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RISK FACTORS IN DEVELOPMENT OF MULTI DRUG RESISTANT TUBERCULOSIS IN THE HOSPITALIZED PATIENTS

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ABSTRACT

The emergence of multi-drug resistant tuberculosis (MDR-TB) is becoming a global threat. A study was carried out to determine the frequency and risk factors associated in the development of MDR-TB in the hospitalized patients. It was a retrospective study in which five hundred patients of tuberculosis, admitted in the TB wards of Military Hospitals Rawalpindi, were include. Diagnosis of MDR-TB was established based on susceptibility pattern of Mycobacterium tuberculosis by Agar diluted method on Lowenstein Jensen Medium. The isolates which showed simultaneous resistance to INH and Rifampicin either with or without resistance to other drugs were labeled as MDR-TB. Out of 500 diagnosed patients of tuberculosis, 40 (8%) patients developed MDR-TB. Smokers were at high risk to develop MDR-TB (12.9%) as compared to non-smokers (5.6%). MDR-TB was found more in extra pulmonary tuberculosis (35%), secondary tuberculosis (21.4%) and patients taking irregular anti tuberculosis treatment (36.6%) as compared to pulmonary tuberculosis (6.9%), primary cases (1.8%) and patients taking regular treatment (2.4%) respectively ($p<0.05$). smoking, extra pulmonary tuberculosis secondary tuberculosis and poor compliance to the anti-tuberculosis treatment are the main contributing factors in MDR-TB. The development of MDR-TB in community can be reduced by modifying these MDR-TB associated risk factors.

Keywords: MDR-TB, anti- tuberculosis treatment, INH and rifampicin.

INTRODUCTION

Tuberculosis (TB) is an ancient disease which for a long time has been significant public health challenge to the whole world. Even today one third of the whole world population is infected with Mycobacterium tuberculosis and the estimated number of clinical cases is around 21 million [1]. This disease remains a major cause of morbidity and mortality producing an estimated 8 million new cases leading to 2-3 million deaths annually. [2,3]. Pakistan is among those countries in the world (along with India, Indonesia and Nigeria) where tuberculosis disease burden is considered to be high, case detection and cure rate are far from WHO targets. Presently, estimated incidence of TB in Pakistan is more than 250/100,000 population [4]. Tuberculosis is preventable disease and its proper treatment is one of the most cost effective health interventions available, despite these facts it has been comparatively neglected by the international health community over the past 20 years [5].

MDR-TB is defined as those mycobacterium tuberculosis strain which are resistant to isoniazid and rifampicine simultaneously with or without resistant to other anti tuberculosis agents [6]. The

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development of MDR-TB is a complex multifactorial process. It is attributed to factors including patient non-adherence to treatment, inappropriate treatment regimens and a poor health infrastructure in developing countries [7]. According to World Health Organization, Pakistan is one of the hot spots for multi-drug resistant tuberculosis second only to Latvia [8]. DOTS-Plus, a new WHO's strategy is formulated to prevent the spread of MDR-TB in developing countries [9].

Over the years there is an upward trend in the resistance rate in different areas of Pakistan [10]. Present study has been designed to determine the frequency of multi-drug resistant tuberculosis in Hospitalized patients in Rawalpindi and to find out the risk factors associated with MDR-TB. This study will help in developing the strategy for prevention of MDR-TB in our medical setup and implementation of DOTS-Plus in Pakistan.

PATIENTS AND METHODS

The study was carried out in Armed Forces Post Graduate Medical Institute and data was collected from pulmonology department of Military Hospital Rawalpindi from January to December 2003.

It is a retrospective case control hospital based study. Five hundred consecutive patient of tuberculosis admitted in the TB wards of Military Hospital Rawalpindi, were included in this study. Primary identification of mycobacterium tuberculosis was based on the acid-fast character on Ziehl Neelsen (ZN) staining, eugenic colony morphology on Lowenstein Jensen (L.J) medium [11]. All clinical isolates were tested against four first line drugs, streptomycin, isoniazid, rifampicin and ethambutol. Minimum inhibitory concentrations (MICs) were determined by Agar dilution method. Resistance ratio method was employed to interpret the results using control strain H37 Rv [12].

Those isolate which showed simultaneous resistance to INH and rifampicin either with or with out resistance to other drugs were labeled as multi drug resistant tuberculosis. Those patients having incomplete records, lost during follow-up and Children less than 10 years of age were excluded from the study. Patient with associated chronic illnesses like diabetes, hypertension or other cardiac problems etc were also excluded.

The associations of MDR with demographic and clinical variables were studied.

- Age : Less than 50 Years verses > 50 Years
- Gender : Male verses Female
- Level of education: Less than primary verses >primary education
- Smoking habit: Smoker verses Non-smoker
- Site of Tuberculosis: Pulmonary TB verses extra pulmonary TB
- Case status : Primary verses secondary tuberculosis
- Treatment : Taken anti- tuberculosis drugs regularly verses irregularly
- Family history of tuberculosis: Any other member of family suffering from tuberculosis verses no one

STATISTICAL ANALYSIS

The data were compiled and analysis was done by using SPSS software, version 8.0 for Windows (SPSS Inc, Chicago, Illinois). Chi-square test was applied to ascertain whether there is association between risk factors and development of multi-drug resistant tuberculosis and level of significance was taken as $p<0.05$.

RESULTS

A total of 513 patients were admitted in Military Hospital Rawalpindi for treatment of tuberculosis during the period of study.

Thirteen patients were having incomplete record so excluded from the study and record of 500 patients was scrutinized. Out of the remaining 500 cases, forty (8%) patients developed multi drug resistant tuberculosis (MDR-TB) among hospitalized patients (fig-1).

Demographic factors associated with multi drug resistant tuberculosis is shown in Table-1. The result revealed that age, gender and education had shown no association with the development of MRD-TB ($p>0.05$). MDR tuberculosis had shown strong association with smoking (13%) as compared to Non-smokers (5.6%) ($p<0.05$).

The association of clinical variable with multi drug resistant tuberculosis is shown in Table-2. Development of MDR-TB had shown a strong relationship with site of tuberculosis and MDR-TB was significantly high in extra pulmonary tuberculosis (35%) as compared to pulmonary tuberculosis (7%) ($p<0.05$). Primary MDR-TB is defined as presence of resistance strains in patient with no history of prior anti-tuberculosis chemotherapy [13]. Those who developed resistant to anti-tuberculosis treatment after having been sensitive to Anti tuberculosis treatment previously were labeled as secondary cases. MDR tuberculosis was found significantly more (21%) in secondary tuberculosis as compared to (2%) in primary cases ($p<0.05$). The result had revealed strongest relationship between MDR-TB and patients compliance towards treatment. Out of 40 MDR-TB cases, 36.6% of these patients had been taking Anti tuberculosis treatment irregularly or defaulters in taking medicine as compared to regular drug taking patients 2.4% ($p<0.05$). Family history of tuberculosis had shown no association with MDR-TB.

DISCUSSION

Emergence of MDR-TB is a problem of global concern. Present study gave a percentage of 8% MDR-TB among hospitalized tuberculosis patients. Safi and Zai S (1988) reported 8 % prevalence of MDR-TB which is exactly same as of present study [14]. However, most of the studies give a higher percentage. Karamat et al, (1999) reported the prevalence of MDR-TB is 13.66% in clinical isolate in AFIP Rawalpindi [11]. Another study, conducted by Rizwan Iqbal et al, found 16% prevalence of MDR-TB in Lahore [15]. Prevalence of MDR-TB is very high about 24.44% in sind [16].

A global surveillance carried out by WHO for anti-tuberculous drug resistance revealed 22.1% MDR-TB in Latia, followed by 13.3% in India, 3.2% in UK and 2% in USA [8]. This surveillance showed very high rates of MDR-TB in developing countries as compared to developed countries. This is most probably due to poverty, ignorance, lack of health services and poor follow up of patients. Emergence of multidrug resistance in a country like Pakistan is a matter of great concern where combination of already poor management with resistance shows a dangerous trend.

MDR-TB is more prevalent in older age group in our setup. Our study reported high percentage of MDR-TB in old age group (14.1%) as compared to younger age group (6.7%) but this difference is statistically insignificant ($p<0.05$). Poverty, malnutrition and poor social support in old age might be the contributory factors for MDR-TB. A study in UK reported that for every 10 year increase in age, the risk of MDR-TB almost doubles [7]. A korean researcher concluded the same result as of reference 7 [17]. In other study carried out in UK found the high percentage of MDR-TB in younger people aged 15-44 years [18]. Present study reported no relationship between sex and MDR-TB while other studies concluded high rate of MDR-TB among males [7,18].

In our study, MDR-TB is found more in smokers as compared to non smokers indicating smoking as a risk factor for the development of MDR-TB. Sultana reported a

high prevalence of TB among smokers (36.2%) as compared to non-smokers (13.6%) [19].

Table-1: Demographic characteristics of patients association with multiple drug resistance during the treatment of tuberculosis.

Parameters		MDR Cases (%) (n=40)	Control (%) (n=460)	Total (n=500)	P-Value
Age	<50 years	28 (6.7)	387 (93.2)	416	>0.05
	>50 years	12 (14.1)	73 (85.9)	85	
Gender	Male	33 (8.9)	337 (91.1)	370	>0.05
	Female	7 (5.4)	123 (94.6)	130	
Level of Education					
	<Primary	18 (6.6)	254 (93.4)	272	>0.05
	>Primary	22 (9.6)	206 (90.4)	228	
Habit of Smoking					
	Smokers	21 (12.9)	142 (87.1)	163	<0.05
	Non Smokers	19 (5.6)	318 (94.4)	337	

Table-2: Clinical variable association with multiple drug resistance during the treatment of tuberculosis.

Parameters	MDR Cases (%) (n=40)	Control (%) (n=460)	Total (n=500)	P-Value
Site of TB				
Pulmonary	33 (6.9)	447 (93.1)	480	<0.001
Ext Pulmonary	7 (35)	13 (65)	20	
Case Status				
Primary	06 (1.8)	335 (98.2)	341	
Secondary	34 (21.4)	125 (78.6)	159	<0.001
Anti-TB Treatment				
Irregular	30 (36.6)	52 (63.3)	82	<0.001
Regular	10 (24)	408 (97.6)	418	
Family H/O TB				
Positive	12 (7.2)	154 (92.8)	166	>0.05
Negative	28 (8.4)	306 (91.6)	334	

Present study has shown that MDR-TB is more prevalent among cases of extra pulmonary tuberculosis as compared to pulmonary lesions. Tariq Butt (2003) also concluded a gradual rise in magnitude of the problem posed by extra- pulmonary MDR-TB and suggested the requirement for appropriate control measures [20]. This might be because of poor health services in our country where because lack of proper diagnostic facilities, extra- pulmonary lesions go undiagnosed. Another study also showed high prevalence of extra-pulmonary MDR-TB (57%) in Saudi Arabia [21]. A study in UK opposed the result by giving 89.0% cases of MDR-TB with pulmonary lesions [7].

Compliance of the MDR-TB patients towards anti-TB treatment was poor in our study. A number of studies reported the similar high percentages of MDR-TB in patients who had inadequate anti-TB treatment and developed resistant bacilli [15,16,22,23]. Bastian reported that MDR-TB is a 'man-made' disease caused by improper treatment, inadequate drug intake and poor patient supervision. [24]. Non-compliance to the Anti-TB treatment is becoming one of the main obstacles to the success of anti TB therapy [25]. In large numbers of MDR-TB patients, it is the failure to complete the treatment rather than to failure of the treatment itself [26]. Present study revealed high percentage of MDR-TB among secondary cases of TB which are more prone to develop MDR-TB. Various studies in Pakistan [15,16,22] and the countries around supported the result of present study [17,27]. The increase percentage of MDR – TB among previously treated cases suggests either lack of motivation and follow up of the patients on the part of medical professionals or incomplete treatment on the part of patients as defaulters.

CONCLUSION

Multi-drug resistant tuberculosis is an emerging health problem in our country and the percentage is about 8% in a Military Hospital Rawalpindi. Smoking, extra pulmonary tuberculosis secondary tuberculosis and poor compliance to the anti-tuberculosis treatment are the main factors in the development MDR-TB. Proper training of Health Care Providers is necessary for reducing the MDR-TB in our medical setup.

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