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Determinants of multidrug-resistant tuberculosis in patients attending tertiary care teaching hospital, Vijayapur

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Abstract--Background: Multidrug-Resistant Tuberculosis (MDR-TB) has a more rapid course with poor treatment outcomes. Its treatment requires complex multiple 2nd line drug regimens which are longer, more expensive and more toxic Objectives: to identify factors associated with multidrug-resistant tuberculosis in order to identify high risk population who would develop MDR-TB and to suggest possible measures to be taken to reduce MDR-TB incidences in this region. Methods: A structured questionnaire in the vernacular language was used to collect information from study participants and was interviewed privately, and their names were not written on the questionnaire to ensure confidentiality. Secondary data was collected from MDR-TB register. Quantitative data were expressed as mean and standard deviation; the qualitative data were expressed as percentages and proportions Results: correlation of HIV positivity was observed in 9(15.3 %) patients. 14(23.7%) patients lived with TB patients earlier. Other diseases (including HIV) were present in 20(33.9%) patients. Excluding HIV, 6 had Diabetes Mellitus, 4 were chronic alcoholics and 1 had psychiatric illness. 12(20.3%) had a history of smoking. The previous TB treatment history of patients undergoing retreatment included site of TB infection being pulmonary in 41(69.5%) and only

2(3.4%) had extrapulmonary TB. 27 (62.8%) patients were smear positive during first anti-TB treatment. 4(9.3%) patients were never counselled by health workers. Conclusion: this study identifies Non-adherence to the first line anti-TB treatment which was an important factor responsible for development of MDR-TB. Keynote: strengthening DOTS programs to enhance patient adherence to anti-TB treatment and giving special attention to individuals at high risk for MDR-TB and prioritizing them for DST are recommended.

Keywords--HIV-positive, Multidrug-Resistant Tuberculosis (MDR-TB), Structured Questionnaire, Resistant Strains.

Introduction

Multidrug-Resistant Tuberculosis (MDR-TB) has a more rapid course with poor treatment outcomes. Its treatment requires complex multiple 2nd line drug regimens which are longer, more expensive and more toxic.¹ MDR-TB occurs either when a person is infected with a resistant strain or when improper treatment leads to drug selection of the resistant strain.² Drug-resistant TB is a continuing threat.

TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people. An estimated 10.4 million people fell ill with TB in 2016, 56% were in five countries: India, Indonesia, China, the Philippines and Pakistan.³

MDR-TB is defined as resistance to both Isoniazid (H) and Rifampicin (R), and may be any number of other (1st line) drug(s).¹ When an individual who has no history of first-line TB treatment develops MDR-TB, it is termed primary. When insufficient treatment leads to selection of spontaneously resistant strains (i.e., drug resistance is acquired), the disease is termed secondary MDR-TB.⁴ MDR-TB occurs either when a person is infected with a resistant strain or when improper treatment leads to drug selection of the resistant strain.³ Drug-resistant TB is a continuing threat. In 2016, there were 600 000 new cases with resistance to rifampicin (RRTB), the most effective first-line drug, of which 490 000 had multidrug-resistant TB (MDR-TB). Almost half (47%) of these cases were in India, China and the Russian Federation.¹ An estimated 1.47 lakh incident multi-drug resistant TB patients emerge annually in India which includes 84,000 MDR-TB Patients estimates among notified pulmonary cases.

The occurrence of MDR-TB is mainly attributable to human error, although genetic factors are also believed to contribute to a certain extent.⁵ The principal patient-related factor that predicts the occurrence of MDR-TB is non-adherence to treatment.⁶ Patients infected with MDR strains are less likely to be cured from TB particularly if they are co-infected with HIV or suffer from other immune-suppressive diseases.⁷ MDR-TB is associated with a two to four fold increase period of treatment, psychological problems, economic wastage, poor treatment

adherence and consequently treatment failure. It is also associated with higher case fatality rates (50 – 80%) as a result of drug toxicity.^{8,9}

Category II pulmonary TB includes those patients who had failed previous TB treatment, relapsed after treatment, or defaulted during previous treatment. As such patients have already been exposed to anti-TB agents; they are at high risk for harbouring multidrug-resistant strains. Therefore, it is imperative to know the prevalence of MDR-TB among category II pulmonary TB patients¹⁰ The information on risk factors of MDR-TB is important for prevention and control of the spread of the disease in countries where drug resistance is a major threat. In 2017, 54 new MDR-TB cases are registered in BLDEU's Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur. This study is under taken to identify factors associated with multidrug-resistant tuberculosis attending this tertiary care centre in order to identify high risk population who would develop MDR-TB and to suggest possible measures to be taken to reduce MDR-TB incidences in this region.

Aims and objectives of the study were to identify factors associated with multidrug-resistant tuberculosis in order to identify high risk population who would develop MDR-TB and to suggest possible measures to be taken to reduce MDR-TB incidences in patients attending tertiary care teaching hospital at Vijayapur.

Material and Methods

A Cross sectional observational study was conducted in the department of Pharmacology and with the department of Chest and TB, BLDEU's Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur (Karnataka) after taking Institutional ethical clearance the same institute. Study period was 2 months, from 1st June 2018 to 31st July 2018.

Confirmed MDR-TB patients attending OPD and IPD of Dept of Chest & TB in the said institute were considered for the study. The contact information of study subjects were obtained from the chest & TB clinic patient registration book. Individual who were willing to participate and gave verbal consent after telephonic conversation, were scheduled for an interview at the health facility. A structured questionnaire in the vernacular language was used to collect information from study participants and was interviewed privately, and their names were not written on the questionnaire to ensure confidentiality. Secondary data was collected from MDR-TB register.

The collected data were entered in the Microsoft excel data sheet and descriptive statistics was used for the analysis. Quantitative data were expressed as mean and standard deviation; the qualitative data were expressed as percentages and proportions.

Results

Among 92 registered MDR-TB patients contacted by telephone, only 67 patients gave verbal consent for interview over the phone and 42 of them actually came to

give interview. 17 patients, admitted in the ward for complications were interviewed after obtaining their verbal consent. A total of 59 patients were recruited for the study.

Table 1 describes sociodemographic characteristics of study participants. A total of 44 (74.6%) of the MDR-TB cases were males and 15 (25.4%) were females. Married individuals accounted for the majority 48(81.3%) of the cases and only 3 (5.1%) were widow and 8 (13.6%) were single.

Total of 36 (61%) patients lived in houses having 2-3 rooms and 30 (50.8%) patients had a family comprising of 4-6 members. 20(33.9%) patients were illiterates and 14 (23.7%) underwent primary schooling. As many as 16 (27.1%) patients were daily labourers followed by 14(23.7%) patients who were private workers, 13 (22%) were farmers, 11(18.6%) did not work and 4(6.8%) were students.

Table 2 summarizes TB related conditions in MDR cases. Of the 59 MDR TB cases, 16 (27.1%) were primary cases and 43(72.9%) were secondary MDR TB cases (Table 3). 32(54.2%) patients had 2 episodes of pulmonary TB. 1(1.7%) patient had 5 episodes of pulmonary TB and another had 6 episodes.

HIV positivity was observed in 9(15.3 %) patients. 14(23.7%) patients lived with TB patients earlier. Other diseases (including HIV) were present in 20(33.9%) patients. Excluding HIV, 6 had Diabetes Mellitus, 4 were chronic alcoholics and 1 had psychiatric illness. 12(20.3%) had a history of smoking.

The previous TB treatment history of patients undergoing retreatment included site of TB infection being pulmonary in 41(69.5%) and only 2(3.4%) had extrapulmonary TB. 27 (62.8%) patients were smear positive during first anti -TB treatment. 4(9.3%) patients were never counselled by health workers. Drug side effects were encountered by 24(55.8%) patients among which 14 had complains of vomiting. 16(37.2%) patients were satisfied with the health care services provided by the health workers, 14(32.6%) felt it was good, 8(18.6%) found it very good and 5(11.6%) of them felt it was poor.

Duration of first time anti Tb treatment was 2-4 months in 25(58%) patients, 5-7 months in 12 (28%) patients, 8-10 months in 3 (7%) patients and less than 2 months in 3(7%) patients which was directly observed only 16 (37.2 %) patients out of which 2 (12.5%) patients were observed for only 1-2 weeks and 2 (12.5%) of them were observed for 1 month and 12(75%) of them were observed for 2 or more months.

33 (76.7%) patients interrupted anti TB treatment for a day out of which 29(88%) interrupted because of negligence, 1(3%) because of shortage of drug and 3(9%) because of side effects.

34 (79%) patients did not take medications at regular intervals. 33(76.7%) patients were defaulters and 4(9.3%) cases had a treatment failure. 11 patients took treatment 3 or more times out of which 9 (81.8%) took category II regimen 2nd time.

Discussion

A cross sectional study comprising of 59 MDR TB cases was conducted to identify factors responsible for development of MDR TB in a tertiary care teaching hospital situated in one of the resource poor district of North Karnataka. The factors which may be responsible for development of secondary MDR TB: the first site of infection being pulmonary, patient's negligence towards anti TB treatment and drug side effects leading to treatment defaulters. Smear positivity during first TB episode, the poor quality of healthcare provided, having more than 1 TB episodes, undergoing category II regimen without Drug Sensitivity Testing.

In our study of the 59 MDR TB cases, 16(27.1%) were primary cases and 43(72.9%) were secondary MDR TB cases (Table 3). 32(54.2%) patients had 2 episodes of pulmonary TB. 1 (1.7%) patient had 5 episodes of pulmonary TB and another had 6 episodes. So the history of previous treatment of tuberculosis may be a significant factor associated with MDR-TB cases. This may be related to the previous treatment outcome, default, treatment failure, or relapse, or the patient may have had MDR-TB initially.

An individual who is supervised by a health worker is more likely to take the appropriate dose of medicine and less likely to miss a treatment. Furthermore, individuals who come for DOTS have frequent contact with health workers and thus have increased opportunities to get advice and counseling, which might help them to adhere to medication protocol. Mulu et al also observed the previous history of antituberculosis therapy in 79.1% of MDR-TB patients¹¹ Rifat et al observed 98% patients who had a history of previous TB treatment.¹²

Abdulrahman et al found the history of anti-tuberculosis therapy to be the only risk factor associated with drug resistant Mycobacterium tuberculosis, with an odds ratio of 19.9 ($p < 0.00001$) which is again nearer to our finding.¹³

In our study A total of 44 (74.6%) of the MDR-TB cases were males. Being male could be a risk factor for development of MDR TB. Mor et al found 57.9% males were affected with the development of MDR-TB which supports our finding.¹⁴

In our study, The previous TB treatment history of patients undergoing re treatment included site of TB infection being pulmonary in 41(69.5%) and only 2(3.4%) had extrapulmonary TB. 27(62.8%) patients were smear positive during first anti-TB treatment. Smear-positive pulmonary TB individuals have a high bacterial load and may not respond to the treatment within a short period of time, as do those with a low bacterial load.¹⁵

In our study 33 (76.7%) patients interrupted anti TB treatment for a day out of which 29(88%) interrupted because of negligence. Patient's negligence towards anti TB treatment may lead to treatment defaulters. Evidence from a previous study has shown that poor treatment adherence was a risk factor for MDR-TB.¹⁶

In our study 11 patients took treatment 3 or more times out of which 9 patients (81.8%) took category II regimen 2nd time. More than one explanation may be given for the association of Category II treatment and MDR-TB. These individuals

might have had a previous TB treatment history and registered for the treatment as treatment failures, defaulters, or relapse cases, or they might have already had MDR-TB at the initiation of the Category II regimen. Another explanation is that adding one drug in the failing regimen could change susceptible strains and lead to multidrug resistance. "Michael Iseman, the US based MDR-TB specialist, had 10 commandments for the physicians not to change fully drug susceptible organisms to MDR-TB; the first one was never to add a single drug to a failing regimen and the other nine were to repeat the first commandment to make sure it was well understood."¹⁷

Living in crowded houses with large family size occupied in a less space could be a risk factor in development of primary MDR TB. Illiteracy could probably be a determinant of MDR TB as it could predispose to negligence emerging from unawareness. HIV positivity was observed in 9(15.3 %) patients, other diseases (including HIV) were present in 20(33.9%) patients. Excluding HIV, 6 had Diabetes Mellitus, 4 were chronic alcoholics and 1 had psychiatric illness. Datta et al observed 40.3% patients with MDR-TB having co-morbid illnesses like Diabetes, COPD, HIV/AIDS etc.¹⁷

Conclusion

Our study identifies Non-adherence to the first line anti-TB treatment is an important factor responsible for development of MDR-TB. Having more than one pulmonary TB episode is associated with MDR-TB. Individuals who are treated with the Category II regimen were also found to have an increased risk for MDR-TB. Taking medication without interruption, taking medication regularly, and having supervision (DOTS) have protective effect against MDR-TB. Limitations of our study were that, we could not take a control group to compare and find significant difference. Recall bias could be considered one potential challenge.

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Tables

Table 1
Sociodemographic characteristics of study participants:

Variables	Subgroups	N=59	%
Gender	Male	44	74.6
	Female	15	25.4
Age at 1st anti-TB treatment	5 to 25	15	25.4
	26 – 45	29	49.2
	Above 46	15	25.4
Marital status	Married	48	81.3
	Single	8	13.6
	Widow	3	5.1
Number of rooms in residence	<= 1	5	8.5
	2 to 3	36	61
	4 to 5	17	28.8
	6+	1	1.7
Family Size	<= 3	14	23.8
	4 to 6	30	50.8
	7+	15	25.4
Education Status	Primary	14	23.7
	High School	12	20.3
	College	13	22
	Illiterate	20	33.9
Occupation	Daily labourer	16	27.1
	Farmer	13	22
	Government worker	1	1.7
	No Work	11	18.6
	Private worker	14	23.7
	Student	4	6.8

Table2
TB related conditions in MDR cases

Variables	Subgroups	N=59	%
No. of pulmonary TB episodes	1	16	27.1
	2	32	54.2
	3	6	10.2

	4	3	5.1
	5	1	1.7
	6	1	1.7
HIV Status	Negative	50	84.7
	Positive	9	15.3
Ever lived with TB patient	No	45	76.3
	Yes	14	23.7
Presence of other disease	No	39	66.1
	Yes	20	33.9
Ever smoked cigarettes	No	47	79.7
	Yes	12	20.3
Weight measured by health worker before starting treatment	No	1	1.7
	Yes	58	98.3

Table 3
Secondary MDR-TB cases N=43

Variables	Subgroups	N=59	%
Site of TB infection during 1st episode	Extra pulmonary	2	3.4
	Pulmonary	41	69.5
Smear positive during 1st anti-TB treatment	No	16	37.2
	Yes	27	62.8
Ever cancelled by health worker	No	4	9.3
	Yes	39	90.7
Encountered drug side effect	No	19	44.2
	Yes	24	55.8
Suffered the most common side effect (vomiting)	No	29	67.4
	Yes	14	32.6
Perception about the care provided during previous anti-TB treatment	Good	14	32.6
	Poor	5	11.6
	Satisfactory	16	37.2
	Very good	8	18.6
Duration Of First Time TB Treatment (Months)	2 to 4	25	58
	5 to 7	12	28
	8 to 10	3	7
	Less than two months	3	7
Directly observed by health worker while taking anti-TB treatment	No	27	62.8
	Yes	16	37.2
If Yes, How Many Days N=16	1 to 2 weeks	2	12.5
	1 month	2	12.5
	2 month	12	75
Ever interrupted anti-TB treatment at least a day	No	10	23.3
	Yes	33	76.7

Reason For Interruption For At Least A Day (N=33)	Negligence	29	88
Took medication at regular time	Shortage of drug	1	3
	Side effect	3	9
	No	34	79
	Yes	9	21
Outcome of 1st anti-TB treatment	Defaulted	33	76.7
	Treatment failure	4	9.3
	treatment success	6	14
Drug regimen for second time (N=11)	Category I	2	18.2
	category II	9	81.8

Table 4
Type of MDR TB

Type of MDR TB	No. of patients	Percentage (%)
Primary	16	27.1
Secondary	43	72.9
Total	59	100

Table 5
Previous TB treatment history of patients

Variables	Minimum	Maximum	Mean±SD
Age at 1st anti-TB treatment	16	65	35.89±12.7
Rooms in residence	1	6	2.86 (Median=3)±1.15
Family size	2	21	5.71(Median=5)±3.55)
No. Of pulmonary TB episodes	1	6	1.17±0.72
Duration of first time TB treatment (months)	1	8	3.79±1.94