

# Hyponatremia Due to Pulmonary Tuberculosis in Indian Population

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## Abstract

**Introduction:** The magnitude of hyponatremia in hospitalized patients has been estimated to be about 15% in many studies. Hyponatremia in many studies has been correlated with increased mortality. Besides other infectious agents causing pneumonia pulmonary tuberculosis (PTB) has been strongly associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Aims:** The objective of the study was the evaluation of Indian patients of PTB with hyponatremia.

**Materials and Methods:** In this study patient with a diagnosis of secondary PTB admitted to Shri Maharaja Hari Singh Hospital, Jammu and Kashmir, India, from July 2015 to July 2016 were evaluated for various electrolyte abnormalities. The diagnosis of PTB was based on the appearance of acid fast bacilli in sputum smears or sputum cultures, carried by the laboratories authorized by the norms set in according to Revised National Tuberculosis (TB) Control Program, without any evidence of miliary TB.

**Results:** Our study enrolled a total of 58 patients with mean age of  $51.57 \pm 16.3$ , hyponatremia was present in 51.8% (29) of the patients. Mean age of patients with hyponatremia was  $58.24 \pm 15.1$  and mean age of patients with normal sodium was  $44.41 \pm 14.6$ . This was a statistically significant relationship ( $P < 0.001$ ). The patients with hyponatremia were further evaluated for serum osmolality, urine osmolality, urine sodium levels and thyroid-stimulating hormone levels, and 62% of patients with hyponatremia were found to have SIADH according to Schwartz criteria.

**Conclusion:** This study suggested that there was a high incidence of hyponatremia in PTB and age was one of the important predisposing factors for the development of hyponatremia in patients with PTB, SIADH could be one of the major mechanisms through which PTB causes hyponatremia.

**Key words:** Hyponatremia, Pulmonary tuberculosis, Syndrome of inappropriate anti diuretic hormone secretion

## BACKGROUND

The frequency of hyponatremia in hospitalized patients and its association with increased mortality has been validated in many studies in the past. The magnitude of hyponatremia in hospitalized patients has been estimated to be about 15% in many studies.<sup>1,2</sup> Not only does this electrolyte abnormality produce clinical manifestations

varying from asymptomatic state to overt signs such as clinical seizures and coma, but hyponatremia in many studies has been correlated with increased mortality. In euvoletic patients presenting with hyponatremia, strong consideration should be given to syndrome of inappropriate anti diuretic hormone secretion (SIADH), besides other causes. SIADH was initially described by Leaf and Mamby. SIADH consists of hyponatremia, inappropriately elevated urine osmolality, excessive urine sodium and decreased serum osmolality in a euvoletic patient without edema. These findings should occur in the absence of diuretic treatment with normal cardiac, renal, adrenal, hepatic, and thyroid function. Besides other infectious agents causing pneumonia pulmonary TB (PTB) has been strongly associated with SIADH.<sup>3-6</sup>

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PTB is one of the rare pulmonary infections which can induce hyponatremia. Tuberculosis (TB) is considered as one of the common illnesses in developing countries such as India which can present with various clinical manifestations. India is the country with the highest burden of TB. The World Health Organization (WHO) TB statistics for India for 2015 give an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 9.6 million. The TB incidence for India is the number of new cases of active TB disease in India during a certain time period (usually a year).

The estimated TB prevalence figure for 2015 is given as 2.5 million. It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent TB rather than TB disease.<sup>7,8</sup> TB can induce hyponatremia through several mechanisms containing local invasion to the adrenal glands (adrenal insufficiency),<sup>9,10</sup> local invasion to hypothalamus or pituitary gland,<sup>11,12</sup> tubercular meningitis,<sup>13-15</sup> and inappropriate antidiuretic hormone (ADH) secretion through pulmonary infection.<sup>16-18</sup>

### Objective

The aim of the study was to evaluate the incidence of hyponatremia in Indian patients with PTB attributable to SIADH.

## MATERIALS AND METHODS

### Design and Participants

We have prospectively evaluated patients with a diagnosis of secondary PTB and that were admitted in general medicine wards of Shri Maharaja Hari Singh (SMHS) Hospital, Jammu and Kashmir, India, from July 2015 to July 2016. Demographic and laboratory characteristics were recorded. The confirmation of secondary PTB was based on the appearance of acid fast bacilli on two sputum smears or *Mycobacterium* TB on a sputum culture, in the absence of radiological features of miliary TB. The microbiological tests were done in the hospital lab of SMHS which is authorized according to the norms set by Revised National TB Control Program. The patients with abnormal mental status, any evidence of tubercular meningitis, edema forming conditions, uncontrolled hyperglycemia, renal insufficiency or failure, hyperlipidemia, receiving diuretics or any medications related to SIADH or induced vasopressin release were excluded.

### Assessment and Treatment

All the diseases that cause renal loss of sodium were excluded, diseases causing abnormalities of serum sodium and serum and urine osmolalities were also excluded.

Patients were on a normal diet. The patient received antitubercular drugs according to the WHO guidelines, rifampicin, isoniazid, ethambutol, and pyrazinamide during first 2 months and rifampicin and isoniazid for next 4-10 months. Blood samples and urine samples were collected simultaneously for sodium levels and osmolality measurements.

### Statistics

Data were collected to compare the profile and laboratory characteristics of PTB patients with or without hyponatremia. The data were analyzed using SPSS software (17<sup>th</sup> edition) and  $P < 0.05$  was considered significant. Quantitative and qualitative data were reported using mean  $\pm$  standard deviation and infrequency (percentage). After checking normal distribution of quantitative data, the parametric or nonparametric tests were used. For the analysis of qualitative data with normal distribution, Student's *t*-test, ANOVA, and Pearson correlation and for the abnormal distributed variables, Mann-Whitney U, Kruskal-Wallis, and Spearman correlation tests were used.

## RESULTS

A total of 58 patients were enrolled for the study. The mean age of all the patients was  $51.57 \pm 16.3$ . The males were 65.6% (40), mean age of males  $51.38 \pm 14.9$ , and mean age of females was  $52.06 \pm 20.06$  which was statistically insignificant.

Hyponatremia was present in 51.8% (29) of the patients, mean age of hyponatremics was  $58.24 \pm 15.1$  and mean age of eunatremics was  $44.41 \pm 14.6$ . This was a statistically significant relationship ( $P < 0.001$ ).

Mean serum sodium was  $135.73 \pm 6.4$ . Mean serum Na in males was  $136.03 \pm 6.5$  versus mean serum sodium in females was  $135.00 \pm 6.5$ . 50% (20) males versus 56.2% (9) females had hyponatremia there was no significant relationship between gender and hyponatremia.

Hyponatremia and SIADH were found fairly correlated with Spearman's correlation coefficient of 0.7 which was found statistically significant ( $P < 0.001$ ).

The patients with hyponatremia were further evaluated for serum osmolality, urine osmolality, urine sodium levels and thyroid-stimulating hormone (TSH) levels, and 62% of patients with hyponatremia were found to have SIADH according to Schwartz criteria.<sup>19</sup>

Four patients with hyponatremia had TSH levels more than 5 nIU/ml.

## DISCUSSION

Not only has been frequency of hyponatremia established in many studies in the past but also the association of hyponatremia with increased mortality and morbidity has been validated. Longer in hospital stay, osteoporosis, and increased incidence of falls and fractures has been associated with this metabolic abnormality.

Previous studies have shown that hyponatremia frequently develops in hospitalized patients.<sup>20</sup> Various studies have shown an association of general hyponatremia with increased morbidity and mortality,<sup>21-23</sup> longer hospitalization,<sup>24</sup> osteoporosis,<sup>25</sup> and falls and fractures,<sup>25</sup> and cognitive impairment.<sup>26</sup> The most common causes of severe hyponatremia in hospital setting in adults are therapy with thiazides, the post-operative state and other causes of the syndrome of inappropriate secretion of ADH, polydipsia in psychiatric patients, and transurethral prostatectomy.<sup>27-31</sup>

In developing nations, infectious diseases are common causes for hospital admission and PTB being one of them. Previous studies have shown that hyponatremia developed in a significant number of PTB patients. A study conducted by Jafari *et al.*, in year 2012,<sup>32</sup> in Iran concluded that around 51% of PTB patients admitted to hospital developed hyponatremia, this is in accordance with the results of our study where hyponatremia developed in 51.8% of the patients of PTB. Age is an important predisposing factor to the development of hyponatremia in hospitalized patients. The studies have shown that elderly are more prone to the development of hyponatremia, Hoyle *et al.* conducted a study in 2006 where he concluded that hyponatremia developed in almost half of the hospitalized patients who were >65 years of age.<sup>17,25,33-35</sup> Our study demonstrated that the mean age of hyponatremics was 58.24 years. The older age of patients with hyponatremia stresses on the fact that the patients with advanced age need to be strictly screened for hyponatremia such that future complications of this metabolic abnormality can be averted. SIADH is a common cause of hyponatremia.

SIADH is a considerable complication of pulmonary infection, inflammatory and neoplastic disorders. SIADH has been shown to occur in infectious situations such as TB, although very few studies have actually delineated the prevalence and incidence. There have been numerous studies that showed the occurrence of SIADH in both pulmonary as well as meningeal TB. Vorherr *et al.* have reported a case with PTB and hyponatremia and found antidiuretic secreting lesions in tuberculous lung tissues.<sup>17</sup> Bryant have suggested the syndrome of inappropriate secretion of ADH for patients with an infectious pulmonary disease such as PTB.<sup>3</sup>

Cockcroft *et al.* reported a 74-year-old woman with miliary TB which was complicated by severe hyponatremia due to SIADH.<sup>4</sup>

There are many mechanisms of SIADH in TB. These are studies which have shown that more than 60% of patients with tubercular meningitis may present with SIADH.<sup>36</sup> SIADH must be suspected in every case with hyponatremia with low serum osmolality condition, a normal acid-base state, urine osmolality over 100 mOsm/kg, and urine sodium concentration more than 40 mEq/L. In our study, 62 % of the patients with hyponatremia were qualifying for the criteria of SIADH (Schwartz criteria).<sup>19</sup> Although this number could not reach to a statistical significance due to the small number of participants in the study, but it points toward the importance of screening of patients for SIADH in development of hyponatremia. Therefore, further large scale studies need to be conducted to establish a firmer relation between hyponatremia in PTB and SIADH.

## CONCLUSION

This study suggested that there was a high incidence of hyponatremia in PTB and age was one of the important predisposing factors for the development of hyponatremia in patients with PTB, SIADH could be one of the major mechanisms through which PTB causes hyponatremia.

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