http://dx.doi.org/10.4322/2357-9730.75447

Latent tuberculosis among professionals from a referral hospital in oncology

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ABSTRACT

Introduction: Tuberculosis (TB) is an ancient contagious disease, and continues to be the leading cause of morbidity and mortality among infectious contagious diseases. It can be considered an occupational infectious disease when it happens in health professionals. These professionals are directly exposed to TB and are considered to be a high risk population for latent tuberculosis infection (LTBI) and active TB. The primary aim of this study was to estimate the prevalence of LTBI among the clinical and administrative staff of an oncology referral hospital in Rio Grande do Sul. The secondary aim of this study was evaluate tuberculin skin test (TST) conversion rate and the risk factors for TST positivity in this population.

Methods: A cross-sectional study was carried out in a retrospective cohort with data collected in March 2013 and March 2014. Data of professionals from different hospital units were included. Those with induration ≥ 10 mm were considered as reactors, and conversion rate was assessed by an increase ≥ 10 mm in induration in the second TST compared with the first one.

Results: Among the 225 professionals evaluated in 2013, 135 (60%) were reactors and 90 (40%) were non-reactors. The mean age was 32.9 (± 9.55), 176 (78.22%) were female, and most of the reactors worked in the hospital for 4 years or less. Non-reactors in 2013 were recommended to repeat the test in 2014, and the conversion rate was 9.37%. There was no significant difference in prevalence among the different professional categories, and the assessed risk factors were not associated with ILTB.

Conclusions: The prevalence of LTBI in the study population was high, reinforcing the need to implement effective control measures to prevent LTBI in the hospital where the study was conducted.

Keywords: *Latent tuberculosis; occupational risk; tuberculin test; vulnerable populations*

Clin Biomed Res. 2017;37(4):281-287

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Tuberculosis (TB) is a common infectious disease worldwide that is caused by *Mycobacterium tuberculosis* and affects especially the lungs. Pulmonary manifestations are the most frequent and also the most relevant to public health, because of their role in disease transmission. In 2015, 10.4 million new cases of TB were reported. Moreover, 1.8 million patients died from this condition, 400 of which due to TB/HIV coinfection[1]. In Brazil, the incidence of TB in 2015 was 33.2 cases/100,000 inhabitants, with Rio Grande do Sul (RS) being the state with the fourth highest incidence (44.1 cases/100,000 inhabitants). Santa Cruz do Sul is considered a high priority municipality for the control of TB in RS, with an incidence of 46.4 cases/100,000 inhabitants[2].

M. tuberculosis latent infection (LTBI) occurs when an individual is infected but mycobacteria multiplication is controlled due to an effective immune response. If not treated, individuals with LTBI may progress to

active TB. The likelihood of conversion from LTBI to active TB depend on the number of bacilli, time of exposure, and ability of the immune system to control bacilli replication. In individuals with LTBI, mycobacteria remain alive but cannot be transmitted, and patients are asymptomatic[3,4]. It is estimated that nearly 10 out of 100 infected individuals develop disease symptoms throughout life, progressing from LTBL to active TB, especially during the first year of infection[5,6].

For many years, LTBI has been diagnosed by tuberculin skin test (TST), which measures delayed-type hypersensitivity response to more than 200 protein purified derivative (PPD) antigens against *M. tuberculosis*[7]. TST is used for the screening of professionals living or working in risk areas for TB infection, with the advantage of being easy to perform and inexpensive and not requiring laboratory infrastructure[8]. TST conversion is defined as a ≥ 10-mm increase in induration diameter in the second test compared with the first one, considering a maximum interval of two years between the two tests[9]. Calculating TST conversion rates in professionals working at inpatient services or units helps to assess the risk of TB in health care facilities, health care services, and inpatient units[10].

Some groups, such as patients with HIV infection, incarcerated populations, health care professionals, and patients requiring immunosuppressive therapy, are usually considered at high risk for the development of active disease[11].TB in health care professionals is directly related to exposure to *M. tuberculosis*, making them a high-risk population for TBLI and active TB. The risk of infection in this population will depend on factors such as the amount of bacilli eliminated by the infected patient, duration of the infection period, duration of exposure, and individual susceptibility. Conducting tuberculin surveys in hospital workers is essential for the monitoring treatment and inpatient facilities so that to prevent disease transmission in these facilities with the implementation of preventive interventions[12].

With that in mind, the primary aim of the present study was to estimate the prevalence of LTBI in the clinical and administrative staffs of a referral oncology hospital located in the state of Rio Grande do Sul, southern Brazil. The secondary aim of this study was to assess TST conversion rates and risk factors for TST positivity.

METHODS

A cross-sectional study was carried out in a retrospective cohort to assess the prevalence of TBLI and associated factors and TST conversion rates. The study included the clinical and administrative staffs of Hospital Ana Nery and was approved by the Ethics Committee of Universidade de Santa Cruz do Sul (UNISC) (protocol 870.446).

Hospital Ana Nery is medium-complexity hospital with an Integrated Oncology Center that is a referral service in the regions of Rio Pardo Valley and Centro-Serra regions of the state of Rio Grande do Sul. The hospital is located in Santa Cruz do Sul, a city in the central region of the state that is 155 km distant from the state capital, Porto Alegre. In 2014, the hospital staff included 481 employees.

Epidemiological data were collected from questionnaires administered during awareness campaigns of the III and IV TB Weeks in March 2013 and March 2014 respectively. These campaigns took place in the city of Santa Cruz do Sul and were organized by the City Administration of Santa Cruz do Sul, Hospital Ana Nery, and UNISC.

Participants signed an informed consent form, answered a structured questionnaire through a face-to-face interview, and underwent TST. Workers who were TST negative (non-reactors) in 2013 were invited to repeat the test in 2014. Those who were reactors in 2013 were sent for chest X-ray examination to rule out active disease.

The data collection instrument included questions on age, sex (male/female); skin color (white/nonwhite); educational level (elementary school/high school/higher education); monthly income (1-3 minimum wages/4-5 minimum wages/ ≤ 6 minimum wages); unit of work and position, previous BCG vaccine (yes/no); length of employment (< 4 years/≥ 4 years); duration of working shift (6h/8h/other); possible exposure to TB (yes/no); smoking status (smoker/non-smoker/former smoker); HIV infection status (positive/negative/not tested), use of immunosuppressive drugs (yes/no), diabetes mellitus (DM) (yes/no), renal failure (yes/no); chemotherapy treatment (yes/no). Previous BCG vaccine was determined by the presence of a BCG scar on the right arm.

All hospital employees were invited to participate in the campaigns, regardless of professional category or unit of work. Based on the unit of work and position, workers were divided into four groups: nursing staff (practical nurses and nurses); administrative staff (receptionists, patient care agent, marketing team,

human resources team, finance team); diagnostic and therapeutic technicians (professionals working at the hospital pharmacy and in diagnostic services); and general services workers (professionals working at sanitation, kitchen, maintenance, and laundry services, among others).

All professionals who agreed to undergo TST during awareness campaigns in the III and IV TB Weeks were included in the study (n = 225). Those who did not return for TST reading after 72 hours were excluded from the study.

TST was administered using the Mantoux technique, consisting of an intradermal injection of 0.1 mL PPD RT-23 with 2 tuberculin units on the middle third of subjects' forearm. Induration was measured and interpreted 72 h after PPD administration by the same professional. TST positivity was established as an induration diameter ≥ 10 mm. Conversion rate was determined considering an increase of ≥ 10 mm in induration in the second test compared with the first one.

Sample size was calculated using OpenEpi13 considering a prevalence of 40% for LTBI in health professionals (based on literature findings of prevalences ranging from 10% a 40%[9-16]), 95% confidence level, a design effect of 1, and 5% of losses and refusals Data were tabulated on Excel spreadsheets and analyzed using the SPSS software, version 20.0. Descriptive and bivariate analyses were conducted. Bivariate analyses were performed using the Pearson chi-square test or the Fisher's Exact test for categorical variables and the Student t test for continuous variables. Statistical significance for association with TBLI was set at $p \leq 0.05$. Associations with *M. tuberculosis* infection were estimated using odds ratio (OR) and 95% confidence interval (95%CI).

RESULTS

A total of 225 professionals, corresponding to 69.2% of hospital staff, were included in the study. Of these, 135 (60.0%) were rectors. Among these, induration diameter ranged from 10 to 58 mm, with a mean induration diameter of 21.55 mm. Of the 90 non-reactors, 14 had an induration diameter from 8 to 9 mm. Considering a cutoff point of induration diameter of 5 mm, overall prevalence of TBLI in the study population was 72%, with a mean induration diameter of 19.2 mm.

Mean age was 32.9 (±9.5) years for the overall sample, 32.7 (±9.1) years for reactors, and 33.65 (±10.2) years for non-reactors (p = 0.4). Table 1 shows the comparison of epidemiological data related to TBLI between reactors and non-reactors. None of the assessed variables was associated with TBLI

Among females, the prevalence of TST positivity was 75.55%. With regard to length of employment, it was found that 62.0% of the 150 employees who had worked at the institution for less than 4 years were reactors.

Overall, 91 (40.4%) reported previous contact with TB patients; of these, 82 (90.1%) stated that this contact occurred at the workplace and 58 (63.7%) were reactors. One (0.4%) worker reported previous TB. BCG scar was observed in 220 (97.8%) subjects.

None of the participants reported HIV infection or chemotherapy treatment. Four (1.7%) workers had DM, two (0.9%) had renal failure, five (2.2%) reported corticosteroid use, and two (0.9%) reported using immunosuppressives.

Table 2 shows the distribution of reactors according to unit of work. The highest prevalence of LTBI was observed among diagnostic and therapeutic technicians and among the nursing team (65.5% and 61.8% respectively). The nursing staff includes practical nurses and nurses. When assessed separately, the prevalence of LTBI among these professionals was 62.7% and 58.8%, respectively.

All reactors (induration diameter ≥ 10 mm) were sent to chest X-ray examination to investigate possible radiologic abnormalities and attended a medical visit for clinical assessment. Radiographic results were available for 55 (40.7%) workers; of these, one showed a radiological abnormality compatible with LTBI and received treatment. This abnormality consisted of a 5-mm granuloma in the left lung base and was observed in a practical nurse working at one of the hospital's clinics.

Of the 90 non-reactors, 32 (35.5%) repeated the test 12 months later to assess conversion rates. Of these, three (9.4%) showed TST conversion. Among the seroconverted subjects, one was a diagnostic and therapeutic technician (pharmacist), and two belonged to the general service staff (maintenance workers). Additionally, two had been working at the hospital for less than 1 year, and one had been working there for 11 years. None of them had previous TB or reported contact with TB patients. These workers were referred for medical assessment to rule out active disease.

DISCUSSION

Accurate diagnosis of LTBI, i.e., establishing the prevalence of *M. tuberculosis* infection, is important for any TB control program and relies mainly on TST. In countries where TB is endemic, there is a high prevalence of TST positivity[14,15]. The prevalence of LTBI among our study population was 60%, in

Table 1: Epidemiological and clinical characteristics associated with TBLI according to TST results.

CHARACTERISTICS	TOTAL n (%)	Reactors (induration diameter ≥ 10 mm) n (%)	Non-reactors (induration diameter < 10 mm) n (%)	p
SEX				
Female	176 (78.22)	102 (57.95)	74 (42.05)	0.25
Male	49 (21.78)	33 (67.35)	16 (32.65)	
EDUCATION				
Elementary School	27 (12)	13 (48.15)	14 (51.85)	
High School	117 (52)	70 (59.83)	47 (40.17)	0.33
Higher education	81 (36)	52 (64.2)	29 (35.8)	
MONTHLY INCOME				
1-3 minimum wages	202 (89.8)	118 (58.4%)	84 (41.58)	
4-5 minimum wages	21 (9.3)	16 (76.2)	5 (23.8)	0.27
≤ 6 minimum wages	2 (0.9)	1 (50.0)	1 (50.0)	
PROFESSIONAL CATEGORY				
Nursing Staff + Diagnostic and Therapeutic Technicians	105 (46.67)	66 (62.86)	39 (37.14)	0.5
Administrative Staff + General Service Workers	120 (53.33)	69 (57.5)	51 (42.5)	
LENGTH OF EMPLOYMENT				
≤ 4 years	150 (66.67)	93 (62)	57 (38)	0.39
> 4 years	75 (33.33)	42 (56)	33 (44)	
DURATION OF WORKING SHIFT				
4 h	9 (4.0)	6 (66.66)	3 (33.33)	
6 h	112 (49.78)	63 (56.25)	49 (43.75)	0.38
8 h	101 (44.89)	63 (62.38)	38 (37.62)	
12 h or more	3 (1.33)	3 (100)	0 (0)	
PREVIOUS TB				
Yes	1 (0.44)	1 (100)	0 (0)	1
No	224 (99.56)	134 (59.82)	90 (40.18)	
CONTACT WITH TB PATIENTS				
Yes	90 (40.0)	58 (64.44)	32 (35.55)	0.33
No	135 (60.0)	77 (57.04)	58 (42.96)	
SMOKING STATUS				
Non-smoker	184 (81.78)	109 (59.24)	75 (40.76)	
Smoker	25 (11.11)	17 (68.0)	8 (32.0)	0.66
Former Smoker	16 (7.11)	9 (56.25)	7 (43.75)	
HIV				
Negative	186 (82.67)	116 (62.36)	70 (37.62)	0.15
Not Tested	39 (17.33)	19 (48.72)	20 (51.28)	
DIABETES MELLITUS				
Yes	4 (1.78)	2 (50.0)	2 (50.0)	1
No	221 (98.22)	133 (60.18)	88 (39.82)	
IMMUNOSUPRESSIVE THERAPY				
Yes	2 (0.89)	0 (0)	2 (100)	0.16
No	223 (99.11)	135 (65.54)	88 (34.46)	

Table 2: Distribution of reactors according to professional category.

PROFESSIONAL CATEGORY	n	REACTORS n (%)	OR (95%CI)	p
Administrative Staff	59	35 (59.32)	0.96 (0.52 - 1.76)	1.00
Nursing Staff	76	47 (61.84)	1.12 (0.64 - 1.98)	0.77
Diagnostic and Therapeutic Technicians	29	19 (65.52)	0.78 (0.43 - 1.42)	0.45
General Service Workers	61	34 (55.74)	1.31 (0.58 - 2.97)	0.55

OR = odds ratio.

agreement with findings from other studies using the same cutoff point, in which prevalences ranged from 15.4% to 78.3%[6,14-18]. In a study similar to the present one, Severo et al. reported a prevalence of 47.3% for LTBI in a teaching hospital in Santa Cruz do Sul, with higher values among practical nurses compared with nurses, results consistent with results presented here[17]. In the present study, the booster effect was not evaluated, complying with recommendations from the III TB Guidelines of the Brazilian Society of Pulmonology and Phthisiology stating that booster effect testing is not required when assessing health professionals[3].

The highest prevalence of LTBI was observed in males and females from 25 to 45 years of age. This finding is consistent with those reported in other studies[8,15-20]. In developing countries, 80% of infected individuals are aged from 15 to 59 years old. Corroborating previous studies[7,16,17,21,22], our study population was predominantly female (78.2%). TST positivity was higher in males than in females (67.3% *vs*. 58.0%). In Brazil, 66.0% of TB cases occur in males, with subjects from 45 to 54 years of age showing the highest incidence rate[21,23]. Most infected men are of economically active age, which has a negative impact on economic growth and social development, increasing poverty and social exclusion[24]. It bears noting that the highest incidence of TB in older patients may be related to latent infection acquired in childhood or early adulthood.

The presence of some immunodeficiency, comorbidity, or use of immunosuppressive drugs may reactivate a latent infection, favoring the development of the most severe forms of infection[25]. The impact of non-communicable diseases on the incidence of TB has received increased attention. DM may favor the development of TB and account for more than 10% of TB cases, due to immunosuppression. In Brazil, cases of TB patients with DM increased from 380/100,000/year in 2001 to 6,150/100,000/year in 2011 [20,21]. In the present study, HIV status and DM were not associated with LTBI. It is worth investigating the use of corticosteroids and immunosuppressive drugs when performing the TST, because these drugs may decrease delayed-type hypersensitivity to PPD, being one of the factors that may lead to false-negative results[26]. However, this association was not observed in the present study. Many risk factors for TB infection were reported in other studies[3,17], the most common of which are age, sex, skin color, and corticosteroid use. Despite that, none of these variables was associated with TST results in our study.

BCG vaccination is associated with high rates of TST false positive results, especially if vaccination (or revaccination) occurred after the first year of life, when it produces stronger and long-lasting reactions. Nonetheless, this reaction tends to become less intense over time; thus, if TST is performed 10 years or later after the last BCG vaccination, the effect of this vaccine on test results may be minimal. In Brazil, the coverage of BCG vaccination is universal, and children are usually vaccinated within the first years of life[11,17]. BCG scar was observed in 97.8% of study participants and was not associated with LTBI.

There was a high frequency of TST positivity among professionals with a length of employment of 4 years or less (66.66%). This may be related to a previously acquired infection or an infection acquired recently at the workplace[17]. A study with workers of a university hospital showed that the risk for TST positivity increased after 1 year working at the institution, suggesting that prevention should be focused on individuals at the beginning of their career[15,22]. However, our results preclude any conclusion as to the association between TST positivity and length of employment, because TST is not routinely performed as a pre-hiring or periodical screening test for health care workers.

There was no significant difference in TST positivity between the different professions assessed in this study. The highest prevalence of TST positivity was found among diagnostic and therapeutic technicians (65.52%). This may be explained by the fact that patients travel throughout the hospital, exposing workers considered at low-risk for infection to cases of undiagnosed TB[27].

Among the professionals who underwent X-ray examination, one had a radiological abnormality consistent with granuloma. This abnormality is typical of LTBI and may lead to disease progression, depending on the number and virulence of bacilli and on the degree of host hypersensitivity and resistance[26]. Once the possibility of disease is ruled out, the indication of treatment of LTBI with

isoniazid for a period from 6 to 9 months should be considered[18]. This treatment aims to prevent active TB in individuals at high for reactivation of latent foci, such as those with HIV infection, silicosis, on dialysis for chronic renal failure, head and neck neoplasm, or using tumor necrosis factor alpha inhibitors, among other clinical conditions. It has been usually accepted that treatment of TBLI reduces the risk for active TB from 60.0 to 90.0%. Prophylactic treatment with isoniazid is recommended for professionals whose infection was acquired in the last 2 years or those who are considered at high risk for active TB[18,19,21].

Several previous studies assessed TST conversion rates among health care workers and students, with rates ranging from 1.4 to 20.7%[16,18,20,28]. Our rate (9.3%) was similar to that found by Pérez-Lu et al.[28], who conducted a retrospective study about TST conversion in 4,842 health students and found a conversion rate of 12.4%. Kiertiburanakul et al.[16] found a TST conversion rate of 4.8% at a hospital in Thailand. Roth et al.[20] observed a conversion rate of 10.7%.

In developing countries, the risk for infection/disease among health care professionals would decrease if TB control was considered a priority by government and health authorities. Health care professionals are valuable resources for infection control as long as they take individuals self-protection measures. Educational programs are essential for understanding the basic concepts of disease transmission and symptoms and understanding the importance of personal protection measures for TB control[17].

One limitation of this study was the unavailability of PPD in the market to complement the tests for assessment of conversion rate. As informed in the Circular Letter 25/CGPNCT/DEVIT/SVS/MS, released by the Brazilian Ministry of Health, there are no plans to provide the health care system with PPD. Other limitations included small sample size and lack of testing for diagnosis is immunosuppressive diseases such as HIV infection (HIV status was based only on self-report at the time of interview). Another important limitation was the lack of a question to assess working a double shift, a common practice especially among the nursing staff. The non-inclusion of physical therapy and medical professionals, who have high rates of exposure, may have influenced the prevalence of LTBI in the present sample. In our study, conversion rates were calculated based only on data from the 32 non-reactors who repeated the test and thus may have been underestimated.

The prevalence of LTBI as assessed by the TST was 60%, and TST conversion rate was 9.37% among the professionals assessed in this study. No association was found between LTBI and epidemiological or clinical characteristics. Additionally, there was significant difference in the prevalence of LTBI between clinical and administrative staffs, with diagnostic and therapeutic technicians showing the highest rates. LTBI is a major occupational problem among professionals working in the hospital environment, especially those who work in direct contact with patients. Our findings suggest that preventive strategies and health personnel surveillance should be improved. Currently, TST is not performed as a pre-hiring for health care workers, but we suggest including this test in the pre-hiring and periodical routine assessment of TST-negative workers. Other similar studies need to be conducted in different hospitals and health care units, in order to complement our data and emphasize the need for screening of all hospital workers.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

National Council of Scientific and Technological Development (Conselho Nacional de Desenvolvimento Cientifico e Tecnológico, CNPq) - Undergraduate Research Scholarship (process 125968/2014-0).

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Received: Aug 03, 2017
Accepted: Oct 27, 2017