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Original Article

Internal Medicine Section

Clinical Profile and Aetiopathogenesis of Patients with Sodium and Calcium Abnormalities in Tuberculosis: A Cross-sectional Study

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ABSTRACT

Introduction: Tuberculosis (TB) is one of the major public health concerns in India. Hyponatraemia is one of the most common electrolyte abnormalities in TB patients. Calcium abnormalities have also been reported in them.

Aim: The study was done to determine the prevalence of sodium and calcium abnormalities in TB patients in the population and to assess the relationship between the type of TB and electrolyte abnormalities.

Materials and Methods: A cross-sectional study was conducted at Guru Nanak Dev Hospital, Government Medical College, Amritsar, Punjab, India from June 2023 to May 2024. The study included 60 adult patients with active TB. Measurements of serum electrolytes and serum osmolality were done. Tests like urine sodium were done if hyponatraemia was present. Pearson's Chi-square test was used to discover if any relationship between two categorical variables, t-test and Analysis of Variance (ANOVA) analysis were used to differentiate means among two or more groups.

Results: The mean age in the study was 47±14.7 years and comprised 42 males and 18 females. They were stratified into pulmonary, extrapulmonary, Central Nervous System (CNS) and disseminated TB. A 75% of patients had hyponatraemia and 25% had eunatraemia. Mean serum sodium in patients with eunatraemia was 139.13±2.26 mMol/L and with hyponatraemia was 129.5±4.15 mMol/L. There was a statistically significant relation between hyponatraemia and age group 51-60 years and >60 years (p-value <0.05). Mean age of eunatremic patients were 42.93±16.25 years and of hyponatraemic patients were 48.49±14.08 years. A significant relation between the type of TB (CNS, pulmonary and disseminated) and hyponatraemia was established (p-value<0.05). Euvolaemic hyponatraemia likely due to Syndrome of Inappropriate Anti Diuretic Hormone (SIADH) was found in 73% of cases. A significant relation was established between the frequency of euvolaemic hyponatraemia among CNS vs disseminated TB (p-value <0.05). There were 80% of patients with eucalcaemia and 13% with hypercalcaemia. Mortality was seen in cases of severe hyponatraemia and severe hypercalcaemia but it was not significant.

Conclusion: Electrolyte abnormalities like hyponatraemia and hypercalcaemia are common in TB. The most common cause of hyponatraemia is SIADH.

Keywords: Hyponatraemia, Inappropriate anti diuretic hormone syndrome, Kochs disease

INTRODUCTION

The TB stands as a significant worldwide health concern, with substantial morbidity and mortality rates. Before the onset of COVID-19, TB held the position of the primary cause of death from a single infectious agent, surpassing Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) [1]. TB is transmitted via aerosol droplets containing the mycobacteria, which are expelled by individuals with active TB when they sneeze, cough or talk. TB is capable of affecting virtually all organs, the most common being the lungs. There may be involvement of organs other than lungs, as well as dissemination to other sites leading to involvement of more than one primary site [1].

TB can lead to several complications, both local and systemic. Systemic complications in the form of electrolyte disturbances may occur with hyponatraemia being the most common one. Hyponatraemia can be induced by various mechanisms in TB such as local invasion of the adrenal glands causing adrenal insufficiency, local invasion of the hypothalamus or pituitary, tubercular meningitis, SIADH, Cerebral Salt Wasting syndrome (CSW) and excessive loss of electrolytes through conditions like diarrhoea, vomiting, and sweating, which are frequently observed in TB patients [2,3]. SIADH in TB may be caused due to Arginine Vasopressin (AVP) being secreted as a response to intracranial pressure in an effort to raise mean arterial pressure and maintain adequate cerebral perfusion pressure [4]. In another study, hypoxemia associated with pulmonary TB may stimulate baroreceptors, leading on to AVP release from the posterior pituitary [5]. CSW is an aetiology of hypovolemic hyponatraemia in TB. It can be differentiated from SIADH on the basis of volume status of patient and urinary sodium is raised in both, but excessively in CSW. Another mechanism that may lead to hypovolemic hyponatraemia in a TB patient is adrenalitis (Addison's disease). This can be caused by hematogenous spread of TB bacilli to the adrenals and formation of granulomas, cold abscesses and at times atrophy of the gland. It should be suspected in a patient of TB with orthostatic hypotension, hyperpigmentation, hyponatraemia and hyperkalaemia [6].

Calcium regulation is also known to get affected in the course of the disease. Parathyroid Hormone (PTH) and vitamin D are the main regulators of serum calcium. In TB patients, the likely source of high calcitriol levels is dysregulated production of 1,25(OH)2D3 by activated macrophages in pulmonary alveoli and granulomas. The 1-alpha-hydroxylase activity in macrophages is activated by mechanisms such as gamma interferon [7]. The 1,25(OH)2D3 produced by T-cells plays a crucial role in the immune response against mycobacteria. Normally, this locally produced vitamin D doesn't affect systemic calcium metabolism. However, if large

quantities are produced, hypercalcaemia may develop [8]. The reported incidence of hypercalcaemia among TB patients ranges from as low as 2.3% to as high as 28%. This variability is attributed to factors such as differences in vitamin D and calcium intake, sunlight exposure, and the extent of the disease. However, the majority of these patients do not exhibit symptoms of hypercalcaemia and the condition is typically detected only through routine screening [9]. Therefore, it is crucial to understand the mechanism behind these electrolyte abnormalities and the effects they may have. Prompt diagnosis and management is the key to reducing patient's morbidity and mortality.

Since there have been limited studies [9,10] in Indian subset of population regarding relation between type of TB and electrolyte abnormality, this study aims to determine the clinical picture of tubercular patients with sodium and calcium abnormalities Punjab, India.

MATERIALS AND METHODS

A cross-sectional study was conducted at Guru Nanak Dev Hospital, Government Medical College, Amritsar, Punjab, India between June 2023- May 2024 to assess sodium and calcium levels in patients of different types of TB and to determine the etiology of any dyselectrolemias. The study protocol was approved by the Institutional Review Board and Ethical committee with certificate no. 10784/D-26/2021. Written and informed consent was taken.

Sample size calculation: According to a similar study done, the maximum proportion of patients with hyponatraemia in TB was 0.407 (p) [11]. To estimate the prevalence to within 10 percentage points of the true value, 95% confidence was considered and a sample size of 60 was calculated. All measures for a research participant were taken at the same time, despite the fact that recruitment occurred across time. To minimise selection bias, samples were picked at random.

Inclusion criteria: The study included patients with age greater than 16 years, those admitted with the diagnosis of TB, or reactivation of TB, irrespective of whether the patient is on treatment or not. Patients with multi drug resistant/extreme drug-resistant TB and those with HIV positive, Hepatitis C, Hepatitis B and other comorbidities such as diabetes, Hypertension (HTN) were also included.

Exclusion criteria: Patients with age less than 16 years, women who are pregnant and patients with comorbidities such as nephrotic syndrome, cirrhosis, heart failure and thyroid disorder were excluded.

Study Procedure

Patients of TB were stratified on the basis of site of TB into four sub types which were pulmonary TB (alone), extrapulmonary TB (excluding CNS TB), CNS TB and disseminated TB (involving two or more non-contiguous sites as a result of haematogenous spread). Serum sodium, calcium, albumin and serum osmolality were analysed by multichannel automated analyser. Measured total serum calcium concentration was corrected for serum albumin concentration considering protein binding of calcium. Baseline samples were collected for all new patients before initiating Anti Tuberculosis Therapy (ATT). If hyponatraemia was present, serum osmolality was measured and clinical volume status of the patient was documented. Urine spot sodium and TSH were measured to further characterise the cause of hyponatraemia. Urine sodium >20 mEq/L is seen in conditions such as hypothyroidism, glucocorticoid deficiency and SIADH [12]. If required, adequate samples of cerebrospinal fluid, pleural fluid and ascitic fluid for diagnostic purposes were withdrawn under aseptic conditions for biochemical investigations. Information regarding the type of TB, treatment details (including duration), HIV status, comorbid illnesses and outcome at discharge were documented. In patients with hypoalbuminaemia the corrected calcium levels were estimated using the following formula measured total serum calcium (mg/dL) + 0.8 (4–serum albumin) (mg/dL) [9].

STATISTICAL ANALYSIS

The collected data was entered in clinical research form (CRF). The CRF was filled by the principal investigator. Data from the CRF was entered into the epidata v 3.1 data entry software and then exported to Statistical Package for Social Sciences (SPSS) version 17, IBM Corporation, USA for analysis. Pearson's Chi-square test was used to discover if there is a relationship between two categorical variables. The t-test and ANOVA analysis were used to differentiate means among two or more groups. The p-value of <0.05 was considered significant. All analysis was performed by a biostatistician.

RESULTS

Study of sodium and related abnormalities: [Table/Fig-1] implies that significant relation was seen between the prevalence of hyponatraemia in TB and older age groups (>51 years). It was observed that CNS and disseminated TB patients were more likely to have hyponatraemia (p-value 0.001).

Variables		Eunatraemia Number (%) 15 (25)	Hyponatraemia Number (%) 45 (75)	p-value
Gender	Female	4 (27)	14 (31)	0.74
	Male	11 (73)	31 (69)	
Age (years)	≤30	4 (40)	6 (60)	0.42
	31-40	4 (31)	9 (69)	0.21
	41-50	2 (18)	9 (82)	0.06
	51-60	3 (21)	11 (79)	0.03
	>60	2 (17)	10 (83)	0.02
Mean age (years)	47±14.7 (Total mean value)	42.93±16.25	48.49±14.08	0.0001
Type of TB	CNS	1 (6.7)	10 (22)	0.001
	Disseminated	1 (6.7)	10 (22)	0.001
	Extrapulmonary	5 (33.3)	2 (4.4)	0.022
	Pulmonary	8 (53.3)	23 (51.1)	0.011
Treatment Status	Naïve	14 (93.3)	36 (80)	0.23
	On ATT	1 (6.7)	9 (20)	
HIV	Non-Reactive	15 (100%)	41 (91.1%)	0.232
	Reactive	0 (0%)	4 (8.9%)	
DM	No	11 (73.3%)	39 (86.7%)	0.230
	Yes	4 (26.7%)	6 (13.3%)	
HTN	No	11 (73.3%)	38 (84.4%)	0.335
	Yes	4 (26.7%)	7 (15.6%)	
Outcome	Survived	15 (100)	38 (84.4)	0.10
	Expired	0 (0)	7 (15.6)	
Mean serum sodium (mMol/L)	131.95±5.62 (Total mean value)	139.13±2.26	129.5±4.15	0.20

[Table/Fig-1]: Sodium status and demographic parameters.

It was observed that in case of euvolaemic hyponatraemia, all the patients had urine sodium ≥20 mEq/L while in hypovolemic hyponatraemia majority of patients (7/10) had urine sodium ≥20 mEq/L [Table/Fig-2].

Volume status	Urine sodium ≥20 mEq/L	Urine sodium <20 mEq/L	Total
Euvolaemic hyponatraemia	33	0	33
Hypovolemic hyponatraemia	7	3	10
Hypervolemic hyponatraemia	2	0	2

[Table/Fig-2]: Urine sodium and volume status in hyponatraemia.

[Table/Fig-3] implies that euvolaemic hyponatraemia was seen in majority of patients, most likely caused by SIADH after excluding other causes like hypothyroidism. The diagnosis of SIADH was also supported by the urine sodium values mentioned in [Table/Fig-2].

Type of TB	Euvolaemic hyponatraemia Number (%)	Hypovolemic hyponatraemia Number (%)	Hypervolemic hyponatraemia Number (%)
CNS	10 (100)	0 (0)	0 (0)
Disseminated	4 (40)	6 (60)	0 (0)
Pulmonary	17 (74)	4 (17)	2 (9)
Extra pulmonary	2 (100)	0 (0)	0 (0)
Total	33	10	2

[Table/Fig-3]: Types of Tuberculosis (TB) and hyponatraemia based on volume status.

As per [Table/Fig-4], there is a significant relation between frequency of euvolaemic hyponatraemia among CNS vs disseminated TB. This implies that euvolaemic hyponatraemia, most likely caused by SIADH, as per the urine sodium values and after ruling out other causes, was a fairly common aetiology of hyponatraemia in tubercular patients.

Subtypes of TB	p-value
Pulmonary TB vs CNS TB	0.07
Pulmonary TB vs Disseminated TB	0.06
Pulmonary TB vs Extrapulmonary TB	0.40
CNS TB vs Disseminated TB	0.003
Disseminated TB vs Extrapulmonary TB	0.12

[Table/Fig-4]: Comparison of frequency of euvolaemic hyponatraemia among types of TB.

As per [Table/Fig-5], it was observed that the most common calcium related finding was eucalcaemia followed by hypercalcaemia.

Variables		Eucalcaemia Number (%) 48 (80)	Hypercalcaemia Number (%) 8 (13)	Hypocalcaemia Number (%) 4 (7)	p-value
Gender	Female	13 (27)	2 (25)	3 (75)	0.12
	Male	35 (73)	6 (75)	1 (25)	
Age (years)	≤30	10 (100)	0 (0)	0 (0)	0.22
	31-40	12 (92)	0 (0)	1 (8)	0.28
	41-50	8 (73)	3 (27)	0 (0)	0.23
	51-60	10 (71)	3 (21)	1 (7)	0.58
	>60	8 (67)	2 (17)	2 (17)	0.25
Type of TB	CNS	8 (16.7)	3 (37.5)	0 (0)	0.23
	Disseminated	11 (22.9)	0 (0)	0 (0)	0.18
	Extrapulmonary	6 (12.5)	1 (12.5)	0 (0)	0.75
	Pulmonary	23 (47.9)	4 (50)	4 (100)	0.13
Treatment status	Naïve	38 (79.2)	8 (100)	4 (100)	0.22
	On ATT	10 (20.8)	0 (0)	0 (0)	
HIV	Non-reactive	45 (93.8%)	7 (87.5%)	4 (100%)	0.69
	Reactive	3 (6.3%)	1 (12.5%)	0 (0%)	
Diabetes Mellitus	No	40 (83.3%)	7 (87.5%)	3 (75%)	0.86
	Yes	8 (16.7%)	1 (12.5%)	1 (25%)	
Hypertension (HTN)	No	41 (85.4%)	5 (62.5%)	3 (75%)	0.28
	Yes	7 (14.6%)	3 (37.5%)	1 (25%)	
Outcome	Survived	44 (91.7)	6 (75)	3 (75)	0.27
	Expired	4 (8.3)	2 (25)	1 (25)	
Mean serum calcium (mg/dL)	9.42±.89	9.27±0.56	11.06±0.31	7.98±0.26	0.0001

[Table/Fig-5]: Calcium levels and demographic parameters.

DISCUSSION

The TB stands on the forefront of infectious diseases in India. The tendency to cause symptomatic disease increases exponentially in case of people who are immunocompromised, malnourished and those with past history of TB.

This study focuses on the electrolyte complications caused by TB and their relation with various parameters. Male predominance of our study (70%) was consistent with the findings by Kaur J et al., (males=77%) [10]. The patients were further stratified on the basis of their treatment status, viral markers and comorbidities. The prevalence of HTN was found to be 18% and that of Diabetes Mellitus (DM) 17%, which is quite aligned with the data published by World Health Organisation (diabetics=15%) [13]. There was no significant relation between the sodium status and these demographic parameters as corroborated with various studies [14]. The chief sodium abnormality detected in the current study was hyponatraemia (75%), which was comparable to 72% by Ganiger A et al., [2]. A statistically significant relation between age and hyponatraemia has been established, with p-value of 0.03 for 51-60 years and p-value of 0.02 for more than 60 years. This is comparable to a study by Khan K et al., where mean age of patients with hyponatraemia was 58.24±15.1 years, which suggests likelihood of hyponatraemia in older people [15].

A significant relation (p-value<0.05) was found between types of TB and the sodium status, with likelihood of hyponatraemia in CNS, disseminated and pulmonary TB. Na S et al., concluded a significant relation between low sodium level and CNS TB with p value <0.001 [16]. In another study, a significant relation between pulmonary TB and hyponatraemia was proven (p value<0.001) [2]. The mean sodium level in CNS TB was 129 mMol/L which was comparable to another study (128 mMol/L) [17]. Mean sodium level for pulmonary TB in the current study was 132 mMol/L and a value of 132.4 mMol/L was found in another study [10]. Patients with thyroid disorders were excluded from this study. Further, urine sodium level was measured which were ≥20 mEq/L in all 33 patients with euvolaemia, suggesting a likely diagnosis of SIADH. As for hypovolemic hyponatraemia, the likely aetiologies could be hypoaldosteronism due to dissemination to the adrenals and CSW syndrome. Both the conditions have urine sodium ≥20 mEq/L. They can be further diagnosed with the help of

tests such as urine osmolality, MRI Brain, CT Abdomen etc. Other causes can be vomiting, malaise, anorexia which are commonly seen in TB patients and have urine sodium <20 mEq/L. In case of hypervolemic hyponatraemia, causes like congestive heart failure, liver cirrhosis and nephrotic syndrome were excluded. Euvolaemic hyponatraemia most probably due to SIADH is a leading cause for electrolyte abnormality in TB as seen in the present study. A study reported hyponatraemia in 65% patients admitted with tubercular meningitis and all the patients had SIADH [18] which is comparable to the current study in which 91% patients with CNS TB having euvolaemic hyponatraemia likely due to SIADH.

Henceforth, a statistically significant relation between frequency of euvolaemic hyponatraemia (likely SIADH) among CNS vs disseminated TB (p-value 0.003) was noted, thereby signifying increased likelihood of euvolaemic hyponatraemia in cases of CNS TB when compared to disseminated TB which can have hyponatraemia due to different aetiologies leading to different volume statuses such as hypovolemic hyponatraemia in case of dissemination to adrenals [19,20]. There was 74% prevalence of euvolaemic hyponatraemia in pulmonary TB patients which is comparable to several studies [21,22].

The proportion of hypercalcaemia in the present study (13%) falls between the range of 12 to 51% as quoted by different studies [23-25]. No significant relation between calcium levels and gender, treatment status and comorbidities was elucidated from the present study, as corroborated with another study [26]. Roussos A et al., stated that there is no relation between the type of TB and calcium levels aligning with our study [25]. No relation has been established between the calcium levels and the extent of severity of disease in the present study as also seen in other studies [27]. As per several studies conducted to ascertain an association between calcium levels and TB, one such attributes their possible cause of hypocalcaemia to malnutrition and malabsorption related to TB [28]. Studies have provided ample evidence indicating that extrarenal 1- alpha hydroxylation of 25(OH)D3 to 1,25(OH)2D3 significantly contributes to the development of hypercalcaemia in patients with TB (p=0.0001) [9,25,29]. This becomes even more consequential since India is a country where many people are exposed to abundant sunlight. Cholecalciferol is a precursor to vitamin D3 which further increases calcium reabsorption from the gut. The extent of sunlight exposure and the levels of circulating 25(OH)D3 may contribute to this pathophysiology [30]. But this may vary among our population as there are some people who do not get as much sunlight exposure, depending on their habitat, occupation and other determinants. Such people are more prone to hypocalcaemia, with accompanying factors such as reduced oral intake of calcium and vitamin D3.

Hence, there may be alterations in calcium level among the population depending on numerous factors. But it is important to recognise signs and symptoms of altered calcium levels and treat them accordingly, as otherwise they may cause increased morbidity in various forms, one such being dysrhythmias which may ultimately contribute to mortality.

Limitation(s)

Considering the burden of TB in our population, a sample size of 60 is not entirely representative of the population. As this was a cross-sectional study, trends of sodium and calcium levels could not be assessed over time and their response to treatment. To rule out the possibility of hypercortisolism while determining aetiology of euvolaemic hyponatraemia, serum cortisol levels could not be carried out as it was beyond the scope of this study.

CONCLUSION(S)

Hyponatraemia is an important electrolyte disturbance frequently encountered in TB patients, especially the older ages. The prevalence of hyponatraemia as per this study was a whopping 75%. Euvolaemic type of hyponatraemia (likely SIADH) is one of the most common causes. Calcium levels may also get altered due to the pathophysiology of TB as evidenced by this study with 13% patients having hypercalcaemia and 7% with hypocalcaemia. It is of prime importance to detect these electrolyte disturbances and treat them well in time to avoid any further complications which may arise in the setting of very low sodium or high calcium levels.

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