Different risk factors of recurrent pulmonary tuberculosis between Tibetan and Han populations in Southwest China

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Abstract. – **OBJECTIVE:** The geographical environment and living habits are different between Tibetan and Han populations. The present study aimed to investigate the risk factors of recurrent pulmonary tuberculosis (TB), and analyze the differences between the two populations.

PATIENTS AND METHODS: A total of 480 TB patients, including 80 Tibetan and 80 Han patients with recurrent pulmonary TB, and 320 patients without recurrent pulmonary TB, were included in present study. All patients with pulmonary TB were diagnosed between 2000 and 2001 and followed until December 2012. Multivariate logistic regression was used for the statistical analysis.

RESULTS: Among all patients, the independent risk factors associated with recurrent pulmonary TB were no use of directly observed therapy, short course (DOTS) (HR 5.867, 95% CI 2.557-13.461), diabetes (HR 3.288, 95% CI 1.301-8.312), smoking (HR 2.387, 95% CI 1.328-4.291) and malnutrition (HR 1.910, 95% CI 1.110-3.285). The independent risk factors of recurrent pulmonary TB for the Tibetan patients included no use of DOTS and malnutrition, while the independent risk factors for the Han patients were diabetes and smoking.

CONCLUSIONS: The risk factors of pulmonary TB recurrence were different between Tibetan and Han patients. To reduce the recurrent rate of pulmonary TB, especially for Tibetan populations, pursuing high-quality DOTS is essential.

Key Words:
    Recurrent tuberculosis, Directly observed therapy, Diabetes, Smoking, Malnutrition.

Introduction

Pulmonary tuberculosis (TB) is a common infectious disease of respiratory tract, causing at least 1.4 million deaths in the world annually, and recurrent pulmonary TB should be taken seriously since recurrent cases are more likely to result in multi-drug resistance[1,2]. The rate of recurrent pulmonary TB was dissimilar among different populations, which has been reported from 3.3% to 20.0%[3,4]. Screening risk factors of recurrent TB would identify the most susceptible populations to adopt efforts and measures of treatment follow-up, TB control strategies and application of public health resources[5].

To our knowledge, causes and risk factors of recurrent pulmonary TB have still not been well described in Southwest China, which is a relatively backward region and is also a high burden TB region. The majority populations in this region are Han and Tibetans. Most Tibetans live in the plateau area and take herds as lives. The level of urbanization in the district which Tibetans live is relatively low. Naked barley flour, beef and butter is the staple food for generations. It is unknown whether the differences of geographical environment and living habits between Tibetan and Han populations are associated with TB recurrence. No data have so far been published on recurrent TB in Southwest China. Therefore, the aim of the present study was to investigate the risk factors of recurrent TB in Southwest China, and analyze the differences between Tibetan and Han populations.

Patients and Methods

This study was approved by the West China Hospital institutional Review Board. This is a retrospective case-control study, both cases and controls were selected from the West China Hospital, which is a University-Affiliated Teaching Hospital with more than 4,300 beds. It is the

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largest general hospital in West China and is the only general hospital with independent tuberculosis wards in China.

Patients over 18 years old, who were Tibetans or Han in Southwest China with pulmonary TB confirmed by bacteriologically positive (smear or culture), were assessed for inclusion in the study. The bacteriology examination was performed by our Department of Laboratory Medicine, which has passed the authentication of the College of American Pathologists for 6 consecutive years. Patients were excluded if they could not be contacted so that we were unable to obtain the information of patients after being discharged.

Recurrent cases were patients who had been declared cured or treatment completed for their first TB episode[6]. A cured patient was defined as a patient whose sputum became culture-negative, who became asymptomatic or could not produce sputum at completion of treatment. We selected control cases when we found each recurrent pulmonary TB patient. Every case was matched to two controls. The controls were made up of patients who were cured after completion of adequate therapy for a first episode of TB and who had been free of the disease for at least 1 year after discharge from supervision. Cases were matched using a stratified random sampling method on age stratum and gender.

All available medical records of patients were reviewed to collect demographic data and clinical information. Patients were identified between the years 2000 and 2001, and followed until December 2012. Demographic variates for each patient included ethnic group, age and gender. Clinical history variates included alcoholism (≥ 1 drink per day), smoking status (smoker or nonsmoker), HIV infection, chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic hepatitis, immunosuppressor treatment, malnutrition (body mass index < 18.5 and/or serum albumin < 30 g/L), and whether use of DOTS (directly observed treatment, short course).

Statistical Analysis

Categorical variates were analyzed at first using bivariate methods to test for differences between cases and controls. X^2 test or Fisher's exact test was used for the association analysis. Hazard ratios (HRs) for demographic and clinical factors were calculated from univariate analysis. Variates associated with a *p* value < 0.25 or with a HR > 1.5 were included in multivariate analysis. Stepwise logistic regression analysis was per-

formed to identify independent risk factors among cases and controls. Adjusted HRs was used as the measure of association, and 95% confidence intervals (95% CIs) were calculated. Hazard analyses were also performed looking specifically at the subset of Tibetan and Han patients respectively. Statistical analyses were all conducted using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Univariate Analysis

80 Tibetan and 80 Han patients with recurrent pulmonary TB were identified as case group, and a total of 320 patients without recurrent pulmonary TB as predefined were included in the control group. Table I shows demographic and clinical variates that were compared between cases and controls. Cases were significantly more likely than controls to be malnutrition (41.9% vs. 25.0%; *p* = 0.003) and HIV positive (26.9% vs. 18.8%; *p* = 0.222). Cases were also more likely than controls to have a history of alcoholism (61.9% vs. 48.4%; *p* = 0.036) and smoking (79.4% vs. 60.9%; *p* = 0.005), have a diagnosis of COPD (55.0% vs. 45.0%; *p* = 0.144), diabetes (35.0% vs. 13.4%; *p* < 0.001) and have accepted immunosuppressor treatment (48.1% vs. 27.8%; *p* = 0.005). Controls were more likely than cases to have use of DOTS on first episode (81.9% vs. 40.0%; *p* < 0.001).

Multivariate Logistic Regression Analysis

Table II describes the risk factors associated with recurrent TB among all cases included Tibetan and Han patients and their controls in a multivariate logistic regression model. Factors independently associated with a greater risk of recurrent TB were no use of DOTS on first episode, diabetes, smoking and malnutrition.

Multivariate analysis at the subset of Tibetan and Han patients respectively showed the independent risk factors for the Tibetan patients included no use of DOTS on first episode and malnutrition (Table III), while the risk factors for the Han patients were diabetes and smoking (Table IV).

Discussion

In this study, we analyzed the demographic and clinical characteristics of patients with and without recurrence of TB. We found that after comple-

Table I. Univariate analysis of demographic and clinical characteristics of patients with and without recurrence of tuberculosis.

Variates		Recurrence n = 160	(%)	No recurrence n = 320	(%)	HR (95% CI)	p
Ethnic group	Han	80	50.0	160	50.0		
	Tibetan	80	50.0	160	50.0	1.00 (0.59-1.71)	1.000
Age (years, mean [SD])		42 (16)		42 (16)			
Gender	Male	72	45.0	144	45.0		
	Female	88	55.0	176	55.0	1.00 (0.58-1.72)	1.000
Smoking	No	33	20.6	125	39.1		
	Yes	127	79.4	195	60.9	2.41 (1.29-4.49)	0.005
Alcoholism	No	61	38.1	165	51.6		
	Yes	99	61.9	155	48.4	1.79 (1.04-3.09)	0.036
HIV positive	No	99	61.9	205	64.1		
	Yes	43	26.9	60	18.8	1.50 (0.78-2.88)	0.222
	Unknown	18	11.2	55	17.1		
COPD	No	72	45.0	176	55.0		
	Yes	88	55.0	144	45.0	1.49 (0.87-2.56)	0.144
Diabetes mellitus	No	104	65.0	277	86.6		
	Yes	56	35.0	43	13.4	3.56 (1.86-6.82)	< 0.001
Chronic hepatitis	No	80	50.0	152	47.5		
	Yes	30	18.8	44	13.8	1.29 (0.61-2.77)	0.504
	Unknown	50	31.2	124	38.7		
Immunosuppressor treatment	No	83	51.9	231	72.2		
	Yes	77	48.1	89	27.8	2.19 (1.26-3.84)	0.005
Malnutrition	No	93	58.1	240	75.0		
	Yes	57	41.9	80	25.0	2.33 (1.32-4.12)	0.003
Use of DOTS on first episode	Yes	64	40.0	262	81.9		
	No	96	60.0	58	18.1	6.78 (3.71-12.37)	< 0.001

tion of adequate therapy for a first episode of TB, no use of DOTS, diabetes mellitus, smoking and malnutrition were associated with recurrent TB. Moreover, it was observed that no use of DOTS and malnutrition were risk factors for having a recurrent episode of TB for the Tibetan patients. While diabetes and smoking were risk factors of TB recurrence for the Han patients.

To date, this is the first report indicating that risk factors of TB recurrence for Tibetan and

Table II. Independent risk factors associated with recurrent tuberculosis among all cases included Tibetan and Han patients and their controls in a multivariate logistic regression model.

Variates	Multivariate logistic regression recurrence	
	HR (95% CI)	p value
No use of DOTS on first episode	5.867 (2.557-13.461)	< 0.001
Diabetes	3.288 (1.301-8.312)	0.012
Smoking	2.387 (1.328-4.291)	0.004
Malnutrition	1.910 (1.110-3.285)	0.019

Table III. Independent risk factors associated with recurrent tuberculosis among Tibetan patients and their controls in a multivariate logistic regression model.

Variates	Multivariate logistic regression recurrence	
	HR (95% CI)	p value
No use of DOTS on first episode	10.483 (2.247-48.915)	0.003
Malnutrition	2.371 (1.092-5.667)	0.052

Table IV. Independent risk factors associated with recurrent tuberculosis among Han patients and their controls in a multivariate logistic regression model.

Variates	Multivariate logistic regression recurrence	
	HR (95% CI)	p value
Diabetes	3.835 (1.378-10.675)	0.010
Smoking	2.337 (1.265-4.318)	0.007

Han patients in Southwest China are different. Most Tibetan patients in the study were from the Tibet autonomous region, which is located in the north of Himalaya Range. The Tibet autonomous region, which lies at an average of 4000 metres above sea level, is the main part of Qinghai-Tibet plateau. The atmosphere in the district is severely dry. Low temperatures are prevalent throughout these regions. Most Tibetan people make a living by herding. The geographical environment and living habits are very different between Tibetan and Han persons. These may be the reasons that the risk factors of TB recurrence are different between Tibetan and Han patients. Li et al[7] analyzed 337 pulmonary TB cases and 738 healthy controls, including 318 Tibetan and 757 Han individuals, and found that single nucleotide polymorphisms within miRNAs were different between Tibetan and Han persons. The G allele of rs2910164 and the C allele of rs3746444 played different roles in the two populations. It is unknown whether the differences of single nucleotide polymorphisms between Tibetan and Han populations are associated with TB recurrence.

The DOTS strategy for TB control was launched by the World Health Organization in 1994[8]. The strategy, which based around a minimum of six months course treatment regimens, includes tenets such as political commitment, good management practices, sputum smear microscopy for diagnosis, and the direct observation of doses to ensure adherence. To date DOTS strategy remains the cornerstone of global efforts at TB control[9]. In a study by Weis et al[10], using DOTS strategy resulted in a significant reduction in recurrence of TB, from 20.9% to 5.5%. Similarly, our study found that using DOTS strategy was the most important protective factor against TB recurrence, especially for the Tibetan patients. The associations observed between TB recurrence and no use of DOTS for the Tibetan patients could be explained by the undeveloped conditions of medical care in these populations.

Due to the special geographical location and the hard living conditions, Tibetans rarely eat vegetables and fruits. This kind of living habits is detrimental to the immune system, and some people may be suffering from malnutrition. Cellular immune function in patients with malnutrition is often impaired, including reduction in the number of T lymphocytes, and weakened activity of alveolar macrophage. These cause organism difficult to resist and clear mycobacteria. And patients with TB are vulnerable to malnutrition because of disease consumption and anorexia. Bidirectional relationship exists between TB and malnutrition[11]. However, the researches in developed countries did not find the link between malnutrition and recurrence of tuberculosis[12,13]. It is not clear whether this is because of different ethnic types.

A study from Wang and Shen[14] demonstrated smoking was common in patients with pulmonary TB in China. Our study found similar results. Smoking was an independent predictor of recurrent TB, especially for the Han patients. Smoking has been related to increased TB occurrence[15-17]. Some hypotheses have been posed to interpret this association: bronchoalveolar macrophages among smokers contain high levels of iron, promoting the growth of *M. tuberculosis*[18,19]; iron loading causes decrease in tumour necrosis factor-alpha and nitric acid, which play an important role in suppressing the intracellular growth of *M. tuberculosis*[20]. In this study, 79.4% of patients were smokers and were twice as likely to recurrence as those who did not smoke. It is necessary to emphasize the importance of smoking cessation in patients with pulmonary tuberculosis.

The connection between diabetes mellitus and pulmonary TB has been found. It is known that diabetes mellitus could affect chemotaxis, phagocytosis, and antigen presentation by macrophages in response to *M. tuberculosis*. Production of interferon γ, growth, function, and proliferation of T lymphocytes might be adversely affected by diabetes. If diabetes changes body immunity for tuberculosis, leading to higher baseline mycobacterial burdens and longer time to sputum culture negative conversion with treatment, a higher rate of recurrence might result[21]. This study indicated that diabetes was an independent risk factor associated with recurrent TB, particularly for the Han patients.

Conclusions

To our best knowledge, this is the first investigation of risk factors of recurrent TB in Tibetan and Han populations. The results of our study in detecting risk factors provides crucial information for TB control strategies, and it raises some important questions for further research. In summary, no use of DOTS, diabetes, smoking and malnutrition were associated with the highest

probability of pulmonary TB recurrence for the patients in Southwest China. The risk factors were different between Han patients with Tibetan patients. To reduce the recurrent rate of TB, especially for Tibetan populations, pursuing high-quality DOTS is essential.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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