FREQUENCY OF SECONDARY MULTI DRUG RESISTANCE TUBERCULOSIS AND ITS COMMON FACTORS IN PATIENTS PRESENTING WITH CATEGORY II FAILURE

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ABSTRACT

Background: Tuberculosis is a major cause of morbidity and mortality throughout the world and drug resistance tuberculosis may threaten efforts to control tuberculosis in the world by reducing the effectiveness of standard short course chemotherapy.

OBJECTIVE: To determine the frequency of secondary multi drug resistance tuberculosis and common factors leading to it in patients presenting with category II failure.

Study design: Descriptive (Cross Sectional) Study

Duration of study: 8 months from 1st sep 2011 to 30th april 2012.

Subjects and Methods: 156 CAT- II failure patients of either gende of 10 years old and above sputum was sent for AFB microscopy. All sputum positive samples for AFB were tested for resistance to Isoniazid and Rifampicin to detect MDR TB and detailed clinical history was taken to detect common factors leading to MDR TB. Data was analyzed with SPSS 16.0.

Result: The Mean duration of the Category II treatment at presentation was 26.164weeks ±.49 SD weeks ranging from 20 to 32 weeks. Multi Drug Resistance TB was found in 61(39.1%) patients and among these patients 35(57.4%) were females and 26(42.6%) were males. Inadequate treatment and irregularity in treatment were 10(16.4%) patients, un completed first course of treatment in 7(11.5%), Non observed treatment in 6(9.8%), Non availability in 2(3.3%) patients.

Conclusion: Secondary MDR-TB is 39.1% and the two main factors responsible for more than 50% of secondary MDR-TB at the end of 2nd month are Non DOTs treatment and Non smear conversion

Key words: Secondary MDR-TB; Catogary II failure; Category II treatment; DOTs treatment.

INTRODUCTION

Tuberculosis is a major cause of morbidity and mortality throughout the world, killing 2-3 million people every year[1]. More than 90% of these deaths occur in the developing world that includes Pakistan[2,3]. Drug resistance tuberculosis (TB) may threaten efforts to control TB in the world by reducing the effectiveness of standard short course chemotherapy and by absorbing most of the resources of the natural TB control program[4]. The prevalence of multi drug resistance tuberculosis (MDR TB) is low in countries with high success rate[5]. According to WHO estimate, more than 50 million people may be infected with drug resistance tuberculosis and its presence in some countries has reached epidemic levels. In high burden countries previously treated cases are responsible for 4.4-26.9% resistance.[6]

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Despite the availability of effective chemotherapy, tuberculosis (TB) still remains a major health problem in most of the countries of the world.[7,8] Drug resistance is a threat to TB control programs worldwide. Patients infected with multiple-drug resistant strains are less likely to become cured, particularly if they are infected by HIV or suffer from another immune disease. The treatment is much more toxic and much more expensive (about 700 times) than the one of patients with sensitive organisms.[9]

The prevalence of MDR TB is increasing throughout the world both among new tuberculosis patients and as well as previously treated ones and previous treatment with TB is the strongest risk factor for MDR TB.[10]

In Pakistan the prevalence of MDR TB patents who have taken Anti tuberculosis treatments in the past accounts for 28% of all TB cases.[5] The consequences of resistant TB are enormous. Such patients who are sputum Smear positive remain infectious for much longer time and are catastrophic to the patient and his family and have a much higher morbidity and mortality.[1] So it is very important to identify MDR TB cases as early as possible and to initiate the treatment. A definitive diagnosis of MDR TB requires that Mycobacterium

tuberculosis be isolated on Culture and drug sensitivity completed. The duration of drug susceptibility testing has decreased from 4 to 6 weeks to 10 to 14 days with liquid media.[7]

Various factors have been identified which can cause secondary multidrug resistance tuberculosis in patients who have received anti tuberculosis treatment in the past and include non directly observed treatments (non DOTs) 35.8%, non observed treatment 37.3%, inadequate treatment 33.8%, incompleted first course of anti tuberculosis treatment 25.4%, irregularity in the course of treatment 41.8%, non availability of anti TB drugs 9% and non smear conversion at the end of second month of treatment 34.9%.[8]

Certain factors not related to previous anti tuberculosis treatment are also identified which can play role in the development of MDR TB and include advanced age, female gender, alcohol abuse, smoking, low socio economic status, illiteracy, concomitant infections with Diabetes Mellitus, HIV/AIDS, chronic lung diseases, cavitary tuberculosis[9] and extra pulmonary tuberculosis, malnutrition and low body mass index.[11]

The rationale behind doing this study is that more reliable estimates of the magnitude of MDR TB will be available locally that would be helpful for planning and expanding the programmatic management of drug resistance TB to a tertiary care hospital by disseminating the result of this study to other health professionals and government and non-government agencies working for the control of TB in Pakistan. By looking into the magnitude of the factors leading to MDR TB in this study, pre existing guidelines regarding TB treatment can be modified in our population which can be based upon most frequent factor found through the result of this study.

OBJECTIVE

To determine the frequency of secondary multi drug resistance tuberculosis and common factors leading to it in patients presenting with category II failure.

MATERIAL AND METHODS

This descriptive (Cross Sectional) study was carried out at Pulmonology Unit, Ayub Teaching Hospital Abbottabad during 8 months from 1st sep 2011 to 30th april 2012 recruiting 156 patients of category II treatment for tuberculosis by consecutive (non probability) sampling technique. The inclusion criteria adopted was; CAT- II failure patients of either gende of 10 years old and above who were on category II treatment and at the end of fifth month sputum were still positive for AFB, complaining of productive cough and fever of more than 99ºF. All patients who were smear negative pulmonary tuberculosis, on Quinolones (because they act as second line ATT and will interfere with our result) and who had not taken ATT in past were excluded from the study.

After approval from the Ethical committee, patients were included in the study from out patients department and casualty, fulfilling the inclusion criteria and informed written consent was taken. Category II patients were defined as patients who had taken Anti tuberculosis treatment comprising of Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin in the past, suggested by history. Category II treatment was defined as Intensive phase: First two months treatment with five drugs, Isoniazid 4-6mg/kg, Rifampicin 8-12mg/kg, Ethambutol 15-20mg/kg, Pyrazinamide 20-30mg/kg, Streptomycin 12-18mg/kg.Third month streptomycin was stopped and the remaining drugs were continued for one more month. Continuation phase: After intensive phase, five months treatment with three drugs Isoniazid 4-6mg/kg, Rifampicin 8-12mg/kg, Ethambutol 15-20mg/kg. Category II Treatment Failure was defined as Patients who were on category II treatment and at the end of fifth month sputum was still positive for AFB on culture sensitivity result and patient was having history of productive cough and fever of more than 99º F. Secondary MDR T.B was defined as resistance to at least Isoniazid and Rifampicin confirmed on pure culture and sensitivity of the organism mycobacterium tuberculosis in a patient who has already taken ATT in the past, suggested by history and pervious treatment card.

All patients were interviewed to obtain clinical data like age, sex, clinical symptoms. Initial base line investigations like chest x-ray, full blood count, urea, and creatinine were obtained. Sputum was sent for AFB microscopy to the hospital laboratory. Only patient with positive result were included in the study. All samples were collected in the early morning and in special sterilized container. All sputum samples positive for AFB were sent to AGHA KHAN UNIVERSITY laboratory to test for resistance to isoniazid and Rifampicin to detect MDR TB.

Among patients who are found to be MDR TB positive, careful history was taken in presence of a fellow of CPSP to detect common factors leading to secondary MDR TB as Non DOTs Treatment (Which was not observed by DOTs facilitator and was detected through history taking0, Non Observed Treatment (Which was not observed by treatment supporter which was detected through history), Inadequate Treatment (ATT taken in sub therapeutic dosage, for a shorter duration and lesser number of drugs prescribed as evident by the history and the previous record), Uncompleted First Course (Defaulter, taken ATT for more than one month and discontinued for more than two months as detected by previous record and history), Irregularity in the Course of Treatment (someone who had taken ATT for more than one month and discontinued for less than two months as detected by previous record), Non Availability of Anti TB Drugs (History of non availability of Anti TB drugs

in nearby of the respondent), Non Smear Conversion in the 2nd month of Treatment (Patients whose sputum smears do not become negative at the end of second month detected through medical records). Exclusion criteria was strictly followed to minimize bias in study.

Data was analyzed by using SPSS version 16.0 and result were presented in the form of tables and graphs.

RESULTS

Total of 156 patients fulfilling inclusion criteria were admitted to pulmonology unit ATH, Abbottabad.

Out of 156 patients, 68(43.6%) were male and 88(56.4%) were female. Majority of the patients 128(82.1%) were 40–70 years of age, with only 11 (7%) below 40 years and 17(10.9%) above 70 years of age. Maximum age of patient was 95 and minimum age was 20 years.

All patients included in the study were taking anti tuberculous therapy and the Mean duration of the Category II treatment at presentation was 26.163 weeks ±2.49 SD ranging from 20 to 32 weeks.

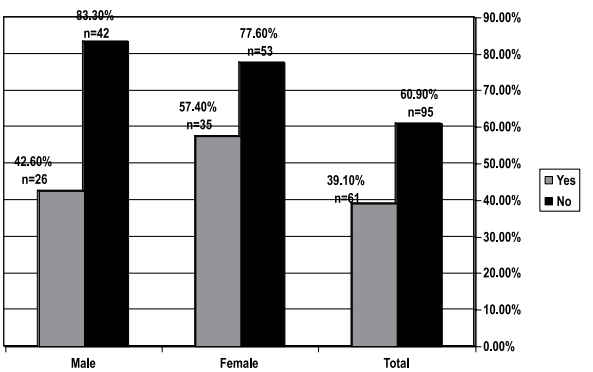

Fig No 1. Distribution of Multi Drug Resistance in Tuberculous Patients Taking Category Ii Treatment

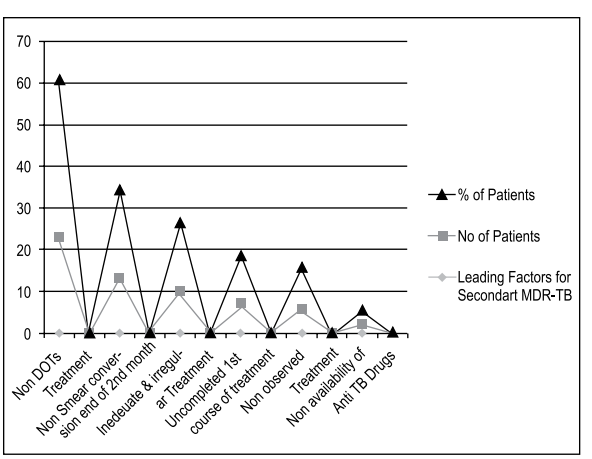

Fig No 2. Common Factors Leading to Secondary Multi Drug Resistance Tuberculous In Tuberculous Patients Taking Category Ii Treatment

Out of 156 patients Secondary Multi Drug Resistance TB was found in 61(39.1%) patients and among these patients 35(57.4%) were females and 26(42.6%) were males. Out of 156 patients, 95(60.9%) patients came out to be Non MDR-TB, with 53(77.6%) female & 42(83.3%) males

Among 61 patients having secondary (MDR-TB), Non DOTs treatment was the leading factor for MDR-TB mounting up to 23(37.7%). Non smear conversion at the end of second month was documented in 13(21.3%) patients. Inadequate treatment and irregularity in treatment were found in 10(16.4%) patients. Seven patients (11.5%) had uncompleted first course of treatment. Non observed treatment was responsible for 6(9.8%) MDR-TB. Non availability was documented in 2(3.3%) patients. (figure 1)

DISCUSSION

Tuberculosis (TB) is a contagious disease, which spreads as a droplet infection. It is the leading killer of young adults worldwide. Each year, 8 million people develop active TB and 3 million die. The largest number of cases occurs in the South-East Asia Region, which accounts for 33% of incident cases globally. Overall, one third of the world's population is currently infected with the TB bacillus and someone is newly infected with TB bacilli every second. The emergence of Resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB), has become a significant public health problem in a number of countries and an obstacle to effective global TB control. In many other countries, the extent of drug resistance is unknown and the management of patients with MDR-TB is inadequate. In countries where drug resistance has been identified, specific measures need to be taken within TB control programs to address the problem through appropriate management of patients and adoption of strategies to prevent the propagation and dissemination of drug-resistant TB, including MDR-TB.[12]

In our study we observed very high levels of resistance in patients already taking Category II treatment. The frequency of multi-drug resistance (39.1%) among Mycobacterium tuberculosis was much higher than the figures reported by other studies. A study from Punjab, AFIP by Ikram et al reported MDR TB of only 30.7%[13]. This figure is bit low then our reported proportion of MDR TB (39.1%). This difference is probably due to poor selection of patients in study of Ikram et al. similarly Khan J et al conducted study in Karachi in 1992 observed primary resistance to one or more anti-tuberculous drugs in 17% and secondary resistance in 36%[14]. China has reported the results of its first ever nation-wide drug resistance survey, with documented proportions of MDR-TB of 5.7% among new cases and 25.6% among those previously treated[15].

Incomplete and irregularity in Treatment was found in 10(16.4%) patients in our study while Sharma

SK et al found that errors in TB management such as the use of single drug to treat TB, the addition of a single drug to a failing regimen, the failure to identify preexisting resistance, the initiation of an inadequate primary regimen, the failure to identify and address nonadherence to treatment, inappropriate isoniazid preventive therapy, and variations in the bioavailability of anti-TB drugs predispose the patient to the development of MDR-TB.[16]

Inadequate Treatment Adherence is often underestimated by the physician and is difficult to predict. In the West, demographic factors such as age, sex, marital status, education level, and socioeconomic status have not been found to correlate with the degree of treatment adherence. On the other hand, certain factors such as psychiatric illness, alcoholism, drug addiction, and homelessness do predict nonadherence to treatment.[17]

Non observed treatment was responsible for 6(9.8%) cases in our study. The directly observed treatment, short course (DOTS) strategy, which has been endorsed by the WHO as the only effective way to control TB, has to some extent addressed these problems.[18] In India, innovative measures such as public-private mix and the use of Anganwadi workers have been tried out under program conditions to improve treatment adherence in patients with TB in general, and these measures would help patients with MDR-TB also.

Non availability of anti tubercular drugs and logistic issues is always been a problem and development of MDR TB. We found in our study 2(3.3%) patients were not having to access to antituberculus drug. Good, reliable laboratory support is seldom available in developing nations. When facilities for growing cultures and sensitivity testing are not available, therapeutic decisions are most often made by algorithms or inferences from previous treatment.[19]

Deriemer et al shown that DOTS has been shown to reduce the transmission and incidence of both drug-susceptible and drug-resistant TB even in settings with moderate rates of MDR-TB.[20] Our study showed that non DOTs treatment was the leading factor for MDR-TB mounting up to 23(37.7%). It has been observed that the "programmatic approach" to the management of patients who do not respond to treatment may fail in certain settings.[21]

First-line treatment was not sufficient in 7(11.5%) patients in our study as has been observed by Coninx R. et al. that first line therapy may not be sufficient in settings with a high degree of resistance to anti-TB drugs.[22]

Although the DOTS strategy is the basis of good TB control, the strategy should be modified in some settings to identify drug-resistant cases sooner and to make use of second-line drugs in appropriate treatment regimens.[23]

CONCLUSION

In our study we found secondary MDR-TB in 61 patients i.e. 39.1%.Most of the patients were females as compared to males, which also shows the gender discrimination in the diagnosis and treatment in our set up.

During my study, I tried to point out the factors involves, leading to secondary MDR-TB. The study shows that Non DOTs treatment and Non smear conversion at the end of 2nd month are the two main factors responsible for more than 50% of secondary MDR-TB.

While other factors are Inadequate and irregular treatment, Uncompleted 1st course of treatment, Non observed treatment and Non availability are the other factors in ascending order.

To ensure optimal utilization of limited resources we strongly advocate that these at risk groups should be a particular focus of DOTS program. The optimal approach would be primary prevention through vaccination, continued surveillance and appropriate therapeutic decisions with monitoring of the patients to help reduce this alarmingly high rate of secondary MDR TB.

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