Original Research

Prevalence of hyponatremia in pulmonary tuberculosis – A pilot study from a tertiary care center in south India

Bhanu Rekha Bokam[1], Vijayalakshmi Udipi Badikillaya[2]

[1]Department of Pulmonary Medicine, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation, Chinoutpalli, Vijayawada, Andhra Pradesh, India.
[2]Department of Biochemistry, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation, Chinoutpalli, Vijayawada, Andhra Pradesh, India.
Correspondence to: Vijayalakshmi Udipi Badikillaya, E-mail: [drpvijayalakshmi68@gmail.com]

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Abstract

Background: Pulmonary tuberculosis (PTB) is one of the common illnesses in developing countries which can present with various clinical manifestations. TB can induce hyponatremia via several mechanisms. The prevalence of hyponatremia is variable in previous studies.

Objectives: To study serum sodium levels and prevalence of hyponatremia in PTB patients.

Material and Methods: It was a cross-sectional study. Patients of 18 years and above, having active PTB over 2 years were included. Demographic and laboratory data of the patients were recorded and analysed.

Results: A total of 410 patients having PTB of an age ranging from 18 to 80 years; mean of 44.49 ± 13.8 years were taken. About 55.12% were in the age group of 40–60 years and 72.2% were males. Out of 410, 254 (61.95%) had hyponatremia, i.e., serum sodium < 135 mmol/L in which 182 (71.65%) were males and 72(28.34%) females. Most patients 156 (38.05%) had mild hyponatremia, 72 had moderate and only 26 had severe hyponatremia. Briefly, 132(84%) in the mild hyponatremia category, 48(62.6%) in the moderate and 26(92.3%) in the severe hyponatremia were sputum AFB positive. Patients having extensive lung field lesions had severe hyponatremia (76.9%). Most patients were asymptomatic; only 6 patients with severe hyponatremia were hypotensive and 2 of them required vasopressors.

Conclusions: Hyponatremia was observed to the extent of 61% in patients with PTB, with mild and asymptomatic hyponatremia being more common. Severity of hyponatremia was directly proportional to sputum positivity and extensive involvement of pulmonary parenchymal lesions.

KEY WORDS: Hyponatremia, pulmonary tuberculosis, AFB

Introduction

Pulmonary tuberculosis (PTB) is one of the common diseases with high prevalence of mortality and morbidity in developing countries. Despite the advances in diagnosis and treatment TB remains still one of the world's biggest threats.

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Globally, TB prevalence in 2015 was 42%. Briefly, 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women and 1.0 million children. Of the 9.6 million new TB cases in 2014, 58% were in the South-East Asia and Western Pacific regions. India, Indonesia and China had the largest number of cases: 23%, 10% and 10% of the global total, respectively. In 2014, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). The toll comprised 890,000 men, 480,000 women, and 140,000 children. TB now ranks alongside HIV as a leading cause of death worldwide.[1] India is the country with the highest burden of TB. India ranks 14th out of 22 Countries with high TB Prevalence. The World Health Organization (WHO) statistics for 2014 give an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 9.6 million. The estimated TB prevalence

figure for 2014 is given as 2.5 million.[1] It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB and the majority of people with TB are sputum smear positive.[2]

Hyponatremia is considered as one of the most common and important electrolyte abnormalities which must be considered in all seriously ill hospitalized patients.[3] It is a common complication of malignancy, neurosurgical conditions, cardiac, liver, and renal failure and pulmonary disorders. Hyponatremia occurs in 15–30% of hospitalized patients.[3,4] The commonest cause of hyponatremia is the syndrome of in appropriate antidiuretic hormone (SIADH).[5] This syndrome was first described by Bartter and Schwartz.[6] Hyponatremia is defined as a serum sodium concentration less than 135 mmol/L, between 130 and 134 mmol/L as mild hyponatremia, between 125 and 129 mmol/L as moderate hyponatremia and severe hyponatremia as a serum sodium concentration < 125 mmol/L.[7]

PTB is considered as one of the common illnesses in developing countries which can present with various clinical manifestations. TB can induce hyponatremia via several mechanisms like local invasion to the adrenal glands (adrenal insufficiency),[8,9] local invasion to hypothalamus or pituitary gland,[10,11] tubercular meningitis,[12–14] and inappropriate ADH secretion via pulmonary infection.[15–17] Tuberculosis (TB) is known to affect adrenal glands directly. Adrenal destruction by TB may lead to overt or subclinical adrenal insufficiency and it continues to be the most common cause of Addison's disease in India.[18]

Various inflammatory diseases including pneumonia, severe acute respiratory distress syndrome, TB, meningitis, encephalitis, human immunodeficiency virus infections and malaria are associated with the development of hyponatremia.[19] However, the pathophysiology of hyponatremia with these conditions remains elusive. Recent research has demonstrated that inflammatory cytokines, such as interleukin (IL)-1β and IL-6, are involved in the development of hyponatremia.[20–22] While SIADH is a well-known complication of pulmonary inflammatory and infective diseases, the mechanism is poorly understood and has been attributed to hypoxia and decreased vascular volume. Hyponatremia is attributed to the inappropriate production of ADH from the posterior pituitary, which is therefore eutopic.[22,23]

Mild hyponatremia (130–134 mmol/L) has traditionally been regarded to be asymptomatic, with nausea, headaches, and anorexia occurring at moderate hyponatremia (125–129 mmol/L) and more severe hyponatremia (< 125 mmol/L) associated with confusion, coma, seizures or even death. However, the classic publication of Arieff and colleagues demonstrated clearly that symptoms can occasionally occur at higher plasma sodium concentrations, with severe hyponatremia sometimes producing no perceived ill effects.[24]

Aims and Objectives: To study the serum sodium levels and to see the prevalence of hyponatremia in patients with PTB.

Material and Methods

It was a cross-sectional observational study, patients presented to the department of Pulmonary medicine Dr PSIMS & RF over a period of two years from 2014 to 2016 were studied. Diagnosis of PTB was made on the basis of clinical presentation, chest radiograph findings and microscopic detection of acid-fast bacilli (AFB).

Inclusion criteria: Patients aged 18 years and above, diagnosed as having active PTB.

Exclusion criteria: Patients with old TB, renal failure patients, endocrine abnormalities, patients receiving diuretics and medications related to SIADH. This study was approved by the institutional ethical committee. Case records of the patients having PTB were collected. Demographic profiles and laboratory data of the patients were recorded and analysed.

Serum sodium concentration less than 135 mmol/L was taken as hyponatremia. Patients were divided into three groups, serum sodium concentration between 130 and 134 mmol/L as mild hyponatremia, between 125 and 129 mmol/L as moderate hyponatremia and severe hyponatremia as a serum sodium concentration < 125 mmol/L .

Reading of the chest radiographs was focused on extent of lung parenchymal lesion as upper lung field and both lung fields (extensive). Upper lung field was defined as lesion involving the upper zone and lower lung field as the involvement of mid and lower zone.

The grade of sputum smear at base line was defined as: negative -no bacilli in 100 high power fields; scanty as less than 10 bacilli in 100 high power fields; 10–99 bacilli in 100 high power fields = 1+; 1–10 bacilli in one high power field = 2+; more than 10 bacilli in one high power field = 3+. The pooled data were described as mean with S.D. and frequencies.

Results

About 410 patients having active PTB were taken into the study of an age ranging from 18 to 80 years with a mean of 44.49 ± 13.8 years. Most of the patients were in the age group of 40–60 years, i.e., 55.12% and more patients were males, 72.2%. The mean serum sodium level in the subjects was 133.1 ± 5.8 mmol/L. The age, sex distribution, and mean serum sodium levels are shown in Table 1. As shown in the table the mean sodium levels are less in the age group of >60 years and in males when compared to females.

Out of 410 patients 254 had hyponatremia, i.e., serum sodium levels <135 mmol/L (61.95%) in which 182 were males (71.65%) and 72 (28.34%) were females, as shown in Figure 1. As shown in Table 2 most of the patients had mild hyponatremia with serum sodium levels of 130–134 mmol/L, i.e., 156 (38.05%) with 72 patients having moderate hyponatremia of 125–129 mmol/L and only 26 with severe hyponatremia of <125 meq/l. There were more females than males with mild (45.6% versus 35.1%, respectively) and severe hyponatremia (8.7% versus 5.4%, respectively). In the moderate group

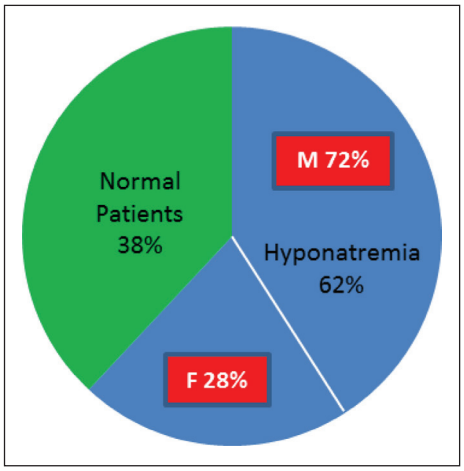

Figure 1: Prevalence of hyponatremia.

there were more males when compared to females (20.9% versus 8.7%).

As shown in Table 3, of the 156 patients with mild hyponatremia, 132 were sputum AFB positive (84%), in moderate 48 out of 72 patients (62.6%) and 24 out of 26 with severe hyponatremia were sputum positive (92.3%). As per the radiographic presentation of pulmonary lesions, patients with both upper and lower lung field lesions, i.e., extensive had severe hyponatremia (76.9%).

Out of 410 patients, 138 had diabetes as a comorbidity (33.65%) and 10 have retroviral disease. Of 138 with Diabetes Mellitus (DM) and Pulmonary Koch's, 80 had hyponatremia 65.21%, i.e., the prevalence is more when compared to pulmonary Koch's without comorbidity. Most patients with hyponatremia were asymptomatic, only 6 patients with severe hyponatremia were hypotensive, out of them 2 patients required vasopressors.

Discussion.

About 410 patients having active PTB were taken as subjects for the study. Their ages ranged from 18 to 80 years with a mean of 44.4 ± 13.81 years. Around 72.2% of the subjects were males, the rest being females. Out of 410 subjects with PTB 254 (61.9%) patients had hyponatremia, a serum sodium value less than 135 mmol/L with 182 (72%) males and 72 (28%) females.

In a study by Jafari et al in Tehran reported that the mean age of the patients was 59 ± 20 years ranging from 13 to 102 years.[25] In the present study most of the patients belonged to the ages ranging from 40 to 60 years (55.12%). Mukherjee et al in their study reported that more subjects were in the age group between 20 and 40 years when compared to other

Table 1: Demographic characteristics

Demographic character	Distribution	Frequency (%)	Mean serum sodium level in mmol/L
Age	< 40 years	144 (35.12)	133.78 ± 5.63
	40–60 years	226 (55.12)	132.38 ± 5.72
	> 60 years	40 (9.75)	131.97 ± 5.84
Sex	Male	296 (72)	132.9 ± 5.8
	Female	114 (27.8)	133.06 ± 5.84

Table 2: Grading and gender distribution of serum sodium status

Serum sodium level in mmol/L	Males (%)	Females (%)	Total (%)
> 135	114 (73)	42 (27)	156 (38.05)
130–134	104 (67)	52 (33)	156 (38.05)
125–129	62 (86)	10 (14)	72 (17.56)
< 125	16 (62)	10 (38)	26 (6.34)

Table 3: Radiographic and microbiological parameters in relation to serum sodium

Serum sodium level in mmol/L	Sputum positive (%)	Sputum negative (%)	Upper lung field (%)	Extensive – both lung fields (%)
> 135	128 (82)	28 (18)	80 (52)	76 (48)
130–134	132 (84)	24 (16)	72 (47)	84 (53)
125–129	48 (66.6)	24 (33.3)	36 (50)	36 (50)
< 125	24 (92.3)	2 (7.7)	6 (23)	20 (77)

age groups.[26] Chadha et al in their study on a rural South Indian population found that prevalence of TB was more in the younger age group 25–45 years.[27] The reason as to why subjects belonging to 40–60 age group were more in number in our study could be that ours being a tertiary care hospital, patients come after delayed diagnosis, stopping the treatment course and after being treated by other doctors. Hence, their treatment encounter in our hospital is delayed. A study by Mukherjee et al has shown TB was more in males when compared to females, the values being 69.3% male and 30.3% female.[26] Mukherjee et al have observed that TB notification rates were similar in both sexes till puberty but differ after this age and becomes more pronounced after 35–40 years. The high male preponderance was also found in the Revised National Tuberculosis Programme (RNTCP).[28] Our study group mostly comprised of subjects between 40 and 60 years and this could explain the male preponderance. It was thought that because of lack of proper access to money, education, information and health, women were less likely to contact health authorities. In the study by Jafari et al males were less being 45.5%.[25]

Out of 410 subjects with PTB 254 (61.9%) patients had hyponatremia, with 182 (72%) males and 72 (28%) females. Jafari et al in their study observed that 51% of subjects with TB had hyponatremia.[25] As seen in Table 2 there were more subjects with mild hyponatremia and very few with severe hyponatremia. Al-Barqawi et al observed that 6% of the patients admitted to a medical unit have hyponatremia; out of them in 50% the cause was diuretic therapy.[29] They also observed that mild to moderate hyponatremia was associated in those with chest infections. Crook et al observed that of those with hyponatremia 61% had chest infection.[30] According to Biswas et al syndrome of inappropriate anti diuretic hormone secretion (SIADH) is the most commonly encountered form of hyponatremia.[31]

Overall the mean serum sodium level in the subjects was 133.1 ± 5.8 mmol/L. The mean serum sodium levels in the subjects above 60 years of age was slightly lower, when compared to those between 40 and 60 years and below 40 years (131.9 ± 5.8 versus 132.3 ± 5.7 and 133.8 ± 5.6 mmol/L), respectively. Soiza et al have observed that chronic mild hyponatremia is common in old and frail individuals. The cause of hyponatremia was found to be multifactorial.[32] The mean serum sodium level in males was 132.9 ± 5.8 mmol/L and in females was 133.3 ± 5.6 mmol/L. The preponderance of hyponatremia in males was more than in females being 72% and 28%, respectively. Unlike the present study Jafari et al observed that hyponatremia in males was 42.1% and females was 52.9%.[25] The gender difference in the prevalence of hyponatremia between the present study and the study by Jafari et al, could be the higher TB notification rates in males in our country. There were more females than males with mild (45.6% versus 35.1%, respectively) and severe hyponatremia (8.7% versus 5.4%, respectively). In the moderate group there were more males when compared to females (20.9% versus 8.7%). Wang et al have found gender differences in sodium metabolism in female rats. They found a greater sensitivity of arginine vasopressin release in response to osmotic changes in female rats.[33]

Around 204 patients out of the 332 who were sputum positive had hyponatremia (61.4%). Of those with severe hyponatremia (serum sodium value less than 125 mmol/L), 92.3% were sputum positive. Among those with severe hyponatremia 76.9% had involvement of both lung fields when compared to 23% who had only upper lung field involvement.Generally extensive involvement indicates the severity of PTB and the present findings indicate that the severity of TB and hyponatremia were directly proportional to each other.

Out of 410 patients 138 have diabetes as a comorbidity (33.65%). Jangir et al, in their study observed that the prevalence of DM in patients with TB was 7.4%.[34] According to TB India 2012 DM accounts for 14.8% of TB cases and 20.8% smear positive TB cases.[35] Of the 138 subjects with DM and pulmonary Koch's 90 subjects had hyponatremia (65.21%), i.e., the prevalence is more when compared to pulmonary Koch's without comorbidity. Liamis et al in their review on diabetes and electrolyte disorders have explained the reason for hyponatremia in diabetes mellitus DM.[36] Hyperglycemia increases serum osmolality which draws water from the intracellular compartment into the extravascular space, causing dilutional hyponatremia. Certain drugs used to treat DM may also cause hyponatremia.

Most of the patients in the present study had asymptomatic hyponatremia. Six patients, out of 26 subjects with severe hyponatremia were hypotensive, yet only 2 needed vasopressors. A review by Biswas and Davies noted that patients with mild hyponatremia showed no symptoms.[31] Similarly patients with chronic hyponatremia (hyponatremia lasting for > 48 h) also did not exhibit any symptoms. Symptoms occurred only when there was acute exacerbation in patients with chronic hyponatremia or when serum sodium fell below 110 meq/l. In the present study there were no patients with serum sodium values less than 115 meq/l. Waikar et al have also found increased incidence of mortality in patients with hyponatremia, irrespective of the degree of hyponatremia.[37]

Conclusions

Hyponatremia was observed to the extent of 61% in patients with PTB; with mild and asymptomatic hyponatremia being more common. Severity of hyponatremia was directly proportional to sputum positivity and extensive involvement of pulmonary parenchymal lesions. There was no gender difference with relation to hyponatremia. This is the first study that has reviewed the prevalence of hyponatremia in rural patients, to the best of our knowledge. The limitation of the study was that the cause of hyponatremia was not looked into. As hyponatremia may lead to further morbidity, it should be kept in mind when treating a patient with TB.

References

1. Global TB Report 2015.
2. http://www.tbfacts.org/tb-statistics-india/#sthash.BOzXZkeW.dpu
3. Upadhyay A, Jaber BI, Madias NE. Incidence and prevalence of hyponatremia. Am J Med 2006;119:S30–5.
4. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 2007;356:2064–72.
5. Huda MS, Boyd A, Skagen K, Wile D, van Heyningen C, Watson I, Wong S, Gill G. Investigation and management of severe hyponatremia in a hospital setting. Postgrad Med J 2006;82:216–9.
6. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 1957;23:529–42.
7. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatremia. Intensive Care Med 2014;40:320–331 DOI 10.1007/s00134-014-3210-2.
8. Jacobi J, Schnellhardt S, Kulschewski A, Amann KU, Kuefner MA, Eckardt KU, et al. An unusual case of hyponatremia. Nephrol Dial Transplant 2010;25(3):998–1001.
9. Kinjo T, Higuchi D, Oshiro Y, Nakamatsu Y, Fujita K, Nakamoto A, et al. Addison's disease due to Tuberculosis that required differentiation from SIADH. J Infect Chemother 2009;15(4):239–42.
10. Lam KS, Sham MM, Tam SC, Ng MM, Ma HT. Hypopituitarism after tuberculous meningitis in childhood. Ann Intern Med 1993;118(9):701–6.
11. Berger SA, Edberg SC, David G. Infectious disease in the sellaturcica. Rev Infect Dis 1986;8(5):747–55.
12. Nagotkar I, Shanbag P, Dasarwar N. Cerebral salt wasting syndrome following neurosurgical intervention in tuberculous meningitis. Indian Pediatr 2008;45(7):598–601.
13. Dass R, Nagaraj R, Murlidharan J, Singhi S. hyponatremia and hypovolemic shock with tuberculous meningitis. Indian J Pediatr 2003;70(12):995–7.
14. Anderson NE, Somaratne J, Mason DF, Holland D, Thomas MG. Neurological and systemic complications of tuberculous meningitis and its treatment at Auckland City hospital, New Zealand. J Clin Neurosci 2010;17(9):1114–8.
15. Lee P, Ho KK. Hyponatremia in pulmonary TB: evidence of ectopic antidiuretic hormone production. Chest 2010;137(1):207–8.
16. Vorherr H, Massry SG, Fallet R, Kaplan I, Kleeman CR. Antidiuretic principle in tuberculous lung tissue of a patient with Pulmonary Tuberculosis and hyponatremia. Ann Intern Med 1970;72(3):383–7.
17. Schorn D. Inappropriate antidiuretic hormone secretion. Two cases presenting with Pulmonary Tuberculosis. S Afr Med J 1974;48(27):1161–2.
18. Gupta R, Ammini AC, Karmarkar MG, Berry M, Ahujha MMS. Adrenal insufficiency: CT adrenal imaging and endocrine studies. In: *Endocrinology, Metabolism and Diabetes*. Kochupillai N (ed.). Delhi: MacMillan India Ltd.; pp. 231-5.
19. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol 2011;118:45–51.
20. Ohta M, Ito S. Hyponatremia and inflammation. Rinsho Byori 1999;47:408–16.
21. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med 1998;128:127–37.
22. Ellison DH ,Berl T . Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 2007;356 (20):2064–72 .
23. Robertson GL. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. Am J Med 2006; 119: S36 - S42.
24. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine 1976;55:121–9.
25. Jafari NM, Izadi M, Sarrafzadeh F, Heidari A, Ranjbar R, Sabur A. Hyponatremia due to pulmonary tuberculosis: Review of 200 cases. Nephro-Urol Mon 2013;5(1):687–91. DoI: 10.5812/numonthly. 7091.
26. Mukherjee A, Saha I, Sarkar A, Chowdhury R. Gender differences in notification rates, clinical forms and treatment outcome of Tuberculosis patients under the RNTCP. Lung India 2012;29:120–2.
27. Chadha VK, Kumar P, Anjinappa SM, Singh S, Narasimhaiah S, Joshi MV et al. Prevalence of pulmonary tuberculosis among adults in a rural sub-district of South India. PLoS ONE 2012; 7(8):e42625. doi:10.1371/journal.pone.0042625.
28. Directorate General of Health Services. Ministry of Health and Family Welfare. New Delhi, India. *Revised National Tuberculosis Control Programme.Technical Guidelines for Tuberculosis Control*, 2005.
29. Al-Barqawi AR. A study of hyponatremia in hospitalised patients. Qatar Med J 2007;3(4):12–22.
30. Crook MA, Velanthar U, Griffith N. Review of investigation and management of hyponatremia in a hospital population. Ann Clin Biol 1999;9(3):107–9.
31. Biswas M, Davies JS. Hyponatremia in clinical practice. Postgrad Med J 2007;83:373–8. doi: 10.1136/pgmj.2006.056515.
32. Soiza RL, Cumming K, Clarke JM, Wood KM, Myint PK. Hyponatremia: Special considerations in older patients. J Clin Med 2014;3:944–58. doi:10.3390/jcm3030944.
33. Wang YX, Crofton JT, Miller J, Sigman CJ, Liu H, Humber DP, et al. Sex difference in urinary concentration ability of rats with water deprivation. Am J Physiol 1996;270:R550–5.
34. Jangir SK, Mishra VK, Gaur N, Kuldeep R. A study to assess prevalence and clinical profile of diabetic pulmonary tuberculosis patients treated under RNTCP. Int J Sci Res 2016;5(3):599–602. ISSN No. 2277-8179.
35. Annual Reports: TB India 2012. Central TB Division. Director General of Health Services, Ministry of Health and Family Welfare. Government of India. www.tbcindia.nic.in.
36. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. World J Clin Cases 2014;2(10):488–96. DOI: http://dx.doi.org/10.12998/wjcc.v2.i10.488.
37. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 2009;122(9):857–65. doi:10.1016/j.amjmed.2009.01.027.

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