Frequency of *Mycobacterium Tuberculosis* Infection among Iranian Patients with HIV/AIDS by PPD Test

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Abstract- Persons infected with the Human Immunodeficiency Virus (HIV) are particularly susceptible to tuberculosis, either by latent infection reactivation or by a primary infection with rapid progression to active disease. This study was done to determine the frequency of tuberculosis infection among Iranian patients with HIV/AIDS. A total of 262 HIV/AIDS patients attending all three HIV/AIDS health care centers of Tehran, Iran were enrolled in this study. A detailed history and physical examination were obtained from all HIV patients suspected of having pulmonary *M. tuberculosis*. A positive PPD skin test was used as a diagnostic parameter for probability of TB infection. Out of 262 HIV/AIDS patients, a total of 63 (24%) were shown to have the tuberculosis infection based on a positive PPD skin test. Of the patients with positive PPD skin test, 22 (35%) had pulmonary Tuberculosis, 2 (3.2%) had extrapulmonary tuberculosis, and 39 (53%) had no evidence of *M. tuberculosis* infection (latent infection). Also 8 (12.7%) had history of long term residence in a foreign country, 32 (50.8%) were exposed to an index case, and 9 (14.3%) had past history of pulmonary tuberculosis, while only 33.3% had clinical manifestations of TB (active disease). There was no resistant case of *tuberculosis*. Our study showed that near 24% of Iranian patients with HIV/AIDS were infected with *M. tuberculosis*. This finding denotes the need to improve the diagnostic and preventive measures, and also prompt treatment of this type of infection in the HIV infected individuals.

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Key words: HIV; acquired immunodeficiency syndrome; tuberculosis; tuberculin

Introduction

The World Health Organization (WHO) estimates that one-third of the world's population is infected with Mycobacterium tuberculosis, resulting in an estimated 8 million new cases of tuberculosis and nearly 2 million deaths each year (1).

Approximately 10 million people are estimated to be co infected with M. tuberculosis and HIV, and over 90% of these dually infected individuals reside in developing nations (2). Worldwide, tuberculosis is the most common cause of death among patients with AIDS, killing 1 of every 3 patients (3).

The HIV epidemic has had a dramatic impact on rates and public control of tuberculosis (TB) and on TB control in populations where both infections are prevalent (4). HIV infection, in particular advanced HIV infection (AIDS), is more important than any other risk factor for the progression to disease of recent or remotely acquired TB infection (5). Among people co infected with Mycobacterium tuberculosis and HIV before the availability of highly active antiretroviral therapy, the estimated risk of active TB relative to patients with no other known risk factor for active TB was 170.0 times greater for AIDS and 113.0 times greater for HIV infection without AIDS (5). Cases of reactivation TB attributable to HIV infection increase the risk of transmission of *M. tuberculosis* within the community, thereby constituting a second, indirect mechanism by which HIV increases TB morbidity (6). To prevent further spread of TB, intensified efforts are needed such as active case finding, and reducing the risk of reactivating TB in persons with latent tuberculosis infection, through prophylactic and antiretroviral treatment. Progression of the HIV epidemic can aggravate the problem of tuberculosis both as an early opportunistic infection in those infected with HIV and through increased spread to the general population (7).

There is limited data to show frequency of tuberculosis among people living with HIV/AIDS in

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Iran. This research is performed to describe the burden of tuberculosis among Iranian patients with HIV/AIDS at the Imam-Khomeini Hospital, the largest referral center for these patients in Iran, and a private infectious diseases clinic.

Patients and Methods

This study was a multi centric study evaluating the frequency of *Mycobacterium tuberculosis* infection in persons infected with HIV. The study was conducted in three HIV/AIDS health care centers of Tehran, Iran "(Infectious Diseases Clinic" and "Infectious Diseases Ward" at the Imam-Khomeini University Hospital, and a "private infectious diseases clinic)". From January 2006 to February 2007, a total of 262 HIV-seropositive patients were recruited in the study. The institutional review board of University of Tehran/ Medical Sciences approved the study protocol.

A detailed history and physical examination were obtained from all HIV patients suspected of having *M. tuberculosis* infection. These were done using a prepared questionnaire accomplished by the attending physicians. Personal and clinical information including age, sex, marital status, history of drug addiction, previous prophylaxis for TB, tuberculosis risk factors, exposure to an index case with sputum positive TB and history of long term residence in a foreign country was registered. CD4 counts were determined for all of the patients. A written informed consent was achieved from each subject.

Mantoux skin test was performed by intradermal injection of 0.1 ml of 2 TU of PPD into the volar surface of the forearm using a disposable tuberculin syringe with one half inch bluntly beveled, gauge 26 steel needle.

The injection site was prepared by cleaning with alcohol and allowing the area to dry. Reading of Mantoux reaction was done 72 hours after injection and the palpable induration was measured at its widest diameter with a flexible ruler and was recorded in millimeters (mm). All diameters were recorded. Two testers and one reader who were adequately trained were designated. Infection with *M. tuberculosis* was defined by the presence of an induration of at least 5mm or more.

The statistical analysis was performed using SPSS, version 11.5 (SPSS Inc., Chicago, IL, USA). Values were tested for statistical significance using chi-square test where appropriate. A *P*-value of 0.05 or less was considered significant.

Results

A total of 262 patients with HIV/AIDS were enrolled in this study. The age of the patients ranged from 1 month to over 60 years with a mean of 30 years. Among these patients, 235 (89.7%) were male (Table 1). HIV/AIDS rate of infection in singles was more than married ones (55.7% *vs* 42.4%), the marital status of 1.9% patients wasn't known. 59 (22.5%) of the participants had history of long term staying in a foreign country. Age groups of 20-29 and 30-39 years had the highest risk for HIV infection (23.7% and 37% respectively). Routes of transmission of HIV in 262 patients are as follows: 97 (37%) blood transfusion, 64 (24.4%) sexual contact, 65 (24.8%) injection drug use, 2 (0.87%) maternal-fetal transmission and others routes 34 (13%). Opportunistic infections pathogens diagnosed in 262 patients is as follows: 137 (52.3%) patients had *Candida albicans*, 66 (25.2%) *Pneumocystis carinii*, 38 (14.5%) *Toxoplasma gondi*, 28 (10.7%) *Herpes Simplex Virus*, 24 (9.16%) *Cryptosporidium parvum*, and 5 (1.9%) had *Cryptococcus neoformans*. Among the patients, 26% had undiagnosed opportunistic infections.

Table 1. Baseline data of studied patients with HIV/AIDS

Characteristics	Patients with HIV/AIDS (n=262)
Gender (%)	
male	235 (89.7%)
female	27 (10.3%)
Martial Status (%)	
single	146 (55.7%)
married	111 (42.4%)
unknown	5 (1.9%)
History of drug addiction (%)	93 (35.5%)
History of jailing (%)	89 (34%)
Hemophilia (%)	92 (35.1%)
Malignancy (%)	10 (3.8%)
Exposure to an index case with TB (%)	77 (29.4%)
***M. tuberculosis* infection** (%)	63 (24%)
History of TB (%)	24 (9.2%)
Long term residence in a foreign country (%)	59 (22.5%)
Clinical manifestations of TB (%)	73 (27.9%)
Prophylaxis for TB (%)	20 (7.6%)
Drug resistance (%)	0
Opportunistic infections other than TB (%)	194 (74%)
CD_4 cell count	
less than 200	89 (34%)
200-500	92 (35%)
more than 500	79 (30%)

Table 2. Frequency of tuberculosis in patients with HIV/AIDS based on the PPD skin test

	No of patients	
	PPD Positive (n=63)	**PPD Negative (n=199)**
Gender		
male	57 (90.5%)	178 (89.4%)
female	6 (9.5%)	21 (10.5%)
Long term residence in a foreign country	8 (12.7%)	51 (25.6%)
Exposure to an index case with TB	32 (50.8%)	45 (22.6%)
History of *M. tuberculosis* infection	9 (14.3%)	15 (7.5%)
CD_4 cell count		
less than 200	14 (22.2%)	75 (37.7%)
200-500	26 (41.2%)	68 (34.2%)
more than 500	24 (38.1%)	55 (27.6%)
Prophylaxis treatment for TB	10 (15.9%)	10 (5%)
Opportunistic infections except TB	43 (68.2%)	151 (75.9%)
Active TB infection		
pulmonary	9 (14.3%)	13 (6.53%)
extrapulmonary	0	2 (1%)
Hemophilia	15 (23.8%)	77 (38.7%)

Table 2, indicates the frequency of tuberculosis in patients with HIV/AIDS based on PPD skin test. Overall, 63 (24%) patients with HIV/AIDS were positive for PPD skin test of them, 22 patients (35%) had pulmonary tuberculosis, 2 (3.2%) extrapulmonary tuberculosis, and 39 (53%) had no evidence of *active tuberculosis* infection. Among the 63 patients with positive PPD skin test, 6 patients (9.5%) were female, 35 (55.5%) were single, 8 (12.7%) had history of long term residence in foreign countries, 32 (50.8%) had exposure to an index case of pulmonary TB.

There was no statistically significant difference in history of TB between patients with and without active tuberculosis infection (P= 0.1).

Discussion

Tuberculosis and HIV have been closely linked since the emergence of AIDS. HIV infection has contributed to a significant increase in the worldwide incidence of tuberculosis (8, 9). Although HIV-related tuberculosis is both treatable and preventable, incidence rates continue to climb in developing nations where HIV infection and tuberculosis are endemic and resources are limited. Worldwide, tuberculosis is the most common opportunistic infection affecting HIV-seropositive individuals (8). Its relative virulence and potential for person-to-person transmission distinguishes *Mycobacterium tuberculosis*. Persons infected with the human immunodeficiency virus (HIV) are particularly susceptible to tuberculosis, either by the reactivation of latent infection or by a primary infection with rapid progression to active disease (10-13).

The frequency of *Mycobacterium tuberculosis* infection in the current study was 24%, whereas this frequency was reported 1.4% in Bogota, Colombia (14). Our results are also different to the ones reported in a general hospital, AIDS reference center, in Rio de Janeiro, Brazil (15) where mycobacteria were recovered from 20.6% (313 of 1517) of all patients, and *M. tuberculosis* was identified in 94.2% cases (295/313). Results of Murcia-Aranguten *et al* study suggested that when antiretroviral therapy is introduced the relative frequency of *M. tuberculosis* infections is reduced (14).

In the present study there were no resistant strains of *M. tuberculosis*. This result is the same as Murcia-Aranguten *et al* (14). Paralleling the increase in tuberculosis cases in the United States was an increase in the number of cases of drug-resistant tuberculosis (16). In fact, HIV infection has only heightened the recognition of the problem that is caused by failure to apply adequately known principles of tuberculosis control (17). The reported outbreaks of multi-drug resistant tuberculosis among HIV patients in New York City and Miami were due to failure in ensuring that patients are treated properly thus leading to high rates of initial drug resistance together with high infection rates due to inadequate infection control practices in HIV care facilities (18).

Of the 63 patients who had tuberculosis infection based on a positive PPD skin test, only two had extra-pulmonary tuberculosis. This is a relatively low incidence of extra-pulmonary tuberculosis compared to other studies (19).

We found no significant correlation between *M. tuberculosis* infection and past history of TB in patients who had active tuberculosis. Only nine out of 63 patients had positive history of past tuberculosis.

This study suffers from an important limitation; unfortunately diagnosis of *M. tuberculosis* infection was based on a positive PPD skin test in patients. The main drawback of the Tuberculin Skin Test (TST) based on Purified Protein Derivative (PPD) is the lack of specificity due to cross reactivity with proteins present in other mycobacteria such as the Bacille Calmette Guerin (BCG) vaccine strain, *M. avium* complex organisms, and other non tuberculous mycobacteria (20-23). In addition, the sensitivity of the TST is reduced in HIV positive patients (20, 24, 25). Therefore, positive cases of M. tuberculosis infection in patients with HIV/AIDS should be more than that reported in this study.

Our study found that more than 24% of Iranian patients with HIV/AIDS were infected with *M. tuberculosis*. It becomes evident the need to improve the preventive measures and prompt treatment of this type of infection in the HIV infected individuals. Having clinical suspicion to tuberculosis infection as the most prevalent opportunistic infection in HIV/AIDS patients is the key point for earlier diagnosis and mortality reduction.

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