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Original Research

Drug resistance pattern in Tuberculosis patients

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ABSTRACT:
Background: To study the drug resistance pattern in tuberculosis. **Materials & Methods:** A collection of Mycobacterial strains was gathered from 100 patients who had been diagnosed with smear-positive tuberculosis. These strains were subjected to testing for susceptibility to drugs such as ethambutol, isoniazid, and streptomycin. Additionally, multiple logistic regression analysis was conducted to pinpoint the risk factors associated with MDR-TB. The strength of these associations was quantified using odds ratios (OR) with a 95% confidence interval (95% CI), and statistical significance was considered when the two-tailed p-value was less than 0.05. **Results:** A total of 100 cases were evaluated. Among them, 86 subjects were older and remaining were the new cases. The smear was taken and examined. The study found a significant association between an initial smear grading of 2+ and 3+ and drug-resistant tuberculosis (p=0.02). However, this same association did not hold importance in the context of multidrug-resistant tuberculosis (MDR-TB) (p=0.7). **Conclusion:** The primary factors contributing to the development of multidrug-resistant tuberculosis (MDR-TB) were individuals under the age of 48, a history of previous TB treatment, and having a positive smear at the end of the second month of treatment.
Keywords: Streptomycin, Tuberculosis, Resistance.

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INTRODUCTION

Tuberculosis (TB) remains a major global health problem, especially in high TB burden countries with large numbers of TB patients and poorer sanitation. TB ranks as the second leading cause of death among infectious diseases worldwide, following only the human immunodeficiency virus (HIV).[1] According to the 2012 WHO global TB report, China ranks as 2nd among the world's 22 high burden countries with a TB incidence around 1 million, and the prevalence rate of TB was 104 per 100,000 patients (95% confidence interval [95% CI] 91–119) and the incidence rate was 75 per 100,000 patients (95% CI 66–85) in 2011.[1]In a nationwide survey in China in 2007, the estimated multidrug-resistant tuberculosis (MDR-TB) rate was 5.7% for new cases and 25.6% for previously treated cases. Approximately 8% of the patients with MDR-TB had extensively drug-resistant tuberculosis (XDR-TB).[2] However, information on the prevalence of MDR and XDR-TB remains scant in the region. Drug-resistant Mycobacterium tuberculosis(MTB) strains, MDR-TB and XDR-TB strains may be the potential propellers for the spread of TB, and through now we put great efforts in TB control and treatment, the situation has not greatly improved. Despite poor compliance to chemotherapy duration, drug resistance of MTB would be another important factor for treatment failure among new TB cases, which may lead to a fall in successful TB cure rates. [3,4]

Today, the continuing spread of MDR-TB is one of the most urgent and difficult challenges facing global TB control. In 2012, there were approximately 450,000 new cases of MDR-TB and 170,000 deaths. Globally, MDR-TB is present in 3.8% of new TB patients and 20% of patients who have a history of previous treatment. The highest MDR rates are found in countries of Eastern Europe and central Asia, where MDR strains threaten to become as common as pan-susceptible strains. In some countries, MDR strains account for up to 20% of new TB cases and well over 50% of patients with a history of previous TB treatment. In 2011, Minsk, Belarus reported that 35% of new patients had MDR-TB, as did 75% of those

who had been treated previously for TB. [5]Equally worrisome rates have emerged from China and India, which have the highest and second-highest number of MDR-TB patients in the world. In 2012, the China Centers for Disease Control and Prevention reported that 10% of China's 1.4 million TB patients had MDR-TB, and the great majority of MDR-TB patients had never been treated for TB—evidence of unfettered human-to-human transmission. [6]MDR-TB is also a growing problem in South Africa, where high rates of HIV (human immunodeficiency virus) have exacerbated both the spread and deadliness of MDR-TB, raising the specter of a "perfect storm" of MDR-TB/HIV coinfection. [7]The burden of TB accompanied with the emergence of drug resistance in clinical settings is a well-recognized problem. MDR-TB, defined as TB caused by strains of MTBC that are resistant to at least rifampicin and isoniazid, is public health problem. Patients can be infected with drug resistant TB from index patients of a primary drug resistance or drug susceptible MTBC strains can develop resistance to anti-TB drugs resulting in acquired drug resistance. Acquired drug resistance is observed often among re-treatment cases since these groups are more likely to harbor strains with full or partial drug resistance for drugs used in previous treatment. [8,9] Hence, this study was conducted to study the drug resistance pattern in tuberculosis.

MATERIALS & METHODS

A collection of Mycobacterial strains was gathered from 100 patients who had been diagnosed with smear-positive tuberculosis. These strains were subjected to testing for susceptibility to drugs such as ethambutol, isoniazid, and streptomycin. The study also aimed to identify the factors that could influence the development of drug resistance. The average age of the participants was 55.84 years. The study determined the prevalence of drug resistance, both single-drug and multi-drug, among patients who were newly diagnosed and those who had received treatment in the past. The obtained data were subjected to analysis using SPSS software. Categorical data, specifically the presence or absence of multi-drug-resistant tuberculosis (MDR-TB), were compared using statistical methods like chi-square and Fisher's exact tests. Additionally, multiple logistic regression analysis was conducted to pinpoint the risk factors associated with MDR-TB. The strength of these associations was quantified using odds ratios (OR) with a 95% confidence interval (95% CI), and statistical significance was considered when the two-tailed p-value was less than 0.05.

RESULTS

A total of 100 cases were evaluated. Among them, 86 subjects were older and remaining were the new cases. The smear was taken and examined. The study found a significant association between an initial smear grading of 2+ and 3+ and drug-resistant tuberculosis (p=0.02). However, this same association did not hold importance in the context of multidrug-resistant tuberculosis (MDR-TB) (p=0.7).The multivariate analysis of risk factors related to MDR-TB revealed several significant findings. First, in cases with a history of previous treatment, the occurrence of MDR-TB was considerably higher compared to newly diagnosed cases (p=0.01). Second, there was a higher frequency of MDR-TB among individuals aged under 48 years old (p=0.03). Lastly, MDR-TB was more prevalent in patients who still had a positive smear at the end of the second month of treatment (p=0.02).

Table 1: analysis of association of risk predictors with MDR-TB

Parameter	Non –MDR-TB (No., %)	MDR-TB	P- value
Age			
<48 year	8 (26.7)	5 (16.7)	0.020 (Significant)
>48 year	16 (53.3)	1 (3.3)	
Gender			
Male	9 (30)	5 (16.7)	0.51
Female	9 (30)	7(23.3)	
Cases			
New	20 (66.7)	3 (10)	0.01 (Significant)
Old TB cases	2 (6.7)	5 (16.6)	
Smear result at end of 2nd month			
Positive	1 (3.3)	2 (6.7)	0.021 (Significant)
Negative	22 (73.4)	5 (16.6)	

DISCUSSION

The highest proportion of any drug resistance was observed to isoniazid (51.4 %). This is comparable with the study done in India (52 %) [10] and recent report from study in Addis Ababa (56.1 %).[11] The higher prevalence of isoniazid resistance has also important implications. Isoniazid is the cornerstone drug used throughout the course of non-MDR-TB treatment. It is also the drug of choice for chemoprophylaxis of TB in developing countries for treating latent TB infection. Loss of the effectiveness of this drug compromises both the preventive therapy and treatment of TB disease. Moreover, it is predictor for MDR-TB in the future since MDR-TB often

develops from initial isoniazid mono-resistant strains.[12]The second highest any resistance was against streptomycin (42.9 %). The figure is high when compared with earlier studies in Ethiopia where streptomycin resistance accounted for 21 % [13] and 28 %.[14] However, the result is lower than that of recent study in Addis Ababa (67.3 %).[11] The high any resistance to streptomycin may be due to its early introduction, its common use for treatment of other bacterial infections and inadequate treatment due to poor compliance by patients. [15] Hence, this study was conducted to study the drug resistance pattern in tuberculosis.

In the present study, a total of 100 cases were evaluated. Among them, 86 subjects were older and remaining were the new cases. The smear was taken and examined. The study found a significant association between an initial smear grading of 2+ and 3+ and drug-resistant tuberculosis (p=0.02). However, this same association did not hold importance in the context of multidrug-resistant tuberculosis (MDR-TB) (p=0.7).A study by Farazi A et al, mycobacterial strains were collected from one hundred fifteen diagnosed smear positive patients in the central province of Iran and tested for drug susceptible against ethambutol, rifampicin, isoniazid and streptomycin and the risk factors influencing the development of drug resistance were determined.The mean age of patients was 52.23±19.75 years. The rate of multi-drug resistant tuberculosis (MDR-TB) was 7.8%. Our study revealed that there were significant associations between prior treatment, age < 45 years, positive smear result at the end of the second month and positive smear result at the end of the third month. However, there was no association found between gender, inhabitant, nationality, close contact with TB patient, HIV infection and size of mantoux test.The results show that about 8% of TB cases in Arak are MDR TB. The age under 45 years, previous TB treatment and positive smear at the end of the second and third months of treatment were the main factors in the development of MDR-TB.[16]

In the present study, the multivariate analysis of risk factors related to MDR-TB revealed several significant findings. First, in cases with a history of previous treatment, the occurrence of MDR-TB was considerably higher compared to newly diagnosed cases (p=0.01). Second, there was a higher frequency of MDR-TB among individuals aged under 48 years old (p=0.03). Lastly, MDR-TB was more prevalent in patients who still had a positive smear at the end of the second month of treatment (p=0.02).A study by Gaude GS et al, prospective study was conducted at J. N. Medical College and its associated Hospitals, Belgaum. Between January 2011 and December 2012, 150 sputum samples of suspected pulmonary TB patients based on the history were examined for the AFB culture by Lowenstein-Jensen (LJ) culture technique. A total of two early morning samples were collected for the smear [Ziehl-Neelsen (ZN) staining] and culture methods. It was observed that ZN staining for AFB was positive in 113 patients (75%), while AFB culture by LJ medium yielded growth in 66 cases (44%). Thus, a total of 66 AFB culture-positive samples by LJ medium were subjected for AFB drug-sensitivity testing (DST). DST was done for Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA), Ethambutol (EMB) and Streptomycin (SM) after isolation by using the resistance proportion method.A total of 66 AFB culture-positive specimens, 20 (30.3%) cases were sensitive to all the five drugs while 46 (69.7%) cases showed resistance to one or more drugs. Among these, the resistance to rifampicin was highest (80.4%), while resistance to isoniazid, pyrazinamide, ethambutol and streptomycin were observed to be 60%, 58.7%, 52.1% and 63%, respectively. It was also observed that, resistance to all five drugs was highest (39.18%). MDR isolates were obtained in 52.2% of the cases. Illiteracy, low socio-economic status, previous history of TB and alcoholism were found to have statistically significant association for the development of MDR.The prevalence of drug resistance in the present study was observed to be 69.7%. More than half of the cases were multi-drug resistant. The most common resistant pattern observed in this study was resistance to all the first-line drugs. Therefore, during initiation of new case proper explaining and completion of the treatment is very important to avoid the development of future drug resistance in the society.[17] Liu Q et al, among the 1012 strains tested, 308 (30.4%) strains were resistant to at least one first-line drug; the prevalence of MDR-TB was 88 (8.7%), 5 (0.5%) strains were found to be extensively drug-resistant tuberculosis (XDR-TB). Female gender was a risk factor for MDR-TB (adjusted odds ratio (aOR) 1.763, 95% CI (1.060-2.934). The aged 28–54 years was significantly associated with the risk of MDR-TB with an aOR: 2.224, 95% CI (1.158-4.273) when compared with those 65 years or older. Patients with previous treatment history had a more than 7-fold increased risk of MDR-TB, compared with those never previously treated.The burden of drug resistant TB cases is sizeable, which highlights an urgent need to reinforce control, detection and treatment strategies for drug resistant TB.[18]Drug resistance is a biological phenomenon that has been observed in Mycobacterium tuberculosis since the discovery of the first anti-TB drug, streptomycin. Many patients who were injected with streptomycin were brought from the brink of death and their sputum became temporarily clear of M. tuberculosis. But despite continuing to receive treatment, they soon began to excrete bacilli that were resistant to streptomycin in the laboratory. [19]With the advent of new drugs—thioacetazone and para-aminosalicylic acid in 1948 and isoniazid in 1952—it became clear that combination chemotherapy was the key to preventing the development of resistance. Initial combination regimens required 18 mo of treatment, but the

invention of rifampicin in 1957, the most powerfully sterilizing anti-TB drug, paved the way for development of the shorter and more effective isoniazid- and rifampicin-containing regimens known as short-course chemotherapy. As part of the global TB control strategy called DOTS (directly observed treatment, short-course), these regimens became the standard of care even in resource-limited settings starting in 1993.Outbreaks of MDR-TB were initially thought to be driven by nosocomial transmission, particularly among HIV-positive patients. One of the largest and best-documented outbreaks occurred in New York in the late 1980s and early 1990s. [20,21]High rates of MDR-TB among treatment failures (72.7 %) can be influenced by the acquisition of resistance in the intensive and continuation phases of treatment or the rate of primary MDR-TB infection.[22] However, the rate of MDR-TB among newly diagnosed TB patients in Jimma was low (1.5 %).[23] Therefore, the most possible reason for higher rate of MDR-TB in a study is acquisition of drug resistance during the intensive or/and continuation phases of treatment. This may provide clue for the importance of evaluation of currently available TB control programs on proper usage of the drugs. Moreover, it supports the necessity of looking in to the adherence of patients to full course of chemotherapy.

CONCLUSION

The primary factors contributing to the development of multidrug-resistant tuberculosis (MDR-TB) were individuals under the age of 48, a history of previous TB treatment, and having a positive smear at the end of the second month of treatment.

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