초회다제내성 결핵의 위험요인

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Risk Factors for Primary Multidrug Resistant Tuberculosis

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Background : Primary multidrug-resistant tuberculosis is defined as *Mycobacterium tuberculosis* isolates that are resistant to at least isoniazid and rifampin in never-been-treated tuberculosis patients, and this malady is caused by the transmission of a resistant strain from one patient, who is infected with a resistant *Mycobacterium tuberculosis* strain, to another patient. The prevalence of primary multidrug-resistant tuberculosis could be a good indicator of the performance of tuberculosis control programs in recent years. We conducted a case-control study to identify the risk factors for primary multidrug-resistant tuberculosis.

Methods : From January 1, 2001 to, June 30, 2003, by conducting prospective laboratory-based surveillance, we identified 29 hospitalized patients with P-MDRTB and these patients constituted a case group in this study. The controls were represented by all the patients with culture-confirmed drug susceptible tuberculosis who were admitted to National Masan Hospital during the same study period. The odds ratios for the patients with primary multidrug-resistant tuberculosis, as compared with those of the patients with drug susceptible tuberculosis, were calculated for each categorical variable with 95% confidence intervals.

Results : Multivariate logistic regression showed that the presence of diabetes mellitus (odds ratio 2.68; 95% confidence interval, 1.05-6.86) was independently associated with having primary multidrug-resistant tuberculosis.

Conclusion : This study has shown that diabetes mellitus might be one of the risk factors for primary multidrug-resistant tuberculosis. *(Tuberc Respir Dis 2005; 59: 600-605)*

Key words : Drug resistance; *Mycobacterium tuberculosis*; Risk factor

Introduction

The number of tuberculosis patients infected with multidrug-resistant strains is on the rise, and particularly in the developing countries; this is largely due to the failure of control programs to provide adequate treatment and it is also due to the markedly increased prevalence of this disease in certain high-risk groups. Multidrug-resistant tuberculosis is associated with higher rates of treatment failure and death than is drug-susceptible tuberculosis, and these resistant strains are is more difficult and expensive to treat[1,2].

In 1995, the federal and local governments of the Russian Federation implemented a pilot project to reverse a trend for the increasing incidence of tuberculosis by using the World Health Organization (WHO) tuberculosis control strategy of direct observed therapy, the short course (DOTS), in the city of Ivanovo in Oblast[3]. Despite implementation of the DOTS program, poor treatment outcomes were reported; primary multidrug-resistant tuberculosis (P-MDRTB), defined as *Mycobacterium tuberculosis* isolates resistant to at least isoniazid and rifampin in never-been-treated tuberculosis patients, was suspected to be a major contributing factor. P-MDRTB is caused by the transmission of

a resistant strain from one patient, who was infected with a resistant *M. tuberculosis* strain, to another patient[4].

A recent summary of antituberculosis drug resistance surveys conducted in 58 countries showed that multidrug-resistant tuberculosis continues to be a serious problem[5]. During the period between 1994 and 1998 in the Republic of Korea, where tuberculosis-control programs have been conducted for many years, there were statistically significant decreases in the prevalence of resistance to at least one drug among the previously treated cases. On the other hand, the prevalence of P-MDRTB slightly increased. Although there were no significant increases in the prevalence of P-MDRTB in most countries, the high prevalence of this malady that's been observed in some countries warrants international attention because the movement of people from country to country may lead to an increase of the prevalence of primary multidrug-resistance.

Until recently, there have been few studies on risk factors for P-MDRTB. The present case-control study was conducted to identify risk factors for P-MDRTB.

Materials and Methods

The study was conducted at National Masan Hospital, a 300-bed government institution in Masan, Korea. From January 1, 2001 to June 30, 2003, by conductingprospective laboratory-based surveillance, we identified 29 hospitalized patients with P-MDRTB, and these patients constituted the case group in this study. The controls were represented by all the patients with culture-confirmed drug susceptible tuberculosis who were admitted to the National Masan Hospital during the same study period. For the case and control groups, we reviewed the hospital records for the following information: sociodemographic data, the family history of tuberculosis disease, smoking, alcohol consumption, details of the disease status, drug sensitivity patterns, past history of tuberculosis and other diseases, details of diabetes treatment, the sputum smear results, and written report of the chest radiographs as interpreted by the radiologists.

Drug susceptibility testing of all the *M. tuberculosis* strains was performed in the laboratory of the National Masan Hospital by the absolute concentration method with using Lowenstein Jenssen medium. The drugs and their critical concentrations for resistance are as follows: isoniazid 0.2 μg/ml; rifampicin 40 μg/ml; ethambutol 2 μg/ml; streptomycin 10 μg/ml; kanamycin 40 μg/ml; prothionamide 20 μg/ml; cycloserine 30 μg/ml; para-aminosalicylic acid 1 μg/ml; and ofloxacin 2 μg/ml. The pyrazanamide susceptibility was determined by the pyrazinamidase test. Every series of testing included a medium containing 500 μg/ml of p-nitrobenzoic acid in order to rule out the presence of mycobacteria other than *M. tuberculosis*. Resistance was indicated by the growth of more than 1% of the colonies on the drug-containing medium.

The data were analyzed with SPSS, version 7.0 (SPSS Inc., Chicago, IL) statistical software. Bivariate analyses were performed by χ^2 tests, Fisher exact tests or t tests as appropriate. The odds ratios for patients with P-MDRTB compared with those with drug susceptible tuberculosis were calculated for each categorical variable with 95% confidence intervals by using univariate logistic regression analysis. Variables that had P values less than 0.2 in the bivariate analyses were included in the multiple logistic regression analysis with using a stepwise approach. The P values were based on the results of 2-tailed test.

Table 1. Comparison of the characteristics of the case patients and the controls*

Characteristics	Case patients (n = 29)		Controls (n = 166)		P
Age, mean (range)	43.8 (20–89)		48.6 (16–87)		.18
Age, y					
15–29	6	(20.7)	29	(17.5)	
30–44	14	(48.3)	40	(24.1)	.03
45–59	4	(13.8)	49	(29.5)	
>59	5	(17.2)	48	(28.9)	
Female sex	9	(31.0)	35	(21.1)	.35
Health insurance					
National health insurance	21	(72.4)	128	(77.1)	.76
Medicaid	8	(27.6)	38	(22.9)	
Jobless	3	(10.3)	30	(18.1)	.42
Family history of tuberculosis disease	6	(21.4)	41	(24.7)	.71
Smoking	12	(41.4)	104	(63.0)	.05
Daily drinking	6	(20.7)	51	(30.7)	.38
Extrapulmonary tuberculosis	4	(13.8)	30	(18.1)	.77
Cavitation	11	(37.9)	61	(36.7)	1.00
Diabetes mellitus	11	(37.9)	41	(24.7)	.14
Other systemic disease	9	(31.0)	54	(32.5)	1.00

*Data are the number of patients (percentage) unless otherwise noted.

Table 2. Risk Factors for primary multidrug-resistant tuberculosis

Characteristics	Bivariate OR* (95% CI[†])	P	Multivariate OR (95% CI)	P
Age, y				
15–29	(Reference)			
30–44	1.69 (0.58–4.93)	.34	1.95 (0.62–6.16)	.26
45–59	0.40 (0.10–1.52)	.18	0.33 (0.08–1.48)	.15
>59	0.62 (0.18–2.10)	.44	0.49 (0.14–1.79)	.28
Female sex	1.59 (0.67–3.78)	.29	–	–
Health insurance				
National health insurance	(Reference)	.67		
Medicaid	1.22 (0.50–2.95)		–	–
Jobless	0.50 (0.14–1.76)	.28	–	–
Family history of tuberculosis disease				
	0.79 (0.30–2.07)	.63	–	–
Smoking	0.39 (0.17–0.85)	.02	0.32 (0.14–0.77)	.01
Daily drinking	0.70 (0.28–1.74)	.44	–	–
Extrapulmonary tuberculosis	0.94 (0.33–2.66)	.90	–	–
Cavitation	0.99 (0.44–2.21)	.98	–	–
Diabetes mellitus	1.75 (0.77–3.98)	.18	2.68 (1.05–6.86)	.04
Other systemic disease	1.06 (0.46–2.42)	.90	–	–

*OR=odds ratio; [†]CI = confidence interval

Results

Twenty-nine P-MDRTB case patients and 166 controls were enrolled in the study. The sputum smears were positive for acid-fast bacilli in all the cases and controls. The mean age of the case patients was 43.8 years and the controls' mean age was, 48.6 years (range: 20-89 years and 16-87 years, respectively; p=0.18) (Table 1). More cases were in the 15-year to 44-year-old range. The proportion of smokers was higher in the control group (63%) as compared to the P-MDRTB case group (41.4%), and this was statistically significant. There were a greater number of diabetes mellitus patients in the case group (37.9%) as compared to the control group (24.7%), although this was not statistically significant. There were no significant differences for the other characteristics betweenin the two groups. On the bivariate analysis, the crude odds ratio for having P-MDRTB in the age range of 30 to 44year was 1.69 (95% CI, 0.58-4.93) (Table 2). For the female patients, the odds of having P-MDRTB was 1.59 (95% CI, 0.67-3.78) times greater. Case patients were more likely than the controls to be smokers (odds ratio 0.39; 95% CI, 0.17-0.85) or daily drinkers (odds ratio 0.70; 95% CI, 0.28-1.74). However, except for smoking, the differences were not statistically significant. Consequently, patient age, smoking, and presence of diabetes mellitus were the factors that had *P* values less than 0.2 and these factors were included in the multiple logistic regression analysis with using a stepwise approach. Multivariate analysis showed that smoking (odds ratio 0.32; 95% CI, 0.14-0.77) and the presence of diabetes mellitus (odds ratio 2.68; 95% CI, 1.05-6.86) were both independently associated with having P-MDRTB.

Discussion

To the best of our knowledge, this is the first report on the factors that are associated with P-MDRTB in the patient background of a low prevalence of HIV. The proportion of HIV-positive cases in all the tuberculosis patients is as low as 1.0% in the Republic of Korea[6]. Our study found that patients who had P-MDRTB were statistically more likely to have diabetes mellitus. There have been several previous studies on the relationship between diabetes mellitus and tuberculosis. Individuals with diabetes mellitus have a 2.0 to 3.6 fold increased incidence of tuberculosis compared to nondiabetics[7,8]. Furthermore, diabetics may present with more advanced disease at the time of the tuberculosis diagnosis and they may have an increased mortality rate[9]. In terms of the relationship between multidrug-resistant tuberculosis and diabetes mellitus, it was reported that there was an increased incidence of multidrug-resistant tuberculosis in diabetic patients[10]. The mechanisms that may predispose the diabetic patient to lower respiratory tract infection are not completely understood. The excess morbidity and mortality may be related in part to specific diabetes-associated host immune defects as well as an increased risk that is due to coexisting conditions such as malnutrition, vascular insufficiency, cardiovascular disease and chronic renal disease[11-14].

Unexpectedly, we found that smoking was inversely associated with having P-MDRTB, even though there are no confirmative evidences for any kind of relationship between smoking and P-MDRTB. It is possible that the patients' general condition was poorer for the P-MDRTB patients than it was for the controls; therefore the case patients were less

likely to smoke. However, detailed information on smoking such as past smoking history was not obtained, and so we could not fully explain this finding. Even though age was not independently associated with P-MDRTB in this study, younger peoples were more likely to have P-MDRTB.

The findings in this report are subject to at least three limitations. First, details about the patients' previous hospitalization history were not available for all the study participants. This limited our ability to identify the specific high-risk exposure areass in the community. Second, the case-patients and controls described in this report were limited to National Masan Hospital and they may not be representative of the general population of tuberculosis patients. However, National Masan Hospital is not a referral center for severe tuberculosis and all patients are able to utilize the hospital for any reason, such as having a poor economic situation. Third, some patients who were identified as never having been treated may have had previous therapy that was not identified. In this context, some authors use the term initial resistance to refer to resistant tuberculosis at the start of treatment because it may be difficult to verify whether a patient has ever received anti-tuberculosis treatment in the past. However, our investigation of each case was at least as thorough as that done in the previous studies.

There is concern that the patients with P-MDRTB might rapidly increase in many developing countries in which the incidence of tuberculosis is high and the incidence of chronic diseases such as diabetes mellitus is sky-rocketing. The prevalence of P-MDRTB might well be a good indicator for the performance of tuberculosis control programs in the recent years. For preventing the emergence of P-MDRTB, it is important to treat multidrug-resistant tuberculosis patients appropriately and to im-

plement an effective infection control program. Further, it may be important to prevent people who have the risk factors for P-MDRTB from having contact with a tuberculosis patient for whom chemotherapy was not successful. This study has shown that diabetes mellitus might be one of the risk factors for P-MDRTB.

국 문 초 록

목 적 :

결핵약으로 치료 받은 적이 없으면서 최소한 아이소니아지드와 리팜핀에 동시에 내성이 있는 결핵균에 감염된 결핵을 초회다제내성 결핵이라 하며 이는 다제내성결핵균에 감염되어 발병한다. 근래에 초회내성결핵은 결핵관리 프로그램의 수행에 있어 중요한 지표로 사용되고 있다. 저자들은 초회다제내성 결핵의 위험요인을 알아내기 위해 환자대조군 연구를 시행하였다.

방 법 :

2001년 1월 1일부터 2003년 6월 30일 동안 국립마산병원에 입원한 29명의 초회다제내성결핵 환자들을 대상으로 환자군을 설정하였고, 대조군은 같은 기간 동안 본원에 입원한 모든 약제에 감성인 결핵환자들을 대상으로 하였다. 초회다제내성 결핵에 대한 의심되는 위험요인들의 교차비를 계산하였다.

결 과 :

다변량로지스틱회귀분석 결과 당뇨병이 초회다제내성 결핵과 통계적으로 유의한 연관성이 있었다(교차비 2.68; 95% 신뢰구간 1.05-6.86).

결 론 :

초회다제내성 결핵의 위험인자로서 당뇨병을 의심할 수 있었으며 향후 추구 연구가 요구된다.

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