Original Article

Rising Menace of Multidrug Resistant Mycobacteria in Pulmonary Tuberculosis

Haji Khan Khoharo, Shoaib Ansari and Fatima Qureshi

ABSTRACT

OBJECTIVE: The study was conducted to determine the rising menace of multidrug resistant mycobacteria in Pulmonary tuberculosis.

SUBJECTS & METHODS: This prospective study was conducted in the Department of Medicine, Muhammad Medical College Mirpurkhas, from May 2007 to July 2008. Sixty cases of pulmonary tuberculosis were selected for multidrug resistant tuberculosis (MDR-TB) study that fulfilled the inclusion criteria. Pulmonary specimens consisted of 2-5 ml, early morning sputa and bronchial washings were sent for the ZN staining (AFB) and culture and drug sensitivity on culture-media. MDR-TB was defined as simultaneous resistance of an isolate to isoniazid and rifampicin.

RESULTS: Drug culture and sensitivity revealed that 22 (36.66%) were sensitive to all the five first-line drugs, while 38 (63.33%) showed one or other type of drug resistance, including 7 (11.66%) resistant to single drug, 15 (25%) resistant to two drugs, 10 (16.66%) resistant to three drugs, while 6 (10%) were resistant to all the first-line drugs. Primary drug resistance was noted in 3 (5%). Resistance to isoniazid, rifampicin, streptomycin, ethambutol and pyrazinamide was seen in 32 (53.33%), 28 (46.66%), 24(40%), 20 (33.33%), and 18 (30%) respectively.

CONCLUSIONS: In view of this increasing level of drug resistance, more organized national strategy against tuberculosis is needed. MDR-TB was most commonly seen in chronic cases/ drug defaulters, and it is a major threat to the tuberculosis control measures.

KEYWORDS: Mycobacterium-tuberculosis, Multidrug-resistant tuberculosis, Pulmonary tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa. Globally, 9.2 million new cases (139 per million population), including 4.1 million new smear-positive cases (44% of the total) and 1.7 million deaths from TB occurred in 2006, of which 0.7 million cases and 0.2 million deaths were in HIV-positive people[1]. This is an increase from 9.1 million cases in 2005, due to population growth. The prevalence of tuberculosis was 14.4 million in 2006 and an estimated 0.5 million cases of multidrug resistant TB (MDR-TB)[1]. In Pakistan, the prevalence of tuberculosis reported in 2006 was 263 cases per million populations and the incidence of 181 per million populations per year. According to latest WHO report, the incidence of MDR-TB in Pakistan in new and previously treated cases is 3.4% and 36% respectively[1]. MDR-TB, defined as resistance of Mycobacterium tuberculosis (MTB) to at least Isoniazid and Rifampicin[2], is a major threat to the tuberculosis control measures. Multidrug resistant strains of MTB are particularly problematic in developing countries because alternative agents, such as pyrazinamide, ethambutol, and the quinolones, are expensive, less effective, and less well tolerated than the standard counterparts[3-5]. Acquired drug resistance of MTB is defined as the acquisition of resistance to anti-tuberculosis drugs by the multiplication of the resistant mutant strains of bacteria as a result of inadequate chemotherapy. Persons at risk for MDR-TB include: previously treated for tuberculosis, contacts of patients previously treated and/or known to have MDR-TB, dwellers from developing countries, and patients with AFB positive sputum after 3 months of therapy[6]. Epidemiologic studies have denoted that multidrug resistance is a man-created phenomenon. Exposure to inappropriate antituberculous therapy selectively allows for multiplication of resistant bacilli, thus becoming dominant and leading to therapeutic failure. Resistant strains may be transmitted from person to person[7]. MDR-TB strains usually acquire resistance through a series of single locus mutations[8]. W-Beijing family, the most common single MDR-TB genotype that originated in Asia has become the dominant strain [9]. The W-Beijing family has spread throughout the world and epidemics have been widely reported, including the United States[10]. The Beijing strain related to strain W from New York City has

been increasing in prevalence and is associated with high levels of treatment failure and acquired drug resistance. WHO has estimated that on average a person with MDR-TB infects up to 20 people in lifetime[11]. In context to these facts and figures, this study was designed to determine the frequency of MDR-TB in our setup as there is not enough attention paid to this important disease that may has the potential to initiate an epidemic if left un-controlled.

SUBJECTS AND METHODS

This prospective study was conducted in the Department of Medicine, Muhammad Medical College Mirpurkhas from May 2007 to July 2008. Sixty cases of pulmonary tuberculosis were selected and studied for MDR-TB who fulfilled the following criteria: i) clinical history suggestive of tuberculosis. ii) Sputa +ve for AFB. iii) CXR findings consistent with the pulmonary tuberculosis. iv) Patients with past and present history of antituberculous drugs who have discontinued the drugs because of unknown reason. Clinical suspicion of tuberculosis was based upon history; such as low-grade fever with evening rise, night sweats, anemia, malaise, weight-loss, elevated ESR and organ specific findings. General physical and detailed chest examinations were performed for the presence of cavitations, consolidation, fibrosis, pneumothorax and pleural effusion. Pulmonary specimens consisted of 2-5 ml of early morning sputa were sent for the ZN staining (AFB) and culture and drug sensitivity on Lowenstein-Jensen (LJ)-medium. Bronchial washings were sent in a few cases having non-productive cough. MDR-TB was defined as simultaneous resistance of an isolate to isoniazid and rifampicin. The quantitative variables were calculated by Student's t-test. The data were analyzed on SPSS version 10.0 for windows.

RESULTS

Most (94%) of our patients belonged to poor socioeconomic status of surrounding rural areas, where basic facilities of life are scanty including District Tharparkar. Out of 60 patients, 48 (80%) were male & 12 (20%) were females. Age range noted was 18-65 years (30 ±16.50). Regarding the antituberculous (ATT) intake, it was found that 16 (26.66%) have never taken ATT, while 54 (90%) had taken ATT previously. Out of these 18 (33.33%) had taken ATT twice, and 36 (66.66%) had taken drugs for multiple times. The results of drug sensitivity revealed that 22 (36.66%) were sensitive to all the five first line drugs [$p < 0.05$]. While 38 (63.33%) showed one or other type of drug resistance, including seven (11.66%) resistant to single drug, 15 (25%) resistant to two drugs, 10 (16.66%) resistant to three drugs, while 6 (10%) were resistant to all the first line drugs [$p < 0.05$]. Total primary, secondary and MDR-TB drug resistance was noted in 3(5%), 38 (63.33%) & 31 (51.66%) respectively (**table I**). Among the resistant isolates 32 (53.33%) were resistant to isoniazid, 28(46.66%) to rifampicin, 24(40%) to streptomycin, 20 (33.33%) to ethambutol, and 18(30%) were resistant to pyrazinamide (**table II**) [$p < 0.04$]. The drug resistance to all first line drugs was more frequent in the chronic cases/drug defaulters [$p < 0.03$]. Other findings/complaints noted were weight loss 54 (90%), anemia 34 (56.66%), clubbing 30 (50%), cyanosis 15 (25%), cervical lymphadenopathy 10 (16.66%), & hemoptysis in 10 (16.66%). CXR findings noted were cavitations 12 (20%), fibrosis 10 (20%), pneumothorax 6 (10%), and pleural effusion in 30 (50%).

TABLE I:
DETAILS OF DRUG SENSITIVITY & RESISTANCE (n=60)

	No	%
Drug sensitive cases	22	36.66
Drug resistant cases	38	63.33
Multi-drug resistant cases (MDR-TB)	31	51.66

TABLE II:
DETAILS OF RESISTANCE TO 1ST LINE DRUGS (n=60)

Drug	Resistance (%)
Isoniazid	32 (53.33)
Rifampicin	28(46.66)
Streptomycin	24(40)
Ethambutol	20(33.33)
Pyrazinamide	18(30)

DISCUSSION

Globally MDR-TB has increased all over the world over the past few decades. The estimates of World Health Organization (WHO) show that over 50 million people in the world are presently infected with the multidrug resistant tuberculosis[11]. Pakistan presently ranks eighth among the list of high tuberculosis burden countries, with an annual TB related death rate of 43/100,000 [1]. Resistance in dividing mycobacteria occurs spontaneously due to random mutations even

in drug-free environment (primary resistance). However, antimicrobials provide the selective drug pressure that allows the pre-existing resistant mutants to become predominant (secondary resistance). Development of multidrug resistance is attributed to inadequate treatment which means inappropriate treatment regimen, sub-standard antimicrobials or poor patient compliance [12]. Our study shows an overall resistance rate to one or other drug of 63.33%, with MDR-TB noted in 51.66% which is comparable to study of Irfan S et al [13]which has reported primary resistance, secondary resistance and MDR-TB of 39%, 79% and 79% respectively, while Ikram A [11]et al have reported 47.6%. Our high levels of drug resistance are mainly because most of our subjects belonged to chronic cases and drug defaulter, which are harboring more resistant isolate (secondary drug resistance). In our study the frequency of single-drug resistance (16.66%) is comparable with the figures reported by two worldwide studies: the World Health Organization (WHO) has reported a global median single drug resistance prevalence of 11.1% (range 2.9-40.8%)[1]. In our study, individual drug resistant isolates noted was; 53.33% resistant to isoniazid and 46.66% to rifampicin, 40% to streptomycin, 33.33% to ethambutol and 30% were resistant to pyrazinamide and these results are comparable with the results of Irfan S et al [13], Karamat[14] et al, Butt[12] et al and Muzzaffar[15] et al. This poses a growing threat to the public health further burdening the resources especially when the MDR-TB burden is already high in the country. Recent hospital based studies from Mumbai (India) and Aga Khan University Karachi (Pakistan) reported 51% and 47% MDR-TB rates respectively[12]. which are very much similar to our results of 51.66%. The optimal approach would be primary prevention through vaccination, continued surveillance and appropriate therapeutic decisions with monitoring of the patients[11]. In Pakistan tuberculosis is mostly diagnosed on clinical suspicion and on therapeutic response to anti-tuberculosis drugs, rather than on the basis of culture isolation. This results in inappropriate use of anti-tuberculosis drugs. Furthermore, compliance with treatment remains poor. Despite TB having been declared a national emergency in 2001, implementation of the National TB Control Programme has been hampered by under-developed health facilities, lack of resources and poor management. The DOTS strategy adopted in 1995 has shown some progress with DOTS coverage at 24% in 2001 but with high drop-out rates of 17%[11]. All these factors appear to be responsible for the high levels of MDR-TB in our population[12].

CONCLUSIONS

In view of this increasing level of drug resistance, more organized national strategy against tuberculosis is needed. MDR-TB was most commonly seen in chronic cases/drug defaulters, and it is a major threat to the tuberculosis control measures.

REFRENCES

1. World Health Organization. Global tuberculosis control: surveillance, planning, financing: WHO report 2008. Geneva 27, Switzerland.
2. Patel D, Madan I. Methicillin resistant Staphylococcus aureus and multi drug resistant tuberculosis: Part 2. Occup Med (Lond) 2000; 50:395-7.
3. Rajabhandary SS, Marks SM, Bock NN. Costs of patients hospitalized for multi-drug resistant tuberculosis. Int J Tuberc Lung Dis. 2004; 8:1012-6.
4. Gupta R, Kim JY, Espinal MA. Responding to market failure in tuberculosis control. Science. 2001; 293:1049-50.
5. Dye C, Espinal Ma, Watt CJ Mbiaga C, Williams BG. Worldwide incidence of multi-drug resistant tuberculosis. J Infect Dis. 2002; 185:1197-203.
6. Mary DN. Multi-drug resistant tuberculosis. JAMA. 2005; 293:2788-90.
7. World Health Organization. Antituberculosis Drug Resistance in the World, Report Number 3. Geneva, Switzerland: World Health Organization; 2005.
8. Gillespi SH. Evolution of drug resistance in Mycobacterium tuberculosis. Lancet. 2003; 361:1355.
9. Glyn Jr, Whiteley J, Bifani PJ, Kremer K, Van Sooligen D. Worldwide occurrence of Beijing/W strains of Mycobacterium tuberculosis: a systematic review. Emerg Infect Dis. 2002; 8:843-9.
10. Munsiff SS, Nivin B, Sacajiu G, Mathema B, Pirani P, Kreiswirth BN. Persistence of a highly resistant strain of tuberculosis in New York City during 1990-1999. J Infect Dis. 2003; 188:356-63.
11. Ikram A, Ali S, Ali W, Wiqar AM. Latest pattern of multi-drug resistant tuberculosis in Pakistan. Inf Dis J PakScience. 2008; 17(1):14-7.
12. Butt T, Ahmad RN, Kazmi SY, Rafi N. Multi-drug resistant tuberculosis in Pakistan. J Pak Med Assoc 2004; 54:469.

13. Irfan S, Hassan Q, Hassan R. Assessment of resistance in multi-drug resistant tuberculosis patients. J Pak Med Assoc 2006; 56(9):397- 400.
14. Karamat KA, Rafi S, Abbasi S. Drug resistance in mycobacterium tuberculosis: a four years experience. J Pak Med Assoc 1999; 49(11):262-5.
15. Shaikh MA, Khokhar NA, Maheshwari N, Qazi I. Prevalence of drug resistance in pulmonary tuberculosis. J Liaquat Univ Med Health Sci 2008; 7(2):79-82.

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