BURDEN OF MULTI-DRUG RESISTANT AND EXTENSIVE DRUG RESISTANT OF MYCOBACTERIUM TUBERCULOSIS

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ABSTRACT

Aims: A cross sectional study was carried out to investigate the of TB, MDR and XDR in Tertiary care Hospital, Peshawar, Khyber PakhtonKhwa province of Pakistan.

Place and Duration of Study: At tertiary care hospital "Lady Reading Hospital" Peshawar, from January to December 2017.

Methodology: Sputum samples were collected from total 847 patients and AFB staining was used for the diagnosis of patients and further analyzed through gene expert procedure. Culture and sensitivity were also used for confirmation of their resistance.

Objective: To determine the burden of multi-drug resistant and extensive drug resistant of mycotuberculosis at Peshawar, Pakistan.

Results: A total 847 patients were included in which 421 (49.70%) patients were TB positive whereas remaining were negative. Mean age of all patients were 29.80±16.32 (10-71 years). Majority positive patients were observed in age 10-25 years. 102 patients were drug resistant patients in which 35 (34.31%) patients were Multi-Drug Resistant while 3 (2.94%) patients were XDR-TB. Pulmonary TB was observed in 97 (95.10%) patients whereas 5 (4.90%) patients were infected with Extra-Pulmonary TB.

Conclusion: It is concluded with the result of present study that still TB is health issue in developing countries. Additionally, MDR-TB is continuously increasing in our setting.

Keywords: Multi Drug Resistant; extensive drug resistant; mycobacterium tuberculosis

INTRODUCTION

Multi-Drug Resistance (MDR) is a serious global threat and major concern which is mainly occur in many developing countries due to poor treatment of TB all around the world[1]. The situation is become worst due to the resistant of tuberculosis to many drugs and exhibiting a new obstacle in the treatment of TB[2,3]. Globally, about 1-2% prevalence of (Multi-drugs resistant tuberculosis) MDT-TB is currently found in all TB cases. MDR-TB mainly observed in developing countries which is a major hurdle in the effective treatment of TB[4]. MDR-TB is not itself a disease condition. It is due misdirection of susceptible TB cases directing to drug resistance and incomplete treatment regimen[1,4]. The problems related to MDR-TB are very toxic and expensive medication required for therapy, as compared to suspected TB its mortality level is higher, time and money is required for accurate diagnosis[4].

MDR-TB is a condition in which TB patients showing resistance to the at least two more potent, effective and less toxic first line anti-TB drugs are Isoniazid (H and INH) and Rifampicin (R, Rif) (Rifampicin and Isoniazid, Rifampicin, Isoniazid and Ethambutol or Rifampicin, Isoniazid, Ethambutaol and Streptomycin) due to the mutation in their genome[5,6]. Isoniazid and Rifampicin are the most efficient, powerful and effective mycobactercidal drug accessible, help in prevention, treatment and lowering the transmission of TB. Therefore, the role of Isoniazid and Rifampicin are the backbone of TB management. Resistance to any of them either Isosniazid or Rifampicin can be treated with the other-one, resistance to Isoniazid or Rifampicin together can make obstacle for treatment and will demands for second line of drugs (Fluoroquinolone) and second line drugs are not for short treatment course. Hence, the treatment will be prolong, expensive and with high toxicity[7].

Mycobacterium becomes resistant to refampicin due to mutation in gene (rpoB gene) coding the subunit beta (β) of RNA polymerase. In addition, >90% mutations occur in 81basepair (507-533 codons) core regions of β subunit of rpo gene in RNA polymerase[5].

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MDR-TB showing resistance to these drugs leads to therapy with less influential, more expensive and toxic second line drugs (SLD)[6]. Fluroquinolones are broad spectrum antibiotics are then most frequently useful drugs for treatment of MDR-TB since 1984 and become main part of anti-MDR-TB. Various reported studies shows that FQ resistance and its poor outcome in MDR-TB[8].

MDR-TB may due to lack of awareness about TB in community, mismanaged cases, long under dosed treatment and undiagnosed cases[4]. Recently, extremely drug tuberculosis (XDR-TB) has observed in the rural areas of South Africa[1]. XDR-TB is defined as TB showing resistance to any family member of fluoroquinolone antibiotics as well as resistance to at least one of three injectable second line drugs such as kanamycin, amikacin and capreomycin along with the multi-drug resistance. These types of XDR and MDR TB do not show any respond in six months medications pattern of first line anti-TB drugs and may take 2 or more years in treatment with less effective drugs[4]. Greatest burden of XDR-TB are observed in China, India and former States of Soviet Union. XDR-TB is complicated in treatment and mortality rate is also high. National anti-TB drug resistance survey in 2007 reported the prevalence of MDR-TB among new and re-treatment cases was 1.1% and 3.9%, respectively. Sometimes, general TB convert to Multi-Drug Resistant-TB then transferred to extensively Drug Resistant-TB then Extremely Drug Resistant-TB and finally change to Total Drug Resistant-TB are noted in some regions of world[9].

Globally, the estimated prevalence of MDR-TB in adults is 4.6% was reported in 2006[8]. In 2010, WHO's report shows that there were 0.44 million (3.6%) of all fresh cases and 0.15 million were deaths due to MDR-TB in 2008[3]. About 50% of world wide were reported from India and China (10). The prevalence of MDR-TB in South Africa adults was found 6.7% (5.5-8.1%) in earlier treated patients and 1.8% (1.4-2.3%) amongst the new treatment cases[8]. In Turkey, 29% resistance was found to any anti-TB in the period of 2000-2007 in which the MDR-TB rate was 4.5%[11]. Prevalence of MDR-TB was observed in UAE (9.2%), Kuwait (5.9%), Saudi Arabia (4.3%), Brazil (3.5%) and Germany 2.2[11,12,13]. 3.4% prevalence of MDR-TB in newly diagnosed cases has been found[7].

According to the World Health Organization (WHO's), Pakistan is on rank 6th in tuberculosis cases and among the 27 countries in which high prevalence of MDR-TB were reported[5,14]. In 2012, laboratory confirmed MDR-TB Retreatment individuals was 55/1,602 in Pakistan[15]. The prevalence of MDR-TB varies from region to region in Pakistan, from 2% to 3.2% (2.3%) newly diagnosed and 17.9% to 35% in earlier treated cases. Recently study reported that gradually increased the number of MDR-TB cases from 1990 to 2007 in Pakistan, which are greater than fifteen thousand infected individuals reported in the study interval[5]. MDR-TB cure rate is low as compared to drug-sensitive TB in Pakistan[14].

The aims and objective of present study was to determine the prevalence of MDR-TB cases in tertiary care hospital, Lady Reading Hospital (LRH), Peshawar, Khyber PakhtonKhwa Province of Pakistan.

MATERIALS AND METHODOLOGY

Study Design: This study cross sectional study was conducted in tertiary care hospital (Lady Reading Hospital), Peshawar, Khyber PAkhtonKhwa, Province of Pakistan in a time period from January 2017 to June 2017. Total of 847 patients were included in present study. All the MDR-TB patients registered for treatment at the hospital from January to June 2017, weeks of Cough were volunteerly included in present study. Patients of XDR and/or history of therapy, unwilling and weeks of cough were excluded from present study.

Sampling: Individual of MDR-TB suspects were initially assessed with three earlier morning samples of sputum for investigation of Acid Fast Bacilli (AFB) by sputum smear microscopy using Ziehl Neelsen (ZN) staining technique. All positive samples through smear and gene Xpert were brought for culture and sensitivity. Antibiotic susceptibility testing (AST) for rifampicin (R), isoniazid (H), streptomycin (S), ofloxacin (Ofx), amikacin (Am), ethambutol (E), ethionamide (Eto), capreomycin (Cm) and kanamycin (Km) was conducted on agar plates (Enriched Middle Brook).

Sputum Culturing: All the sputum specimens were first allowed to digestion and decontamination process that liquefy the debris and destroyed the unwanted normal flora. The modified petroff (Sodium Hydroxide) technique was used due to its reagents availability. Lowenstein-Jensen (LJ) medium was used for TB diagnosis.

Statistical analysis: All the data were analyzed through Microsoft Excel and Statistical Package for Social Sciences version 21 (SPSS-21). Means and Standard Deviations (SD) were computed for continuous data while categorical variables were analyzed as percentages (%) and frequencies (f).

RESULTS

In current study, total of 847 patients were included as suspected for TB. Out of total, 434 were male and 413 were female. Mean age of all patients were 29.80±16.32 years with a minimum age of 10 years while maximum age was 71 years. Majority of participants were newly diagnosed patients. A large number of patients were illiterate, labors and house hold participants while some were students. Additionally, more than half were deprived, poor and class people. Out of total, 421 (49.70%) patients were infected with TB (AFB positive smear) in which 202 (23.85%) were male and

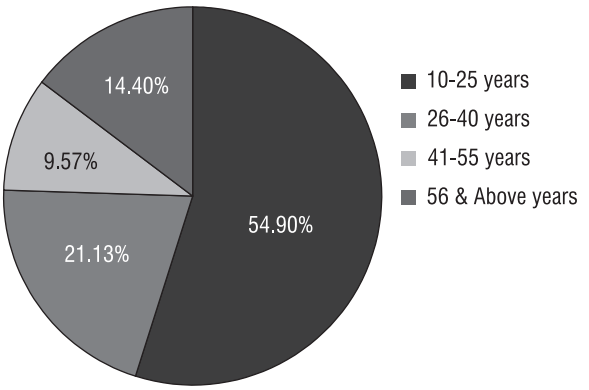

Figure 2:Patients are distributed according to age.

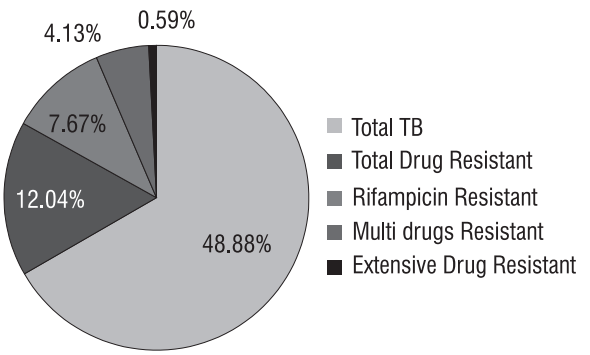

Figure 3: Percentage of TB and drug resistant patients

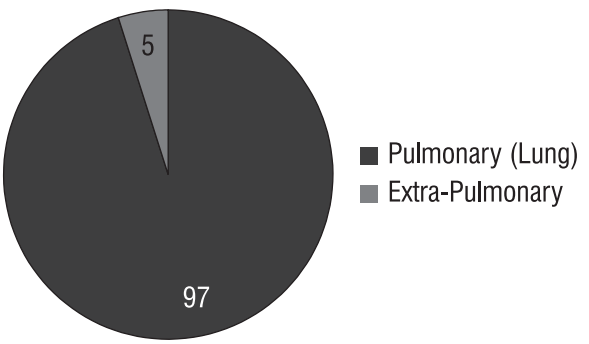

Figure 4: according to the site of infection, drug resistant patients were distributed

219 (25.86%) were female patients whereas remaining were negative as shown in Table and Figure No.1.

Maximum number of patients were observed in age 10-25 years with a percentage of 54.90% (465 patients), followed by age 26-40 years (21.13%) then age 56 & above years (14.40%) while lowest were noted in age 41-55 years with percentage of 14.40% as shown in Table and Figure No.2.

Out of total, 421 were TB positive cases in which 102 patients were showed resistant to different drugs. In 102 drug resistant patients, 64 (62.75) were rifampicin resistant, 35 (4.13%) patients were Multi drug resistant patients while only 3 (2.9%) patients were Extensive drug resistant as shown in Table and Figure No.3.

Majority of drug resistant patients (97) have Pulmonary (Lungs) TB with a percentage of 95.10% while Extra-Pulmonary were observed only in 5 patients with a percentage of 4.90% as shown in Table and Figure No.4.

DISCUSSION

Drug resistant tuberculosis is a rapidly increasing world health problem with a high individual and socio-economic consequence[16]. In the current study, prevalence of TB in general population was 49.70% (n=421) which nearly closed to the finding of Mohammad Ishaq et al. Reports in which prevalence of TB positive samples were 52% (sample size 200 patients)[17]. Another study from Los Angeles also reported 56% sputum positive TB[18]. Present study percentage of TB is also high as compared to the Kerry et al study. This might be due to poor hygienic condition, improper health organization and inappropriate TB diagnostic centers.

In the present, TB in female was comparatively greater with a percentage of 25.86% to male patients in which percentage were 23.85%. Our study support the results of Ahmad *et al*., Ayaz et al. and Ullah *et al*[19-21]. Present revealed that TB is more common in female than male. It's may be due to association with environment, female treat less and poor nutritional status as compared to male and early marriages as well as multiple pregnancies which make defense system become weak and exposed to TB infection. Children and family were at risk due to TB infection in mother[17]. While in contrast with the other studies who reported high percentage of male as compared to female[10].

Current study also revealed that maximum numbers of patients were infected in age 10-25 years with a percentage of 54.90% while 76.03% were under the age of 40 years. Similar result was reported from Peshawar which revealed that 88.7% were under the age of 40 years[5]. Present study report shows that prevalence of drug resistant is 12.04% (n=102) Andrea et al reported data revealed similar results like current report that 9.4% resistant cases were observed[9]. Rifampicin was resistant in 62.75% cases which is too high as compared to study in India which showed that in 27.6% cases TB were resistant to rifampicin[22]. Another study reported 53.03% resistant to rifampicin[19] which is nearly similar to present reported data.

Prevalence of Multi drug resistant is 34.31% in current study which support the finding of Worko Jimma et al[23]. Current report shows higher percentage of MDR as compared with the result of Andrea et al and Muataz et al. who's reported 15% and 10.1% respectively[9]. Also high, this could be due to the frequent self medication at home for the chest infection before the acute diagnosis of TB. More than 3 months delay between the onset of treatment and symptoms of TB were reported[24]. Due to

poverty, poor patients are unable to afford the consultation fee and no proper awareness about TB, initially for treatment of respiratory tract choose local health personnel (paramedics). Additionally, due to easy availability and short waiting duration prefer private clinic for seeking of treatment[25]. Moreover, lack of diagnostic centers, skillful health personnel, inadequate knowledge with private practitioners and frequently prescription of broad spectrum fluoroquinolone (FQ) to patients before treated with TB consultant[26]. Similarly report from India also revealed about the miserable activities by private practitioners[27]. MDR may be due to lack of improvement in clinical setup, expensive laboratory tests and therapy. As no drug susceptibility testing was easily accessible in our majority tertiary care centers and antituberculous therapy (ATT) was only available at the Agha Khan Hospital (Laboratory) which is too much expensive and cannot be afford by poor families[14]. Prevalence of MDR is 26.4% in China which is less than current report[27]. 2.89% percentage of Extensive drug resistant is observed in TB patients in present study. While 8.57% XDR were observed among MDR cases in present which is similar to the report of WHO 2010[28]. In Present study, Pulmonary Tuberculosis was found in 95.10% cases while 4.90% cases were observed with Extra-Pulmonary Tuberculosis whereas no one have both Pulmonary and Extra-Pulmonary tuberculosis. A present study result also coincides with other results reported in different studies at different regions in the world[5,6].

Limitation of present was lack of standard resources to determined the complex cases, could not detect the potential risk factors because of non-availability of information, not specify the antibiotic resistance because of high expenses, not determined the causes of high prevalence in female population, not determined the molecular strain of TB, possible risk factors such as diabetes and HIV were also not measured and mortality ratio were also not determined. Need to increase the accurate and effective diagnosis of TB cases, to make better treatment outcome, to improve the access and fairness, to train the health workers to apply the DOTS effectively, need to open new DOTS and microscopic center for correct diagnosis, awareness about its risk factors among the uneducated population and reduce the financial burden on the poor patients.

CONCLUSION

Present study highlight the growing level of TB, MDR and XDR cases which are persistently increasing in Khyber Pakhtonkhwa, province of Pakistan. Therefore, its a new challenge for the health policy maker. Moreover, should take multiple preventive measures to overcome the MDR-TB before it becomes incurable.

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