ORIGINAL ARTICLE
Infectious Diseases, Microbiology & Parasitology

JKMS

http://dx.doi.org/10.3346/jkms.2012.27.10.1143 • *J Korean Med Sci 2012; 27: 1143-1146*

Proportion of Multidrug-Resistant Tuberculosis in Human Immunodeficiency Virus/*Mycobacterium tuberculosis* Co-Infected Patients in Korea

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Received: 31 January 2012
Accepted: 30 July 2012

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Much controversy surrounds the issue of whether HIV infection is a risk factor for developing multidrug-resistant tuberculosis (MDR-TB). In this study, we evaluated the prevalence of and risk factors for MDR-TB in HIV-infected patients at the National Medical Center of Korea. We reviewed the medical records of HIV/TB co-infected patients from January 2005 to May 2011; the drug susceptibility profiles were available for 55 patients. Of these, 32.7% had MDR-TB, which was approximately 3.6 times higher than the prevalence among the general population. Additionally, there were more additional AIDS-defining clinical illnesses in the MDR-TB group than in the non-MDR-TB group (27.8% vs 5.4%, $P = 0.032$). These results suggest that HIV infection and HIV-related immunosuppresion may contribute to the development of MDR-TB.

Key Words: Tuberculosis; Multidrug-Resistant Tuberculosis; HIV

INTRODUCTION

Since 2000, over 35,000 new cases of tuberculosis (TB) have been recorded annually in Korea, raising concerns about an increasing incidence of multidrug-resistant TB (MDR-TB) (1). Globally, the epidemiological synergy between HIV and TB co-infection and the deadly synergy between HIV and MDR-TB are major public health threats (2). The prevalence of human immunodeficiency virus (HIV) infection in Korea is very low (less than 0.1%), but HIV/TB co-infection is gradually increasing (3, 4). Although the relationship between HIV infection and TB is well understood, the association between HIV and MDR-TB is not clear (5). The aim of this study was to evaluate the prevalence of and risk factors for MDR-TB infection in HIV/TB co-infected patients.

MATERIALS AND METHODS

Study site and subjects

This was a retrospective cohort study at the National Medical Center of Korea, which has 540 beds, is managed under governmental supervision, and has one of the largest HIV care centers in Korea.

Eight hundred and fourteen HIV patients were registered from January 2005 to May 2011. Of these, 55 clinically diagnosed TB patients with records of drug-susceptibility tests (DSTs) were enrolled and analyzed. Patients whose drug-susceptibility profiles were unavailable and those transferred from other institutions without previous laboratory records were excluded.

Measurements

Acid-fast bacilli (AFB) identification was carried out using bacteriological, molecular (AccuPower® MTB Real-Time PCR Kit; Bioneer Co., Daejeon, Korea), and histopathological methods. The DSTs were performed using absolute concentration methods and/or the GenoType® MTBDR plus assay (Hain Lifescience, Nehren, Germany). MDR-TB was defined as in vitro resistance to at least isoniazid (INH) and rifampin (RIF). Extensively drug-resistant tuberculosis (XDR-TB) was defined as MDR-TB with additional resistance to any fluoroquinolone and any of the second-line anti-TB injectable drugs (6). Traditional absolute concentration test data were used when the results of the 2 DST tests were not consistent.

Clinical data including CD4 cell count and viral load were

pISSN 1011-8934
eISSN 1598-6357

collected within 4 weeks of TB diagnosis. Acquired immune deficiency syndrome (AIDS) - defining clinical illnesses were determined using the US Centers for Disease Control and Prevention criteria (7). To explore associated risk factors for MDR-TB in HIV/TB co-infected patients, demographic characteristics, clinical parameters and clinical outcomes were compared between the MDR-TB group and the non-MDR-TB group.

Statistics

Univariate analysis was performed to assess the association between predictor variables and drug-susceptibility patterns of *Mycobacterium tuberculosis* among HIV/TB co-infected cases. *P* values were determined using the independent t-test or the Mann–Whitney U-test in the case of quantitative variables. Fisher's exact test was performed to analyze the association between categorical variables and drug-susceptibility patterns of *M. tuberculosis*. Statistical significance was set at $P < 0.05$.

Ethics statement

This study was approved by the institutional review board of the National Medical Center (Protocol No; H-1105/011-004). Informed consent was waived by the board. All the data collected during this study were kept confidential.

RESULTS

Among the 814 HIV patients registered, 119 patients received anti-TB treatment. Among these 119, 55 patients had records of the DST results. In 55 subjects with available the DST results, eight had past medical history of anti-TB treatment and 47 were primary TB cases. Including 6 XDR-TB patients, 32.7% (18 of 55) were identified with MDR-TB. In 47 primary TB cases, 29.7% (14 of 47) were MDR-TB (i.e., primary or transmitted MDR-TB). In 37 patients with non-MDR-TB, 34 had TB isolates sensitive to both INH and RIF.

There was no difference in demographic factors including age, gender, and body mass index (BMI) between the 2 groups (Table 1). No difference was found regarding the medical history (including previous TB history, treatment adequacy, and use of highly active antiretroviral therapy [HAART]) prior to TB diagnosis. However, patients' immune status differed between the 2 groups: the median CD4 count was lower in the MDR-TB group

Table 1. General characteristics of study subjects (n=55)

Characteristics		Total subjects (n = 55)	MDR-TB (n = 18)	Non-MDR-TB (n = 37)	*P* value
Sex (%)	Male	54 (98.2)	17 (94.4)	37 (100.0)	0.327
Age, mean (yr, range)		42.4 (20-68)	41.1 (20-64)	43.0 (26-68)	0.812
BMI, median (IQR)		18.9 (15.80-21.10)	19.40 (16.15-21.10)	18.69 (12.70-21.15)	0.249
Route of HIV infection No. (%)	MSM	25 (45.5)	8 (44.4)	17 (45.9)	0.771
	Bisexual behavior	3 (5.5)	0 (0.0)	3 (8.1)	
	Heterosexual behavior	10 (18.2)	4 (22.2)	6 (16.2)	
	Unknown	17 (30.9)	6 (33.3)	11 (29.7)	
Log HIV RNA, median (IQR), n = 49		4.64 (3.39-5.46)	4.85 (4.57-5.47)	4.32 (2.45-5.46)	0.212
CD4 count at TB diagnosis, median (cells/μL, IQR)		90 (40-248)	57 (25-219)	121 (45-279)	0.251
Additional AIDS-defining clinical illness other than TB No. (%)*		7 (12.7)	5 (27.8)	2 (5.4)	0.032
Previous TB treatment history No. (%), n = 54	Yes and treatment completion	8 (14.5)	4 (22.2)	4 (10.8)	0.340
	Yes and no treatment completion	5 (9.0)	3 (16.7)	2 (5.4)	
	No	46 (83.6)	14 (77.8)	32 (86.5)	
Simultaneous diagnosis of TB and HIV	Yes	20 (36.4)	7 (38.9)	13 (35.1)	1.000
HAART history No. (%)	Current	7 (12.7)	2 (11.1)	5 (13.5)	1.000
	Ex, not ongoing	18 (32.7)	6 (33.3)	12 (32.4)	
	Naive	30 (54.5)	10 (55.6)	20 (54.1)	
Socioeconomic status No. (%)	Health insurance beneficiaries	19 (34.5)	8 (44.4)	11 (29.7)	0.678
	Medical aid beneficiaries	16 (29.0)	5 (27.8)	11 (29.7)	
	Homeless	18 (32.7)	5 (27.8)	13 (35.1)	
Smoking, current No. (%), n = 47	Yes	30 (63.8)	9 (64.3)	21 (63.6)	1.000
Drinking No. (%), n = 47	Yes	23 (48.9)	8 (57.1)	15 (45.5)	0.534
TB lesion No. (%)	Pulmonary	42 (76.4)	14 (77.8)	28 (75.7)	0.799
	Pleura	1 (1.8)	0 (0)	1 (2.7)	
	Gastrointestinal	5 (9.1)	2 (11.1)	3 (8.1)	
	Musculoskeletal	4 (7.3)	2 (11.1)	2 (5.4)	
	CNS	3 (5.5)	0 (0.0)	3 (8.1)	
Treatment outcome No. (%)†	In-hospital mortality	12 (21.8)	7 (38.9)	5 (16.2)	0.043

*Additional AIDS-defining clinical illness included three cases of esophageal candidiasis confirmed by endoscopic exam, two cases of Kaposi's sarcoma confirmed by histopathologic exam, and one case each of cytomegalovirus colitis and *Pneumocystis jirovecii* pneumonia confirmed by histopathologic exam; †1 patient was excluded because he died of head trauma. MDR, multidrug-resistant; BMI, body mass index; IQR, interquartile range; HIV, human immunodeficiency virus; MSM, men who have sex with men; TB, tuberculosis; CNS, central nervous system; HAART, highly active antiretroviral therapy.

http://dx.doi.org/10.3346/jkms.2012.27.10.1143

than in the non-MDR-TB group (57 vs 121 cells/μL), but this result was not statistically significant (P = 0.251). Notably, the frequency of additional AIDS-defining clinical illnesses other than tuberculosis before or at the time of TB diagnosis was significantly higher in the MDR-TB group (27.8%, 5 of 8) than in the non-MDR-TB group (5.4%, 2 of 37) (P = 0.032).

There were no significant differences between the two groups with regard to the well-reported risk factors for both MDR-TB and HIV, including smoking, drinking, and socioeconomic status as classified by the status of health insurance.

Excluding 1 XDR-TB patient who died of head trauma, in-hospital mortality was significantly higher in the MDR-TB group (38.9%, 7 of 18) than in the non-MDR-TB group (13.5%, 5 of 37) (P = 0.043). In XDR-TB cases, in-hospital mortality was 80% (4 of 5).

DISCUSSION

This is the first study in Korea to address the issue of MDR-TB among HIV/TB co-infected patients in a low HIV-prevalence and intermediate TB-burden setting. The prevalence of MDR-TB among HIV/TB co-infected patients was 32.7% (18 of 55) in our center, which is significantly higher than that among the general population (9% in 2008). In addition, the rate of primary MDR-TB is 29.7% (14 of 47), which is approximately 13 times higher than that in the general population (2.3%, 2003-2008) (8). A wide range of MDR-TB prevalence has been observed in different countries, which implies that there are many local confounders and common factors between MDR-TB and HIV (5).

On an individual level, it has been suggested that immunosuppression is a mechanism that may allow HIV infection to contribute to the development of MDR-TB. Molecular studies have suggested that MDR-TB strains are related to loss of fitness and have a tendency to spread in immunocompromised hosts (9, 10). In this regard, CD4 cell count and AIDS-defining illness are well-established markers of immunosupression, and our results support the suggestion that immunosuppression is associated with MDR-TB infection. The CD4 T-cell counts in the MDR-TB group were lower than those in the non-MDR-TB group, although this result was not statistically significant. Furthermore, AIDS-defining illnesses other than TB were observed more frequently in the MDR-TB group than in the non-MDR-TB group (P = 0.032), suggesting that immunosuppression by HIV infection may be associated with MDR-TB infection.

In Korea, HIV patients tend to be stigmatized and isolated from society. As a result, they tend to be of low socioeconomic status, consume excessive alcohol, and smoke, all of which increase the risk of MDR-TB infection (5, 11). However, our results show no significant difference in these factors between the 2 groups.

The higher in-hospital mortality rate among HIV/MDR-TB-infected patients in our results is consistent with previous findings (12, 13). In this context, the early diagnosis and rapid recognition of DR-TB in HIV patients are necessary to improve prognoses. While DST using conventional methods has a long turnaround time, a new molecular test is fast and sensitive (14, 15). Thus, we propose that this new test should always be performed in HIV patients who are suspected of having TB.

As a retrospective single center study, our study had several limitations. More than half (64 of 119) of the HIV/TB co-infected patients were excluded because their DST data was not available. And the lack of information such as TB exposure history or use of second-line TB drugs may make it hard to analyze risk factors. Given that the prevalence of HIV/TB co-infection is very low, and it is relatively troublesome to confirm the drug susceptibility of *M. tuberculosis* in HIV/TB co-infected patients, however, our results could play a crucial role in understanding of HIV/TB co-epidemic in Korea.

In conclusion, the prevalence of MDR-TB among HIV/TB co-infected patients is significantly higher than that in the general population. Surveillance of drug-resistant TB among HIV infected patients is essential to reduce mortality and prevent the ongoing spread of drug resistance and should be conducted urgently. In addition, HIV-related immunosuppression may be associated with MDR-TB infection.

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http://dx.doi.org/10.3346/jkms.2012.27.10.1143