ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 01, pp.12032-12035, January, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

RISK FACTORS FOR MULTI-DRUG RESISTANT TUBERCULOSIS OF AFGHAN IMMIGRANTS IN A TERTIARY CARE HOSPITALIZED TUBERCULOSIS PATIENTS IN IRAN

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ARTICLE INFO

Article History:
Received 02nd October, 2014
Received in revised form
11th November, 2014
Accepted 06th December, 2014
Published online 31st January, 2015

Key words:

Mycobacterium tuberculosis,
Afghan immigrants,
Multidrug-resistant tuberculosis,
Risk factors.

ABSTRACT

The study aimed to identify risk factors for multidrug-resistant tuberculosis (MDR-TB) among Afghan immigrant patients at a tertiary care hospital in Iran. This was a retrospective analysis of all confirmed Afghan immigrant TB patients from December 2000 – June 2005. Drug susceptibility testing (DST) to isoniazid, rifampicin, streptomycin, ethambutol, and pyrazinamide was performed on Lowenstein–Jensen media according to proportion method. The risk factors associated with MDR-TB were investigated. *Mycobacterium tuberculosis* strains were isolated from 668 Afghan immigrant patients. There were 397 males and 271 females and the mean age was 35.2 ± 16.3 (SD). Based on DST, Afghan immigrant patients were divided into two groups: 493 patients were non-MDR and 175 patients were MDR-TB. The variables significantly associated with MDR were under 45 years of age, male sex, previous TB treatment, poor socio-economic conditions, and smoking. Site of TB disease whether pulmonary or extra-pulmonary, and drug abuse habit were not associated with MDR TB. In conclusion, based on our results an improved TB control programme, which must be coupled with early detection of MDR-TB among Afghan immigrant patients particularly in those with high risk factors, is highly recommended.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as *Mycobacterium tuberculosis* resistant to at least rifampin (RIF) and isoniazid (INH). MDR-TB poses a significant global and public health concern, because of low efficacy rates for first line treatment regimens, requires 18 to 24 months of treatment, and associated with considerable mortality worldwide (Gupta *et al*., 2001; Drobniewski *et al*., 2005). An additional concern was the persistence of high or increasing incidence and spread of MDR-TB in industrialized and the developing world, related to poverty, migration, ethnic conflicts, substance abuse and the increase in human immunodeficiency virus (HIV) infection, sometimes coupled with the poor performance of national programmes. These factors may lead to the development or increase of MDR which, however, is susceptible to proper health control measures (Antunes *et al*., 2000). The measures are aimed at reduction of transmission through rapid identification of infectious patients and fast adequate diagnostic measures, followed by immediate treatment with effective drugs according to resistance, so long as sufficient protection by vaccination is not available (Loddenkemper *et al*., 2002). The World Health Organization (WHO) has estimated that in 2006 approximately 0.5 million cases of MDR-TB occurred worldwide (World Health Organization, 2008a). Although MDR-TB is present in almost all the world, but the highest proportion of MDR-TB among new cases has been reported from former Soviet Union, China, and India (World Health Organization, 2008b). In Iran, TB remains endemic; however the TB incidence and prevalence rates are in decline. The TB incidence and prevalence per 100,000 populations was respectively declined from 36 and 50 cases in 1990 to 22 and 28 cases in 2006. Until now, there is no precise representative survey of drug resistance rate in Iran. However based on national wide survey conducted in 1999, among all *M. tuberculosis* isolates tested for drug susceptibility, 10.9% were resistant to ≥ 1 anti-TB drug, and 6.7% were MDR-TB (World Health Organization, 2000). In further studies, the existence and transmission of extensively drug resistant TB (XDR-TB) strains (i.e., resistant to fluoroquinolones and to at least one of the three injectable second line drugs in addition to isoniazid and rifampin) in epidemiological related MDR-TB patients have been demonstrated (Masjedi *et al*., 2006). Many studies have been conducted on *M. tuberculosis* clinical isolates genotyping and drug resistance encompassing MDR-TB, in Iran. But only few investigations focused separately on MDR in immigrant TB patients. Here, we sought to identify risk factors for MDR-TB and develop a policy and plan for public health TB control for immigrant patients.

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MATERIALS AND METHODS

Setting

National Research Institute of Tuberculosis and Lung Diseases (NRITLD) is a tertiary referral center for TB patients. The Mycobacteriology Research Center (MRC) at NRITLD is the only facility in which cultures and drug susceptibility testing (DST) for *M. tuberculosis* can be performed in Iran.

Study population

From December 2000 to June 2005, all Afghan immigrant TB patients who had positive culture were retrospectively studied. Patients with culture negative, contaminated culture, smear examination only, non tuberculosis culture, and patients without drug susceptibility test were excluded from the study. Therefore, our study population appears to be a representative sample of all Afghan TB patients in Iran. The patients were classified into two groups: MDR-TB and non MDR-TB patients. Patient relevant data were collected by using a standardized questionnaire from patient case notes. Accordingly demographic profile and risk factor information were recorded. The variables investigated included age, gender, history of TB treatment, manifestation of TB whether pulmonary or extra-pulmonary, and socio-economic condition. Data on the smoking and drug abuse were also recorded.

Bacteriological study

Mycobacterium tuberculosis had been diagnosed by smear and microscopic examination. Mycobacterial species identification was performed by conventional biochemical tests (Kent and Kubica, 1985). All isolates were identified as *M. tuberculosis* complex by production of niacin, catalase activity, nitrate reduction, pigment production and growth rate. DST was routinely performed by proportion methods on Lowenstein–Jensen media on isolates of *M. tuberculosis*. The following drug concentrations were used: isoniazid "INH"(0.2 µg /ml), rifampin "RF" (40.0 µg /ml), streptomycin "SM" (4.0 µg /ml) and ethambutol "ETM" (2.0 µg /ml). Susceptibility to pyrazinamide "PZA" (900 and 1200 µg /ml) was tested using a two-phase medium and if at 21st d reading, the proportion of resistant colonies was higher than the critical proportion, the strain was reported as resistant to PZA.

Definitions

Based on guidelines of the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD), MDR-TB was defined as *M. tuberculosis* strains that were resistant to at least isoniazid and rifampin (World Health Organization, 2009).

Statistical analysis

The data obtained were analyzed using SPSS software, version 11.0 (SPSS Inc, Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

Ethical approval

The study was approved by the ethics committee of NRITLD in Tehran.

RESULTS

Patients

A total of 3812 patients with TB disease from December 2000 to June 2005 were referred to NRITLD. Out of 3812 patients, 1582 (41%) were excluded because they were either culture negative (916, 24%) or had smear examination only (667, 17.4%). In addition another 394 patients (10.3%) were excluded because their cultures were contaminated. Further, 93 patients (2.4%) were infected with mycobacterium other than tuberculosis. Another 1074 (28.1%) were Iranian and they were excluded. The study therefore included 668 (17.5%) Afghan immigrant patients. The characteristics of this population are summarized in Table 1.

Risk factors associated with MDR-TB patients

Based on DST, the 668 Afghan immigrant patients were divided into two groups: 493 patients were non-MDR and 175 patients were MDR-TB. Table 2 shows the number of MDR-TB patients for each of the variables analyzed and the crude odds ratios for MDR-TB. The variables significantly associated with MDR were under 45 years of age (OR, 2.048; 95% CI, 1.388-3.027; *p*=0.000), male sex (OR, 1.535; 95% CI, 1.052-2.240; p=0.020), previous TB treatment (OR, 7.162; 95% CI, 4.779-10.754; p=0.000), poor socio-economic conditions (OR, 6.113; 95% CI, 3.974-9.436; p=0.000), and smoking (OR, 1.722; 95% CI, 1.131-2.630; p=0.007) (Table 2).

Table 1. Characteristics of the study population (no = 668)

Variable		No (%)
Mean age	35.2 ± 16.3 (SD)	
Sex	Male	397 (59.4)
	Female	271 (40.6)
History of TB treatment	New cases	408 (61.1)
	Previous TB treatment	260 (38.9)
Manifestation of TB	Pulmonary	612 (91.6)
	Extra-pulmonary	56 (8.4)
Socio-economic condition	Acceptable	333 (49.8)
	Poor	335 (50.2)
Smoking	Smoker	466 (69.8)
	Non smoker	202 (30.2)
Drug abuse	Abuser	66 (9.9)
	Non-abuser	602 (90.1)

Table 2. Risk factors associated with multidrug-resistant tuberculosis

Variable		Non-MDR-TB (493) no (%)	MDR-TB (175) no (%)	Odd ratio (95% CI)	P value
Age	Age < 45 yr	271 (55.0)	125 (71.4)	2.048 (1.388-3.027)	0.000
	Age > 45 yr	222 (45.0)	50 (28.6)		
Sex	Male	280 (56.8)	117 (66.9)	1.535 (1.052-2.240)	0.020
	Female	213 (43.2)	58 (33.1)		
History of TB treatment	New cases	360 (73.0)	48 (27.4)	7.162 (4.779-10.754)	0.000
	Previous TB treatment	133 (27.0)	127 (72.6)		
Manifestation of TB	Pulmonary	457 (92.7)	155 (88.6)	1.638 (0.884-3.017)	0.111
	Extra-pulmonary	36 (7.3)	20 (11.4)		
Socio-economic condition	Acceptable	298 (60.4)	35 (20.0)	6.113 (3.974-9.436)	0.000
	Poor	195 (39.6)	140 (80.0)		
Smoking	Smoker	330 (66.9)	136 (77.7)	1.722 (1.131-2.630)	0.007
	Non smoker	163 (33.1)	39 (22.3)		
Drug abuse	Abuser	46 (9.3)	20 (11.4)	1.254 (0.692-2.256)	0.461
	Non-abuser	447 (90.7)	155 (88.6)		

DISCUSSION

Global surveillance indicates that DR is of serious magnitude and extremely widespread, and that there are high proportions of isolates resistant to three or four drugs (World Health Organization, 2007). It is estimated that 1 to 1.5 million people worldwide are living with MDR-TB. In 2006, one in every 20 of all new cases of TB was MDR. Of the nearly half a million people who became ill with MDR-TB, 50% were in China and India, and 7% in the Russian Federation (World Health Organization, 2008b). The high proportion of drug-resistant TB among new cases suggests a concerning level of transmission of drug-resistant strains (World Health Organization, 2008b). Therefore; careful monitoring of transmission trends of drug resistance strains is priority to ensure successful TB control programme.

In this study, age under 45 years and male sex were significantly associated with MDR-TB, which was in concordance with other literatures (Surucuoglu *et al*., 2005; Choi *et al*., 2007; Granich *et al*., 2005). Faustini *et al*. (2006) in their review found that MDR-TB was more common in patients under 65 years of age, but the association was weak and more heterogeneous in patients under 45 years. The high frequency of drug resistance among a young age group in this study may indicate the occurrence of recent transmission, whereas in the older age group, the infection has been acquired in the past. Hence, strict protocols to monitor trend of transmission of MDR-TB strains should be considered a priority to ensure a successful TB control programme. The higher rate of MDR-TB in males over females might be explained by the fact males are more likely to be outdoors and hence more susceptible to community acquired MDR strains. Additional factor for male susceptibility to MDR-TB is that females are more adherent with long course anti-TB treatment and therefore less likely to receive inadequate treatment than males (Faustini *et al*., 2006; Mirsaeidi *et al*., 2007). In the current study, the association between MDR-TB and previous TB treatment was statistically significant. This finding had been well confirmed in the literature (Antunes *et al*., 2000; Caminero, 2005; He *et al*., 2008; Shamaei *et al*., 2009; Suárez-García *et al*., 2009). The high rate of drug resistance in previously treated patient could result from improper anti-TB regimen, inadequate or irregular drug supply, unsatisfactory compliance by patients or clinicians, lack of supervision of treatment, and absence of proper infection control measures in hospitals. It has been reported that MDR-TB is 10 times higher in previously treated patients (Merza and Masjedi, 2010). In the present study, the prevalence of MDR-TB was higher in patients with poor socio-economic status than non poor living condition, which is in line with other studies (Antunes *et al*., 2000; Sumartojo, 1993; Rubel and Garro, 1992). Generally, patients with poor socio-economic status such as poverty and homelessness assumed to be higher consumers of medicines; however, they are less compliant with treatment that may induce treatment failure and subsequent MDR-TB. Furthermore, in this study, we found that smoking was significantly associated with drug resistance TB. Although, this is uncommon finding in other studies, it has been documented in few reports (Barroso *et al*., 2003).

The main limitation in this study was that we did not include other important risk factors of MDR-TB such as HIV infection status, cavitary lesions in chest, diabetes mellitus and others as adequate information on these variables were not available in the case sheets. In conclusion, in keeping with recorded literatures, MDR-TB is a global public health problem particularly in immigrants. The MDR-TB rate was significantly higher in the younger age less than 45 yr, male gender, previous TB treatment, poor socio-economic conditions, and smokers. Therefore, an improved TB control programme, which must be coupled with early detection of MDR-TB among Afghan immigrants particularly in those with high risk factors, is highly recommended.

Acknowledgments

We would like to thank all the staff at the MRC – NRITLD, Tehran, Iran, for their considerable help and support in this work.

REFERENCES

Antunes, M. L., Aleixo-Dias, J., Antunes, A. F., Pereira, M. F., Raymundo, E. and Rodrigues, M. F. 2000. Anti-tuberculosis drug resistance in Portugal. *Int J Tuberc Lung Dis.,* 4: 223-231.

Barroso, E. C., Mota, R. M. S., Santos, R. O., Sousa, A. L. O., Barroso, J. B. and Rodrigues, J. L. N. 2003. Risk factors for acquired multidrug-resistant tuberculosis. *J Penumol.,* 29: 89–97.

Caminero, J. A. 2005. Management of multidrug-resistant tuberculosis and patients in retreatment. *Eur Respir J.,* 25: 928-936.

Choi, J. C., Lim, S. Y., Suh, G. Y., Chung, M. P., Kim, H., Kwon, O. J., Lee, N. Y., Park, Y. K., Bai, G. H. and Koh, W. J. 2007. Drug resistance rates of Mycobacterium tuberculosis at a private referral center in Korea. *J Korean Med Sci.,* 22: 677-681.

Drobniewski, F., Balabanova, Y., Nikolayevsky, V., Ruddy, M., Kuznetzov, S., Zakharova, S., Melentyev, A. and Fedorin, I. 2005. Drug-resistant tuberculosis, clinical virulence, and the dominance of the Beijing strain family in Russia. *JAMA*., 293: 2726-2731.

Faustini, A., Hall, A. J. and Perucci, C. A. 2006. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. *Thorax.,* 61: 158-163.

Granich, R. M., Oh, P., Lewis, B., Porco, T. C. and Flood, J. 2005. Multidrug resistance among persons with tuberculosis in California, 1994-2003. *JAMA.,* 293: 2732-2739.

Gupta, R., Kim, J. Y. and Espinal, M. A., Caudron, J. M., Pecoul, B., Farmer, P. E. *et al.* 2001. Responding to market failures in tuberculosis control: a model to increase access to drugs and treatment. *Science,* 293: 1049-1051.

He, G. X., Zhao, Y. L., Jiang, G. L., Liu, Y. H., Xia, H., Wang, S. F., Wang, L. X., Borgdorff, M. W., van der Werf, M. J. and van den Hof, S. 2008. Prevalence of tuberculosis drug resistance in 10 provinces of China. BMC Infect Dis., 8:166.

Kent, P. T. and Kubica, G. P. 1985. Public Health Mycobacteriology: A guide for level II laboratory. Atlanta, GA. Public Health Services, US Department of Health and Human Services.

Loddenkemper, R., Sagebiel, D. and Brendel, A. 2002. Strategies against multidrug-resistant tuberculosis. *Eur Respir J Suppl.,* 36: 66s-77s.

Masjedi, M. R., Farnia, P., Sorooch, S., Pooramiri, M. V., Mansoori, S. D., Zarifi, A., Velayati, A. A. and Hoffner, S. 2006. Extensively drug resistant tuberculosis: 2 years of surveillance in Iran. *Clin Infect Dis.,* 43: 840-847.

Merza, M. and Masjedi, M. R. 2010. Extensively drug-resistant tuberculosis (XDR) and extremely drug-resistant tuberculosis (XXDR): risk factors and molecular perspectives. *Iranian Journal of Clinical Infectious Diseases,* 5: 174-188.

Mirsaeidi, M. S., Tabarsi, P., Farnia, P., Ebrahimi, G., Morris, M. W., Masjedi, M. R., Velayati, A. A. and Mansouri, D. 2007. Trends of drug resistant *Mycobacterium tuberculosis* in a tertiary tuberculosis center in Iran. *Saudi Med J.,* 28: 544-550.

Rubel, A. J. and Garro, L. C. 1992. Social and cultural factors in the successful control of tuberculosis. *Public Health Rep.,* 107: 626-36.

Shamaei, M., Marjani, M., Chitsaz, E., Kazempour, M., Esmaeili, M., Farnia, P., Tabarsi, P., Amiri, M. V., Mirsaeidi, M., Mansouri, D., Masjedi, M. R. and Velayati, A. A. 2009. First-line anti-tuberculosis drug resistance patterns and trends at the national TB referral center in Iran--eight years of surveillance. *Int J Infect Dis.,* 3:e236-240.

Suárez-García, I., Rodríguez-Blanco, A., Vidal-Pérez, J. L., García-Viejo, M. A., Jaras-Hernández, M. J., López, O. and Noguerado-Asensio, A. 2009. Risk factors for multidrug-resistant tuberculosis in a tuberculosis unit in Madrid, Spain. *Eur J Clin Microbiol Infect Dis.,* 28: 325-330.

Sumartojo, E. 1993. When tuberculosis treatment fails. A social behavioral account of patient adherence. *Am Rev Respir Dis.,* 147: 1311-1320.

Surucuoglu, S., Ozkutuk, N., Celik, P., Gazi, H., Dinc, G., Kurutepe, S., Koroglu, G., Havlucu, Y. and Tuncay, G. 2005. Drug-resistant pulmonary tuberculosis in western Turkey: prevalence, clinical characteristics and treatment outcome. *Ann Saudi Med*., 25: 313-318.

World Health Organization. 2000. The WHO/IUATLD global project to anti-tuberculosis drug resistance surveillance. Volume *278*. WHO. Geneva, Switzerland, 2000: 1-250.

World Health Organization. 2007. Global tuberculosis control: surveillance, planning and financing. WHO report. WHO/HTM/TB/2004.343. Geneva, Switzerland: WHO.

World Health Organization. 2008a. Global tuberculosis control: surveillance, planning and financing. WHO report. WHO/HTM/TB/2008.393. Geneva, Switzerland: WHO.

World Health Organization. 2008b. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance 2002-2007. WHO/HTM/TB/2008.394. Geneva, Switzerland: WHO.

World Health Organization. 2009. Guidelines for surveillance of drug resistance in tuberculosis-4th ed. WHO/HTM/ TB/2009.422. Geneva, Switzerland: WHO.

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