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Trends of Tuberculosis And Its Determinants In Urban Population of Delhi, India

KEYWORDS: tuberculosis, blood group, diabetes, urban population

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ABSTRACT *Studies on the association of blood groups and tuberculosis have started since the 20th century and till date there is no plausible result on this association. It has also been an established fact that diabetes leads to tuberculosis infection but there are very few studies which support that antituberculosis treatment elevate the random blood sugar level. The present study was aimed at observing the trends of tuberculosis and its determinants in the urban population of Delhi India.*

The ABO blood grouping and rhesus typing were performed by using the standard slide agglutination reaction in 234(104 females and 130males) TB patients enrolled in various DOTS centers of North Delhi and 207controls (101 females and 106 males)in the age group 14-60years.

The highest frequency of the occurrence of blood groups 'B' and 'AB' was found among tuberculosis patients which highlights a possible association between the incidence of tuberculosis and the blood groups 'B' and 'AB'. The patients within 0-2weeks of antituberculosis treatment were found to have higher mean blood sugar levels(167.3 mg/dl) as compared to patients within 2-5weeks of treatment(mean=122.7 mg/dl). A significant association between the incidence of extrapulmonary tuberculosis and negative Rhesus antigen was observed($p<0.001$).

The present study showed that there was an association between tuberculosis and the blood groups 'B' and 'AB'. It is also evident that people with negative rhesus blood group have higher risks of extrapulmonary tuberculosis.

Introduction

Approximately 30% of the population worldwide is infected with Mycobacterium tuberculosis (M.TB), with only a subset (5-10%) of those infected progress to active TB disease (Flynn & Chan, 2001) yet this pulmonary pathogen has been causing two million deaths worldwide annually(Dye et al. 1999). The human response to combat this etiologic agent of tuberculosis -"World Health Organization Stop TB Strategy" has been globally adopted and widely implemented by most countries with a high burden of tuberculosis (TB) but the rate of decline in case numbers associated with Tuberculosis has been slower than expected(Dye et al, 2009; WHO,2010). Improved sanitation, better nutrition and less crowding led to markedly diminished tuberculosis incidence. This rate is a consequential factor of patient and health system delays in diagnosis and treatment, the rise of risk factors includes co-infections (notably with human immunodeficiency virus, HIV), air pollution, alcohol abuse, overcrowding, diabetes, malnutrition, tobacco smoking, urbanization(Lo¨nnroth et al. 2010) and migration especially in developing countries. The associations between tuberculosis and its correlates like ABO blood groups, Rhesus blood group, chronic diseases, other infections, etc. and their synergistic role in causing diseases to humans have been identified for centuries but their recognition in strategy formulation and implementation remains equivocal. For years, numerous attempts have been made to understand some correlations between blood groups and heightened susceptibility to tuberculosis yet clear associations between types of TB and blood types are still veiled.

Diabetes Mellitus (DM) is another epidemic and it is estimated to affect 366 million by 2030 when majority of those affected will be living in low and middle income countries where Mycobacterium tuberculosis infection is endemic. Currently the association between DM and TB is re-emerging because the epidemiology of both diseases is progressive worldwide and cases of

DM is increasing in the developing countries where TB is of high burden (Dooley & Chaisson 2009). In recent decades, tuberculosis has increasingly become a problem in low-income countries, particularly those with HIV epidem-

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ics. Non-insulin-dependent diabetes mellitus (NIDDM) has emerged as a growing worldwide chronic health condition, as a consequence of increase in obesity, changing patterns of diet and physical activity and aging populations. The effect of diabetes on the development and severity of tuberculosis and the complex interrelations between nutrition, obesity, diabetes, and tuberculosis remain provocative issues in the domain of public health and clinical medicine (Bukhary 2008). Robert Koch's recognition in 1882 of Mycobacterium tuberculosis as the microbial cause of tuberculosis (TB) led shortly thereafter to the identification of methods to stain bacilli in clinical specimens, rendering the organisms visible with use of light microscopy (Koch 1882). Such was the birth of TB diagnostics and of diagnostic microbiology in general. Tragically, development and implementation of TB diagnostics kept pace neither with medical technology nor with the catastrophic explosion of TB, including drug-resistant TB, in the wake of the global human immunodeficiency virus (HIV) pandemic. Inadequate tools and weak systems for laboratory-based diagnosis of active TB have contributed to, (a) under-diagnosis of disease, leading to individual morbidity and mortality and to continued transmission; (b) over-diagnosis of disease, leading to unnecessary treatment with attendant consequences to the patient and inappropriate resource utilization by the health care program; and (c) delayed diagnosis of drug resistance, leading to acquisition of additional resistance and to morbidity and transmission (Dorman 2010). Hence, there is a clear need for development, introduction and effective implementation of cost-effective new tools that provide a speedy, effective, accurate and cost-effective diagnostic test, which is central to the goal of rolling back the global tuberculosis epidemic that afflicts nearly a third of the world's population.

Therefore, this article intends to draw associations between ABO blood group and Rhesus blood group with types of TB - pulmonary TB (PTB) and extra pulmonary TB (EPTB) after controlling for BCG status and draw sugar profiles for TB patients enrolled in the DOTS program for 0-5weeks.

Subjects and methods

Study area

The study was conducted amongst the newly diagnosed pulmonary tuberculosis (PTB) and extra pulmonary tuberculosis (EPTB) patients treated under category I of the DOTS program from the urban population of Delhi. The collection of data was started from 1st January 2011. The cross-sectional study was conducted among 234 (104 females and 130 males) TB patients enrolled in various DOTS centers of North Delhi and 207 controls (101 females and 106 males) in the age group 14-60 years. Ethical clearance was taken from Department ethical committee before starting the study. Purpose of the study was explained to all the volunteer subjects prior to data collection and written consent was obtained from each subject.

Case definition

A PTB case was defined as an individual whose sputum was positive for acid fast bacilli by ZN microscopy and/or growth of M. tuberculosis by culture examination and has been identified by the DOTS centre with a valid registration number on anti-TB drugs for 0-5 weeks.

EPTB refers to a case of TB (defined above) involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meningitis. Diagnosis was based on at least one specimen with confirmed M. tuberculosis or histological or strong clinical evidence consistent with active EPTB, identified by the DOTS centre with a valid registration number on anti-TB drugs for 0-5 weeks. Controls were BCG vaccinated individuals with no previous history of TB.

Study design and data collection

Only those subjects who volunteered were studied after the procedure and purpose was explained to them. Informed written consent was obtained from each subject. The patients were contacted at the DOTS centers in Delhi and the addresses of those who agreed to participate in the study were taken but they were examined at their homes. All experiments and disposal procedures were performed in accordance with relevant guidelines and regulations. Ethical clearance was obtained as per rules. Blood groups of all the subjects were determined by testing the individual's red blood cells with anti-sera and by identifying antibodies in his/her own serum, and testing against cells containing known antigens. Random blood sugar was measured with single prick technique using Accu chek glucometer.

Individuals with random sugar level of more than 140 mg/dl were referred to as 'pre-diabetic' in the present study, and the subjects with less than 140 mg/dl as 'normal' blood sugar (ADA 2009).

The data was computerized, edited and corrected for mistakes, if any, and analyzed using SPSS package (17.0 version).

Results

Table 1 displays the basic data of the subjects. The mean age (cases) of males was 31 years and females was 24 years. The mean age of control subjects was 26 years in males and 28 years among females. As per the BCG vaccination status the percentage of cases who were vaccinated were 81.5 & 81.7 in males and females respectively, whereas among controls all the subjects were vaccinated. The mean values of normal random blood sugar for cases were 110.8 mg/dl (males) and 108.1 mg/dl (females) respectively. The mean values of cases classified under pre-diabetic category were 185.1 mg/dl (males) and 182.4gm/dl (females). The total number of cases were 130 males and 104 females, out of which 63.8% males and 61.5% females were suffering from pulmonary tuberculosis (PTB), the other 36.2% males and 38.5% females were confirmed to be extra pulmonary tuberculosis (EPTB) cases.

Table 1: Basic data of the subjects

Variables		Cases		Controls	
		Males (N=130)	Females (N=104)	Males (N=106)	Females (N=101)
		N (Mean± S.D)			
Age in years →		(31 ± 4.58)	(24 ± 1.43)	(26 ± 2.65)	(28 ± 6.34)
BCG[a] status	Yes	106	85	106	101
	No	23	15	-	-
	Don't know	1	4	-	-
Random blood sugar level (mg/dl)	Normal	36 (110.8± 3.13)	23 (108.1±13.81)	-	-
	Pre diabetic	18 (185.1±40.66)	29 (182.4±44.86)	-	-
Type of TB	PTB[b]	83	64	-	-
	EPTB[c]	47	40	-	-

[a]BCG=Bacillus Calmette Guerin; [b]PTB=pulmonary tuberculosis; [c]EPTB=extra pulmonary tuberculosis

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The best predictor for tuberculosis among patients was found to be the BCG vaccination status which is statistically significant at p<0.001 (β=0.225) followed by Rh-factor at p<0.05 (β=0.135). Blood groups (β=0.102) had no significant contribution towards prediction of tuberculosis status.

Table 2: Predictors of tuberculosis among patients

Variable	Coefficient β	Level of significance
BCG	0.225	0.001
Rh factor	0.135	0.020
Blood group	0.102	0.077

Figure 1 displays the distribution of ABO & Rh blood group system among cases and controls. Among blood group 'A' type it was found that 22.5% (N=42) were cases and 37.2% (N=38) controls. In blood group 'B' type 33.1% (N=62) were cases and 19.6% (N=20) were controls. In blood group 'AB' type 23.5% (N=44) were cases and 31.4% (N=32) were controls; 20.9% (N=39) cases and 11.8% (N=12) controls were found to have blood group 'O' type. The difference in the distribution of ABO blood groups among cases and controls were found to be statistically significant at p<0.01 (χ3=14.1; df=3). Out of the cases, 20.3% (N=38) were found to be Rh –ve and 79.7% (N=149) Rh+ve. Among controls 8.8% (N=9) were found to be Rh-ve and 91.2% (N=93) were Rh+ve. The difference in the distribution Rh blood group system among cases and controls were found to be statistically significant at p<0.01 χ^2=7.37; df=1).

Figure 1: Distribution of ABO & Rh blood group system among TB patients and controls

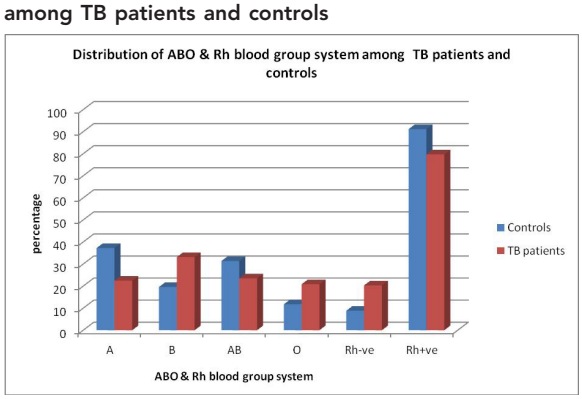
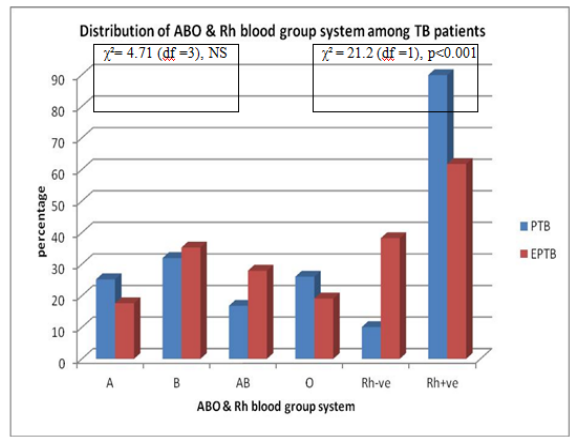


Figure 2 displays the distribution of ABO & Rh blood group system among cases with pulmonary tuberculosis (PTB) and extrapulmonary (EPTB). Among patients with pulmonary tuberculosis 25.2% (N=30) were having blood group 'A' type, 31.9% (N=38) were blood group

'B' type, 16.8% (N=20) were blood group 'AB' type and 26.1% (N=31) were 'O' type blood group. Among patients with extrapulmonary tuberculosis 17.7% (N=12) were having blood group 'A' type, 35.3% (N=24) were blood group 'B' type, 27.9% (N=19) were blood group 'AB' type and 19.1% (N=13) were blood group 'O' type. The difference in the distribution of ABO blood groups among pulmonary tuberculosis cases and extrapulmonary cases was found to be statistically non-significant (χ^2=4.71; df=3).

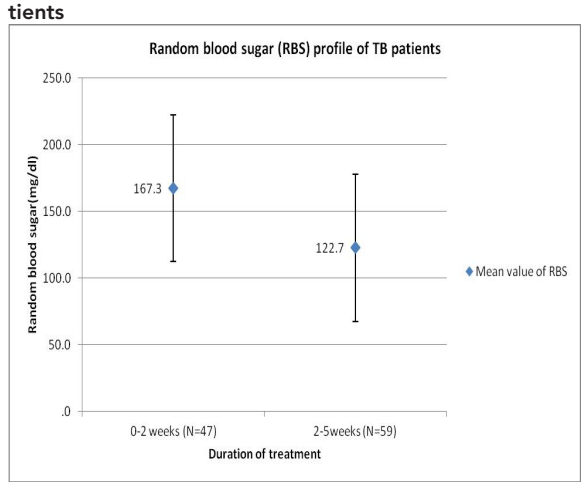
Figure 2: Distribution of ABO & Rh blood group system among cases with pulmonary tuberculosis (PTB) and extra pulmonary tuberculosis (EPTB)



Among patients with pulmonary tuberculosis 10.1% (N=12) were Rh –ve and 89.9% (N=107) were Rh+ve; among extrapulmonary patients 38.2% (N=26) and 61.8% (N=42) were Rh-ve and Rh+ve respectively. The difference in the distribution of Rhesus blood group among pulmonary tuberculosis and extra pulmonary tuberculosis were found to be significant at p<0.001 (χ^2=21.2; df=1).

Figure 3 presents the random blood sugar profile among tuberculosis patients. The mean value of random blood sugar level for patients who were within 0-2 weeks (N=47) of TB treatment was 167.3 mg/dl while that for patients within 2-5weeks (N=59) of TB treatment was 122.7 mg/dl.

Figure 3: Random blood sugar profile among TB patients



Discussion

It is generally believed that susceptibility to most of the diseases in man is influenced by genetic characteristics of man. Studies on the association of blood groups with pulmonary tuberculosis date back to 1926 when Hilber and Hirzfeld (1926) first reported their negative finding on the association of ABO blood groups in the disease. Since then conflicting reports have appeared in the literature published on work in different population groups. A natural resistance to the many infectious diseases is inherent and this natural resistance, to a certain extent, depends on the blood group of an individual as the immunological response to Mycobacterium tuberculosis in individuals differs with blood groups type (Sybirna et al. 1999). Blood group either protects or predisposes an individual to certain in-

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fection or disease.

In the present study it was found that there was a higher incidence of tuberculosis in general among individuals with the blood groups B and AB. While considering the type of tuberculosis i.e. PTB and EPTB, the scenario was similar. The observed high frequency of B group people in pulmonary and extrapulmonary tuberculosis may be attributed to the lack of protection in persons of blood group B, who lacks anti-B to neutralize the tubercle bacilli by reacting with antigen on the bacilli when a person is infected with the tubercle bacilli (Saha 1985). This association of B-antigen in pulmonary tuberculosis fits well with the antigenicity of tubercle bacillus having B-like antigen (Nunome & Akai 1951). This corroborates with the earlier studies done in the Chinese & Singapore populations (Saha, & Banerjee 1968; Saha 1973), Indians (Jain 1970), Japanese (Hirano 1972) and Eskimos (Overfeld & Klauber 1980). However, regression analysis found no significant contribution of blood group towards prediction of tuberculosis status which supports that the susceptibility of the populations with specific blood types depends on the geographic and the racial distribution of the human blood groups (Rao et al. 2012).

The present study revealed that rhesus negative status increases the risk of tuberculosis 2.63 times ($p<0.01$) than rhesus positive status. The risk of having EPTB was 5.52 times ($p<0.001$) more among rhesus negative blood group compared to PTB. This supports the earlier findings that extra-pulmonary lesions with or without pulmonary disease appeared to be more frequent in rhesus-negative than rhesus-positive males (Campbell 1956). Viskum (1975) in his study of 554 patients among bacillary or abacillary pulmonary tuberculosis in the Municipality of Copenhagen found that more rhesus negative patients died from tuberculosis than rhesus positive.

Tuberculosis has been being portrayed as a 'complication' of diabetes parroting "one-sided relationship" which underestimates the incidence of diabetes among tuberculosis patients. In the present study, random blood sugar level among patients who were within 0-2 weeks of TB treatment was higher (mean=167.3 mg/dl) than among patients within 2-5weeks of treatment (mean=122.7 mg/dl) implying 'transitory' diabetes in TB (Engelbach 1954). These patients have reported no earlier history of high blood sugar level. Oral glucose tolerance test has suggested glucose intolerance among patients with tuberculosis than community controls in several studies (Oluboyo & Erasmus 1990; Bell et al. 2007). However, the glucose intolerance occurring in the setting of TB without diabetes is reversible following adequate antituberculosis treatment (Basoglu et al. 1999) which has been revealed by the present study also. This early phase hyperglycemia may be produced by rifampicin which augments intestinal absorption of glucose (Takasu et al. 1982). Karachunskii et al. (1995) has also stated changes in carbohydrate metabolism in TB patients, which include an initial pronounced, enhanced insulin secretion leading to signs of relative insulin deficiency and persistent hyperglycemia. This sets the stage for the more frequent development of severe diabetes mellitus in patients with tuberculosis. Thus, high blood sugar levels subsequent to tuberculosis infection underscore the importance of screening tuberculosis patients for diabetes.

Several studies have argued about the protective efficacy of BCG vaccination (Hart 1967; Fine 1995). The present study found that BCG ($\beta= 0.225$; $p<0.001$) protects an individual against tuberculosis. The effectiveness of BCG however depends on the nutritional status, dose of tuberculin and natural immunity of an individual. In Individuals free of all mycobacterial infection, non-specific infection may confer some degree of natural immunity, with limited additional protection provided by superimposed BCG vaccination (Hart 1967; Arbeláez et al. 2000).

Elimination of tuberculosis in industrialized nations hinges on diagnosis and treatment of latent tuberculosis infection to prevent disease. The basic strategy to the prevention and control of TB require screening populations at high risk for TB or individuals infected with TB and giving complete therapy to prevent the infection from progressing to active, contagious disease. Most infected persons do not experience clinical illness, but are usually asymptomatic and noninfectious. However, infection can persist for years, and infected persons can remain at risk for developing clinical TB, especially if the immune system becomes impaired (CDC 1995). The estimated prevalence rates of latent tuberculosis infection (LTBI) in India ranges from 9 - 80% in various populations (Mayurnath et al 1991). The tuberculin skin test (TST) has been employed for screening latent TB infection (LTBI) but it requires two visits and skilled personnel for test placement and interpretation (Barnes et al. 2002) and has low specificity in Bacille Calmette- Guérin (BCG)-vaccinated populations (Diel et al. 2009).

Conclusion

The present paper have emphasized on various parameters which play a significant role in the trends of tuberculosis. The findings of high random blood sugar levels among patients who have no history of diabetes accentuate the importance of screening tuberculosis patients for diabetes. The association between negative blood group and extrapulmonary tuberculosis needs to be explored further.

Key message:

This study highlights the importance of further exploration of the relationship between blood group and tuberculosis. Tuberculosis has long been associated with the disease of poverty, however, since it is a communicable disease it is not limited to the poor alone, it also afflicts people from all walks of life.

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