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Original Research Article

Epidemiological profile of extrapulmonary tuberculosis and its association with diabetes in tertiary care center in Northern Kerala

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ABSTRACT

Background: India accounts for 24% of the global TB burden and 29% of deaths. Although HIV is considered the most potent risk factor for TB, the high prevalence of diabetes mellitus in the world and its effect on TB burden is greater than HIV infection. DM is common in the south Indian state of Kerala with a prevalence of 16% to 20%. Objectives of current study were to describe the epidemiological profile of EPTB cases diagnosed in a tertiary care center in northern Kerala and to find the association between EPTB and DM cases.

Methods: A record-based descriptive study. All TB cases from first January 2019 to December 2021 at the Government medical college Kannur Pariyaram were the study population. Data was collected from the Nikshay portal, treatment register and CBNAAT register maintained in DOTS center, Pariyaram. The data were analysed using MS Excel and SPSS 26. The Chi-square test was applied to find an association between variables. $p<0.05$ is considered statistically significant.

Results: Of the 882 cases included in the study, 476 (53.96%) were having PTB and 406 (46.03%) were having EPTB. Among males PTB (358, 59.3%) and among females EPTB (160 ,57.6%) were more prevalent ($p<0.001$). In the younger age group EPTB and in the older age group PTB were more reported ($p<0.001$). Among EPTB, the majority of the cases (66.5%) belong to the age group 21-60 years. Smokers among PTB and EPTB were 78 (16.4%) and 33 (8.1%) respectively.

Conclusions: Female gender and younger age were more associated with EPTB compared to PTB.DM and smoking were more associated with PTB compared to EPTB. Common sites of EPTB were the lymph node, abdominal, pleural, and spine.

Keywords: Pulmonary TB, Extrapulmonary TB, Diabetes mellitus

INTRODUCTION

Tuberculosis is a communicable disease that is a major cause of ill health and one of the top 10 causes of death globally. Till the COVID-19 pandemic Tuberculosis was the leading cause of death from a single infectious agent ranking above HIV/AIDs. India accounts for 24% of the global Tuberculosis (TB) burden and 29% of deaths.[1] TB is caused by mycobacterium tuberculosis which affects mainly the lung (pulmonary tuberculosis) but also any part of the body (extra pulmonary tuberculosis). The commonest EPTB reported sites are lymph nodes, lymphatic, TB in the pleural cavity and urogenital tract, GIT, Skeletal, and CNS.[2,3] It is reported that 15% of global TB cases are EPTB and in India accounts for about 20% of all cases. Incidence of EPTB occurs more commonly in persons with impaired innate immunity. EPTB presents challenges to TB control because it is harder to diagnose.[4] Diabetes mainly types 1 diabetes (T1D), type 2 diabetes mellitus (T2D), and gestational diabetes mellitus (GDM) in the world. It is estimated that 463 million have diabetes in 2019. Without urgent and sufficient actions, it is predicted that 579 million people

will have diabetes in 2030 and the number will increase by 51% (700 million) in 2045.[5] The first report of the association between DM and TB was documented by Avicenna (980-1027 AD) over one thousand years ago.[6] Although infection with human immunodeficiency virus (HIV) is considered the most potent risk factor for TB, the high prevalence of DM in the world and its effect on TB burden is greater compared to HIV infection.[7] TB affects DM in many aspects. Although the definite pathophysiological mechanism of the effect of DM as a predisposing risk factor for TB is unknown, some hypotheses are suggested: depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon-gamma, pulmonary microangiopathy, and micronutrient deficiency.[8,9] An analysis of nutrition and DM changes in India also suggests that increased DM prevalence between 1998 and 2008 contributed to an increase in the total number of TB cases in the country which exceeded the rate of population growth in the same time period.[10] About 95% of patients with tuberculosis (TB) and 70% of patients with diabetes mellitus (DM) live in the low and middle-income countries.[11] India is facing the dual problem of being the highest TB-burden country and having a large number of people with diabetes posing a serious challenge for the health care system. In India, there is an estimated 2.7 million incident TB cases. As a consequence of urbanization as well as socio-economic development, there has been an escalating epidemic of DM. Available evidence and modeling studies indicate that nearly 20 % of all TB cases in India may also suffer from DM. It is seen in India that patients with Type 2 DM have a 3 fold increased risk of developing TB. While patients with TB have a 2 fold increased risk of developing DM.[12] DM is common in the south Indian state of Kerala (population 34.6 million), with an estimated community prevalence of 16% to 20%.[13]

Rationale

Although immune deficiency also occurs with diabetes, little is known about the epidemiological or clinical relationship between diabetes and EPTB. It is clear that there is a differential risk existing between diabetes and EPTB. The percentage of patients with EPTB in tertiary care centers in India was between 30% and 53%.[14] So studying in a tertiary care center will yield more on this aspect. Also, few studies have examined the relationship between diabetes and the likelihood of EPTB, especially in India. Being a tertiary care Centre and District DRTB Centre a large number of TB suspects are being referred to the institution. Therefore, we aimed to find the association between diabetes and EPTB and the site distribution of EPTB.

Objectives

Objectives of current study were to describe the epidemiological profile of EPTB cases diagnosed in a tertiary care center in northern Kerala and to find the association between EPTB and DM cases diagnosed in a tertiary care center in northern Kerala.

METHODS

Study design, location and population

It was a record-based descriptive study carried out in a tertiary care center in North Kerala. All TB cases who were diagnosed from first January 2019 to 31st December 2021 at the government medical college Pariyaram were the population for the study.

Inclusion criteria and study tools

All diagnosed TB cases were included. Data were collected from the Nikshay portal, treatment register and CBNAAT register maintained in DOTS Pariyaram after approval from the concerned authority.

Statistical analysis

The data collected was entered in an MS Excel sheet and analyzed using Statistical Package for Social Sciences 26. Results are expressed as percentages. The Chi-square test was applied to find associations between variables, $p<0.05$ is considered as statistically significant.

Operational definitions

Pulmonary TB microbiologically confirmed: a patient with sputum specimens positive for AFB by microscopy or CBNAAT/TRUNAT. Pulmonary TB clinically diagnosed: a patient with symptoms suggestive of TB, sputum specimen which were negative for AFB by microscopy and CBNAAT/ TRUNAT. But the patient has chest radiographic abnormalities consistent with active pulmonary TB (including interstitial or miliary abnormal images), or a patient with two sets of at least two sputum specimens taken at least two weeks apart, and which were negative for AFB by microscopy, and radiographic abnormalities consistent with pulmonary TB and lack of clinical response to one week of broad-spectrum antibiotic therapy. Extrapulmonary TB microbiologically confirmed: this included TB of organs other than the lungs, such as lymph node, abdomen, genitourinary tract, skin, joints bones, meninges, etc. Diagnosis of EPTB was based on CBNAAT/TRUNAT of the sample taken. Extrapulmonary TB clinically diagnosed: this included TB of organs other than the lungs, such as lymph nodes, abdomen, genitourinary tract, skin, joints bones, meninges, etc. Diagnosis of EPTB was based not based on CBNAAT/ TRUNAT of the sample taken but by other investigations like fine needle aspiration cytology or biochemical analyses of cerebrospinal/pleural/ ascitic fluid or histopathological examination or strong clinical evidence consistent with active EPTB, followed by a decision of a clinician to treat with a full course of anti-tuberculosis chemotherapy. Method of diagnosis, others: Histopathology, Ultrasonography, CT, HRCT, MRI,

Biopsy, and X-ray. Microbiologically confirmed TB: Smear or molecular test positive cases. Clinically diagnosed TB: smear /molecular test negative cases diagnosed by other methods of diagnosis.

RESULTS

Demographic profile

Of the 882 cases included in the study, 476 (53.96%) were having PTB and 406 (46.03%) were having EPTB. Among PTB cases 358 (75.2%) were males and 118 (24.8%) were females respectively. Among EPTB cases, males and females were 246 (60.6%) and 160 (39.4%) respectively. Among EPTB, the majority of the cases (66.5%) belong to the age group 21-60 years, including 137 (33.7%) in the 21-40 age group and 133 cases (32.8%) in the 41-60 age group. The majority of the PTB cases were in the age group of 41-80 (70.8%), including 171 (35.9%) in the 41-60 age group and 166 cases (34.9%) in the 61-80 age group. The mean age of the EPTB cases was 41.6 years±18.57, with a minimum age of 1 and maximum age of 85 years. The mean age of the PTB cases was 51.78 years±18.12, with a minimum age of 1 and maximum age of 90 years. Smokers among PTB and EPTB were 78 (16.4%) and 33 (8.1%) respectively. Among PTB cases 166 (34.9%) were diabetic whereas only 42 (10.3%) cases were diabetic among EPTB. HIV status among PTB and EPTB cases were 6 (1.3%) and 2 (0.5%) respectively (Table 1).

Table 1: Distribution of study population based on socio demographic factors (n=882).

Profile		Tuberculosis patients	
	Category	**PTB (n=476, 53.96%)**	**EPTB (n=406, 46.03%)**
Age (years)	≤20	34 (7.1)	62 (15.3)
	21-40	94 (19.7)	137 (33.7)
	41-60	171 (35.9)	133 (32.8)
	61-80	166 (34.9)	71 (17.5)
	>81	11 (2.3)	3 (0.7)
Gender	Male	358 (75.2)	246 (60.6)
	Female	118 (24.8)	160 (39.4)
Tobacco use	Present	78 (16.4)	33 (8.1)
	Absent	398 (83.6)	373 (91.9)
Diabetic status	Diabetic	166 (34.9)	42 (10.3)
	Non diabetic	294 (61.8)	351 (86.5)
	Not evaluated	16 (5.9)	13 (3.2)
HIV status	Positive	6 (1.3)	2 (0.5)
	Negative	442 (92.9)	390 (96.1)
	Unknown	28 (5.9)	14 (3.4)

EPTB cases were mostly clinically diagnosed (81.5%) and 402 cases (84.5%) of PTB were microbiologically confirmed (Table 2). Of patients with any EPTB, common sites of infection included lymphatic (N=123, 30.3%), Gastrointestinal tract (GIT) (N=92, 22.7%) pleural (N=90, 22.2%) and spine (N=28, 6.9%) (Figure 1).

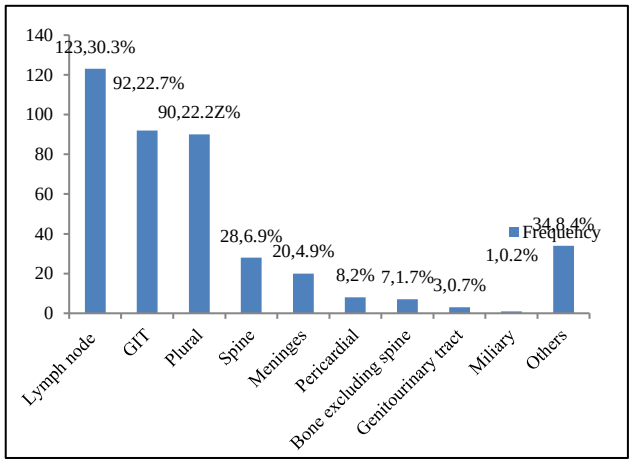

Figure 1: Site distribution in EPTB (n=406).

Relationship between factors associated with PTB and EPTB

There is a significant association between age and type of TB. In the younger age group EPTB and in the older age group PTB were more reported (p<0.001). EPTB cases were more seen among females and PTB cases were seen mostly among males. The relationship is statistically significant (p<0.001). History of tobacco use is mostly seen among PTB cases compared to EPTB (p<0.001). More cases of diabetes were reported among PTB compared to EPTB cases and the relationship is statistically significant (p<0.001). EPTB is mostly seen among non-diabetics.

DISCUSSION

Tuberculosis remains a major global health issue, especially in developing countries like India. In the current study on 882 cases, 476 (53.96%) were having PTB and 406 (46.03%) were having EPTB. It is similar to the study done by Shrivastava et al has done on 491 cases of TB, among them 361(73.53%) had PTB and 130 (26.47%) had EPTB.[2] In another study done in Mukkam, Kerala showed similar results on the prevalence of TB.[15] In the present study, most of the TB cases were seen in the age group of 41-60 years. The incidence of EPTB vs. PTB decreased significantly for each decade increase in patient age (p<0.001). Since the younger age group is most likely to come in contact with other non-infected people, it will be augmenting the risk of the spread of infection. Similar results were found in the study done by Sreeramareddy et al and Lin et al.[16,17] In the present study among PTB and EPTB cases, 604 (68.48%) belong to the male gender (i.e. 358 (75.2%) among PTB and 246 (60.6%) among EPTB respectively).

Table 2: Distribution of study population based on method of diagnosis.

	Category	PTB (n=476, 53.96%)	EPTB (n=406, 46.03%)
Basic of diagnosis	CBNAAT/TRUENAT	242 (50.8)	73 (18)
	Sputum microscopy	160 (33.6)	2 (0.5)
	Chest X ray	38 (8)	7 (1.7)
	Other	36 (7.6)	324 (79.8)
Microbiologically confirmed	Yes	402 (84.5)	75 (18.5)
	No	74 (15.5)	331 (81.5)

Table 3: Relationship between factors associated with PTB and EPTB (n=882).

Factor	Category	PTB (n=476) 53.96%	EPTB (n=406) 46.03%	Total (n=882) 100%	P value
Age (years)	<20	34 (35.4)	62 (64.6)	96 (100)	0.001
	21-40	94 (40.7)	137 (59.3)	231 (100)	
	41-60	171 (56.3)	133 (43.8)	304 (100)	
	61-80	166 (70.0)	71 (30.0)	237 (100)	
	>81	11 (78.6)	3 (21.4)	14 (100)	
Gender	Male	358 (59.3)	246 (40.7)	604 (100)	0.001
	Female	118 (42.4)	160 (57.6)	278 (100)	
History of tobacco use	Present	78 (70.3)	33 (29.7)	771 (100)	-
	Absent	398 (51.6)	373 (48.4)	111(100)	
HIV status	Positive	6 (75)	2 (25)	8 (100)	0.295
	Negative	442 (53.1)	390 (46.6)	832 (100)	
Diabetic status	Diabetic	166 (79.8)	42 (20.2)	208 (100)	0.001
	Non diabetic	294 (45.6)	351 (54.4)	645 (100)	
Microbiologically confirmed or not	Confirmed	402 (84.3)	75 (15.7)	477 (100)	0.001
	Not confirmed	74 (18.3)	331 (81.7)	405 (100)	

It is similar to the study done by Kundu et al, and Pande et al where the percentage of male cases was 67.25% and 71% respectively.[18,19] These findings were in accordance with the statement that PTB is more prevalent among males.[20] The male gender was more significantly associated with PTB, while the female gender was more significantly associated with EPTB (p<0.001). Similar results were observed in studies conducted by Ohene et al, Sreeramareddy et al, Sabu et al and Boum et al.[16,21-23] In the present study, smoking is significantly associated with TB (p<0.001). It is found that among PTB and EPTB prevalence of smoking was 78 (16.4%) and 33 (8.1%) respectively. This finding is similar to the study done by Wang and Shen et al, Gambhir et al and García-Rodríguez et al where smoking is found to be more associated with PTB.[24-26]

In the present study among 882 cases of TB, the prevalence of diabetic patients was 166 (34.9%) among PTB, whereas only 42 (10.3%) were diabetic among EPTB cases. This finding is similar to the study done by Pavlović et al, Raghuraman et al, Pande et al and Jacob et al.[26-28] Many studies proved that DM is more associated with PTB compared to EPTB. A similar result is observed in the study done by Ruslami et al.[7] In the current study HIV status among PTB and EPTB cases were 6 (1.3%) and 2 (0.5%) respectively and it did not show any statistically significant association. This result is in contrast to the study done by Jacob et al, in which HIV as a comorbidity was found to be higher among extra pulmonary TB patients (1.5%) when compared to pulmonary TB patients (1%).[27]

In the present study, EPTB cases were mostly clinically diagnosed (81.5%) whereas 402 cases (84.5%) of PTB were microbiologically confirmed. Main diagnostic modalities for PTB were molecular diagnosis (50.8%), sputum/smear microscopy (33.6%), clinical-radiological data (8%) and others (7.6%); while biopsy, USG, CT, MRI (79.4%), molecular test (18%) and clinical-radiological data (1.7%) were used for confirming EPTB (p<0.001). These findings were consistent with the study done by Sunnetcioglu et al on 411 cases of TB.[28]

In the present study, of 406 cases with EPTB, common sites of infection included lymphatic (n=123, 30.3%), GIT (n=92, 22.7%) pleural (n=90, 22.2%), spine (n=28, 6.9%), meningeal (n=20, 4.9%), pericardial (n=8, 2%), genitourinary tract (n=3, 0.7%) and others. This was similar to the study done by Mavila et al.[3] In another study done by Shrivastava et al at Bopal, India similar observation is made with lymph node, Pleural, abdominal cases in decreasing order.[2] In another study done by Archana et al at Mysore, Karnataka showed pleural TB being commonest followed by lymph node TB.[29]

CONCLUSION

Extrapulmonary tuberculosis remains a significant health problem in developing countries. Our study expands the knowledge regarding the epidemiological factors of EPTB and the association of DM with EPTB. Among males PTB and among females EPTB is more prevalent. The incidence of EPTB vs. PTB decreased significantly for each decade increase in the age of the patient. Young age and female sex were more associated with EPTB compared to PTB. Diabetes mellitus and smoking were more associated with PTB compared to EPTB. The protean and non-specific manifestations of EPTB frequently make accurate diagnosis difficult. Moreover, awareness of these predisposing factors for EPTB may help physicians to maintain a high index of suspicion. Aggressive examinations, including molecular tests, acid-fast staining, TB culture, invasive procedures, or further imaging studies, are required to achieve timely and appropriate diagnosis and treatment of EPTB in suspicious cases. In our study, EPTB sites were lymph node, GIT, pleural, and spine in decreasing order of proportion.

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