Risk Factors for Multidrug Resistant Tuberculosis among patients with pulmonary tuberculosis at Tertiary care hospital

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MY AS FJ conceived idea, FJ HNK NM drafted the study, MY AS collected data, SASN FJ did statistical analysis & interpretation of data, MY FJ NM HNK critical reviewed manuscript, All approved final version to be published.

Declaration of conflicting interests

The Authors declares that there is no conflict of interest.

Abstract

Background: The incidence of multidrug-resistant tuberculosis (MDR-TB) is very high in Pakistan considering the fact that Pakistan is one of the few countries with a high burden of tuberculosis – both drug susceptible and drug resistant tuberculosis.

Objective: This study focused on the risk factors leading to development of MDR-TB in patients diagnosed with tuberculosis.

Methodology: This was a case control study to evaluate the demographic, social, and clinic behavioral risk factors for MDR-TB in patients diagnosed with tuberculosis. Structured questionnaire and review of clinical records were used to collect data for this study which was entered into and analyzed using SPSS 20. Multi-variate logistic regression was used to determine independent risk factors affecting the outcome in patients with tuberculosis. P≤ 0.05 was taken to be significant.

Results: There were 180 study participants divided into two groups of 90 each. Age, close quarter living, treatment with anti-tubercular drugs in the past and diabetes mellitus were found to be independently associated with development of multi drug resistant tuberculosis.

Conclusion: Active case finding strategies for diagnosis and management of multi drug resistant tuberculosis should focus on younger patients, patients who have been treated in the past for tuberculosis and those who live in overcrowded places.

Key Words: Diabetes Mellitus; HIV; Retreatment; Tuberculosis

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Introduction

Despite being completely curable, tuberculosis is responsible for numerous deaths in adults across the globe.[1-3] Every third individual in the world has been at some point in their life been infected by mycobacterium tuberculosis.[4,5]

Development of resistance to anti-tuberculosis drugs is a major challenge to the efforts in controlling

tuberculosis.6 Many forms of drug resistant tuberculosis have been described with multi-drug resistant and extensive drug resistant tuberculosis being the most dangerous.[6-8] As per recent guidelines set by the WHO, all cases with rifampicin resistant tuberculosis are to be treated as multi drug resistant tuberculosis. Multi drug resistant tuberculosis or MDR-TB is defined as emergence of resistance to both rifampicin and isoniazid with or without resistance to other drugs, excluding simultaneous concomitant resistance to injectable such as aminoglycosides and Fluoroquinolones.[7]

Most new cases of MDR-TB have been attributed to either physician error or as a result of poor compliance with medications by the patients which leads to selection of drug resistant strains of mycobacterium tuberculosis and in some cases introduction of primarily drug resistant strains of mycobacterium tuberculosis.[8-11] The incidence and prevalence of MDR-TB varies worldwide. The most MDR-TB estimates for Pakistan range between 9.3%-41% depending on the study population.[12,13]

To our knowledge, little is known about the risk factors for MDR-TB in this region, as not many studies focused on the risk factors for MDR-TB in this region however, it has been hypothesized that being male, young age, co-infection with HIV, comorbidities such as diabetes, malnutrition, chronic alcohol use, past history of anti-tuberculosis treatment, lower socioeconomic status and a positive TB contact history serve as independent risk factors for the development of MDR-TB.[13-16]

We conducted this research to be able to identify potential factors making an individual prone to development of MDR-TB allowing us to enact pre-emptive measures to prevent further spread of the disease affecting the outcome of the disease positively and, as a whole, decreasing the burden of disease in this region.

Methodology

After obtaining permission from the ethics committee of the District Headquarters Teaching Hospital, Haripur, this study commenced in same settings after obtaining written informed consent from the study participants. The study settings was the TB Center, District Headquarters Teaching Hospital Haripur, where patients with MDR-TB were managed from September 2017 to March 2019. All those patients with tuberculosis who were found to have MDR-TB on either Gene-Xpert or on Culture were labelled as cases while patients who underwent sputum conversion during the course of treatment were labelled as controls for the purpose of this study. A sample size of 180 was calculated for this study using 80% power, 40% prevalence of HIV/AIDs in patients with tuberculosis, 95% confidence interval and an odds ratio of 2.55 and 10% non-response rate. Non-probability consecutive sampling was used for sample selection. The study participants were interviewed and their responses collected on a structured questionnaire before their clinical records / details of the current as well as past illness were reviewed.

A number of patient related variables such as demographic factors, socioeconomic factors as well as environmental factors were reviewed in the questionnaire. The cases were enrolled from patients admitted at the various medical units of the hospital as well as those registered as DR-TB patients with the TB center of DHQ, Haripur while controls were selected from patients attending the outpatient department of the hospital who had underwent sputum conversion and were now on continuation phase. The collected data was entered into and analyzed using SPSS 20. Mean and standard deviation were used to describe descriptive variables while frequencies and percentages were used to describe categorical variables. Bi-variate analysis was used to point out the possible association between MDR-TB and different socioeconomic, demographic and environmental variables in the study population. $P \leq 0.05$ was taken as significant and strength of the association was measured by Odds ratio. Multi-variate logistic regression was performed for the variables which showed a significant association with the outcome variable to find independent association.

Results

The mean± SD age of all study participants was 30.2±8.42 years. The mean± SD age for cases was 32.48±5.89 years while the mean± SD age for controls was 35.7±4.98 years. An overwhelming majority of the patients was younger than 35 years (115; 63.88%). 41 (45.6%) controls and 52 (57.8%) cases were males. Overall, Muslims (n=169; 93.88%), literate (n=160; 88.8%), and un-married (n=120; 66.6%) were in majority. Twenty-eight (31.1%) cases eleven (12.22%) controls were students; Among cases and controls, 18 (20%) and 14 (15.5%) respectively were house-wives; 19 (21.1%) cases and 12 (13.3%) controls worked in public sector; 13 (14.4%) cases and 24 (26.7%) controls were unskilled workers on daily wages. The monthly income of most study participants (38 (42.2%) cases and 41 (45.56%) controls) was less than Rs 20,000. An unrefined association between MDR-TB and a number of factors such as diabetes mellitus, HIV infection, TB retreatment cases and poor living conditions such as living in closed quarters was found on bivariate

analysis.

A multi-variable analysis was performed on all variables which showed a statistically significant association with the outcome variable i.e., MDR-TB. These included age, monthly income, marital status, past history of TB treatment, number of rooms in the house and presence of comorbidities such as diabetes mellitus, HIV etc. Four variables were found to be able to independently predict the incidence of MDR-TB in the study population. These included age, past history of anti-tuberculosis treatment, living in close quarters such as in only one room along with TB patients and diabetes mellitus. The risk of occurrence of MDR-TB in younger individuals (age less than 30 years) was eight times more than those older than 30 years (adjusted odds ratio [AOR] = 8, 95% confidence interval [CI]: 3.2–20.12). Similarly, the risk of MDR-TB was twenty times more in patients with a past history of anti-tuberculosis treatment (AOR= 20; 95% CI: 16.70–26.60) while the risk of acquiring MDR-TB with living in a household of only one room was six times more than those who had at least 2 rooms in their house (AOR= 6, 95% CI:2.93–16.89). Presence of concomitant diabetes mellitus meant that the patients were 4 times more likely to have MDR-TB than non-diabetics (AOR= 4.10, 95% CI: 2.32–10.11)

Discussion

We were able to identify some potentially avoidable risk factors associated with the incidence of MDR-TB in our study population. The strongest association was with the young age, past history of anti-tuberculosis treatment and living in close quarters, while diabetes mellitus was found to have a weaker yet statistically significant relationship with the incidence of MDR-TB. We found that patients younger than 30 years of age were 8 times more likely to acquire MDR-TB than those older than 30 years. The association of age with the incidence of MDR-TB has also been noted in other studies.[12,17,18] A study from London showed reported that patients with MDR-TB were found to be younger than patients with drug-susceptible tuberculosis (AOR= 1.83; 95% CI 1.02–1.05).[18] Similarly, a study from Punjab, Pakistan reported that patients in the age range of 15-45 were most likely to get MDR-TB.[12] The increased predilection of young age with MDR-TB can partially be explained on the basis of lack of compliance in the specific age group. We didn't find sex of the patients to be a risk factor for occurrence of MDR-TB even though being female has been reported to be a risk factor for incidence of MDR-TB in patients who have been treated for tuberculosis in the past in a cross-sectional study (AOR= 1.58, 95% CI 1.02–2.32).[17] This could be due to different study population as well as different study design.[17,18] However, some have not found any association between gender and MDR-TB.[12]

We found that patients living in close quarters, i.e., in a household comprising of one room, were 6 times more likely to acquire MDR-TB than those who had at least two rooms in their houses. This can partially be explained by the effect of proximity as well as suspension of mycobacteria in air in crowded places without proper ventilation. A study from Tharparkar, Sindh also reported that close contacts contributed to the spread of drug sensitive as well as MDR-TB in Tharparkar region.[16]

Our results point towards importance of highlighting the mode of transmission of tuberculosis to the masses since its mode of transmission i.e., inhalational route coupled with close proximity as implied by living in close quarters since this can result in acquisition of primary drug resistant tuberculosis as a result of transmission of mycobacterial strains resistant to a number of drugs in these conditions.[19]

We also observed a highly significant association of anti-tubercular treatment history in the past and / or presence of diabetes mellitus with an increased risk of MDR-TB. A positive past history of tuberculosis was associated with a twenty times increased risk of MDR-TB than those who were diagnosed for the first time with pulmonary tuberculosis. Similar, albeit not as huge as the one observed in this study, association has been reported in literature where past history of anti-tubercular treatment was associated with more than 5 times increased risk of acquiring MDR-TB.[12,13,18,20] The mechanisms underlying an increased risk of MDR-TB may involve development of mutations in mycobacteria that cause resistance to anti-tubercular drugs in these patients because of multiple and sometimes inappropriate administration of anti-tubercular drugs.[21-23] Adherence to DOTS principles in addition to enhanced availability of drug-resistance testing can reduce MDR-TB in these patients.

Diabetic patients were found to have a four-fold increased risk of MDR-TB than non-diabetics. Diabetics are known to have an increased predilection for tuberculosis and presence of diabetes mellitus confers an adverse status to the patient with tuberculosis[24-27], this is an interesting finding in our population as far as MDR-TB is concerned and more research needs to be done in exploring the association between the two.

Although an association between HIV and MDR-TB has been reported in literature, we, interestingly did not have any HIV positive patient in our study. Patient selection bias may be responsible for such an anomaly and we recommend further studies with

large sample size to explore this association in our population.

We believe that a lack of treatment centers for drug resistant tuberculosis, coupled with lack of patient and primary care physician education is making it difficult to address the problem of drug resistant tuberculosis in our region. An increase in number of treatment centers focusing on drug resistant tuberculosis as well as spread of case detection programs can help us assess the magnitude of the problem in our population in future.

Conclusion

To sum up, younger age (less than 30 years), diabetes mellitus, past history of anti-tuberculosis treatment and living in crowded places were associated with a significantly increased risk of acquiring drug resistant tuberculosis. The provincial and national tuberculosis control programs should include control of these risk factors by way of patient education as well as targeted case detection with a focus on interventions to reduce transmission of mycobacterium tuberculosis from infected to non-infected individuals. However, we would like to propose that a large scale research should be conducted to validate these findings.

Conflict of Interest

The authors declare that there is no conflict of interests.

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