; 68: 4430–40
20. Hayashi E, Ohta N, Yamamoto H: Syndrome of inappropriate secretion of antidiuretic hormone associated with strongyloidiasis. Southeast Asian J Trop Med Public Health, 2007; 38: 239–46
21. Norbiato G, Galli M, Righini V, Moroni M: The syndrome of acquired glucocorticoid resistance in HIV infection. Baillieres Clin Endocrinol Metab, 1994; 8(4): 777–87
22. Madariaga H, Kumar A, Khanna A: A rare mechanism of hyponatremia in HIV disease. Am J Case Rep, 2015; 16: 707–10

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]