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.

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. 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 in-
fected with a resistant \textit{M. tuberculosis} strain, to
another patient\textsuperscript{4}.

A recent summary of antituberculosis drug resi-
dance surveys conducted in 58 countries showed
that multidrug-resistant tuberculosis continues to
be a serious problem\textsuperscript{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 slight-
ly 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 interna-
tional 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-con-
trol study was conducted to identify risk factors for
P–MDRTB.

\textbf{Materials and Methods}

The study was conducted at National Masan Hospital, a 300-bed government institution in Ma-
san, Korea. From January 1, 2001 to June 30, 2003,
by conducting prospective laboratory-based surveil-
lance, 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 sus-
ceptible tuberculosis who were admitted to the
National Masan Hospital during the same study
period. For the case and control groups, we re-
viewed the hospital records for the following infor-
mation: sociodemographic data, the family history
of tuberculosis disease, smoking, alcohol consump-
tion, 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 radi-
ographs as interpreted by the radiologists.

Drug susceptibility testing of all the \textit{M. tubercu-
losis} strains was performed in the laboratory of the
National Masan Hospital by the absolute concen-
tration method with using Lowenstein Jenssen me-
dium. The drugs and their critical concentrations
for resistance are as follows: isoniazid 0.2 µg/ml;
rifampicin 40 µg/ml; ethambutol 2 µg/ml; strepto-
mycin 10 µg/ml; kanamycin 40 µg/ml; prothionami-
de 20 µg/ml; cycloserine 30 µg/ml; para-aminosalicy-
clic acid 1 µg/ml and ofloxacin 2 µg/ml. The py-
rAzinamide susceptibility was determined by the
pyrazinamidase test. Every series of testing inclu-
ded a medium containing 500 µg/ml of p-nitroben-
zoic acid in order to rule out the presence of myco-
bacteria other than \textit{M. tuberculosis}. Resistance was
indicated by the growth of more than 1% of the co-
lonies on the drug-containing medium.

The data were analyzed with SPSS, version 7.0
(SPP\textsuperscript{3} Inc., Chicago, IL) statistical software. Biva-
riate analyses were performed by $\chi^2$ tests, Fisher
exact tests or $t$ tests as appropriate. The odds ra-
tios for patients with P–MDRTB compared with
those with drug susceptible tuberculosis were cal-
culated for each categorical variable with 95\% con-
fidence intervals by using univariate logistic regre-
sion analysis. Variables that had \textit{P} values less
than 0.2 in the bivariate analyses were included in
the multiple logistic regression analysis with using
a stepwise approach. The \textit{P} values were based on
the results of 2-tailed test.
Table 1. Comparison of the characteristics of the case patients and the controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case patients (n = 29)</th>
<th>Controls (n = 166)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>43.8 (20-89)</td>
<td>48.6 (16-87)</td>
<td>.18</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>6 (20.7)</td>
<td>29 (17.5)</td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>14 (48.3)</td>
<td>40 (24.1)</td>
<td>.03</td>
</tr>
<tr>
<td>45-59</td>
<td>4 (13.8)</td>
<td>49 (29.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;59</td>
<td>5 (17.2)</td>
<td>48 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>9 (31.0)</td>
<td>35 (21.1)</td>
<td>.35</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National health insurance</td>
<td>21 (72.4)</td>
<td>128 (77.1)</td>
<td>.76</td>
</tr>
<tr>
<td>Medicaid</td>
<td>8 (27.6)</td>
<td>36 (22.9)</td>
<td></td>
</tr>
<tr>
<td>Jobless</td>
<td>3 (10.3)</td>
<td>30 (18.1)</td>
<td>.42</td>
</tr>
<tr>
<td>Family history of tuberculosis disease</td>
<td>6 (21.4)</td>
<td>41 (24.7)</td>
<td>.71</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (41.4)</td>
<td>104 (63.0)</td>
<td>.05</td>
</tr>
<tr>
<td>Daily drinking</td>
<td>6 (20.7)</td>
<td>51 (30.7)</td>
<td>.38</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td>4 (13.8)</td>
<td>30 (18.1)</td>
<td>.77</td>
</tr>
<tr>
<td>Cavitation</td>
<td>11 (37.9)</td>
<td>61 (36.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (37.9)</td>
<td>41 (24.7)</td>
<td>.14</td>
</tr>
<tr>
<td>Other systemic disease</td>
<td>9 (31.0)</td>
<td>54 (32.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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

Table 2. Risk Factors for primary multidrug-resistant tuberculosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bivariate OR (95% CI)</th>
<th>P</th>
<th>Multivariate OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>(Reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-44</td>
<td>1.69 (0.58-4.93)</td>
<td>.34</td>
<td>1.95 (0.62-6.16)</td>
<td>.26</td>
</tr>
<tr>
<td>45-59</td>
<td>0.40 (0.10-1.52)</td>
<td>.18</td>
<td>0.33 (0.08-1.48)</td>
<td>.15</td>
</tr>
<tr>
<td>&gt;59</td>
<td>0.62 (0.18-2.10)</td>
<td>.44</td>
<td>0.49 (0.14-1.70)</td>
<td>.28</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.59 (0.67-3.78)</td>
<td>.29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Health insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National health insurance</td>
<td>(Reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>1.22 (0.90-2.59)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jobless</td>
<td>0.50 (0.14-1.76)</td>
<td>.28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Family history of tuberculosis disease</td>
<td>0.79 (0.30-2.07)</td>
<td>.63</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.39 (0.17-0.85)</td>
<td>.02</td>
<td>0.32 (0.14-0.77)</td>
<td>.01</td>
</tr>
<tr>
<td>Daily drinking</td>
<td>0.70 (0.28-1.74)</td>
<td>.44</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td>0.94 (0.33-2.66)</td>
<td>.90</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cavitation</td>
<td>0.99 (0.44-2.21)</td>
<td>.98</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.75 (0.77-3.98)</td>
<td>.18</td>
<td>2.68 (1.05-6.89)</td>
<td>.04</td>
</tr>
<tr>
<td>Other systemic disease</td>
<td>1.06 (0.46-2.42)</td>
<td>.90</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*OR=odds ratio; Cl = 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 between the two groups. On the bivariate analysis, the crude odds ratio for having P-MDRTB in the age range of 30 to 44 year 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. 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. Furthermore, diabetics may present with more advanced disease at the time of the tuberculosis diagnosis and they may have an increased mortality rate. 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. 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.

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 areas 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 implement 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.

References


