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PROFILE OF MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS PATIENTS DIAGNOSED DURING TREATMENT ON RETREATMENT REGIMEN

Microbiology

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ABSTRACT

Introduction: Some of the patients on re-treatment regimen of RNTCP for Pulmonary tuberculosis may have multi drug resistant TB (MDR-TB). Patient's profile and previous treatment history may provide hints as to who are most likely to have MDR-TB.

Aims and Objectives: The aim of study was to determine risk factors which might predict possibility of having Multidrug resistance, in the pulmonary Tuberculosis patients before starting them on re-treatment regimen of Revised National Tuberculosis Control Programme (RNTCP).

Material and Methods The study was a prospective case control study conducted for one year from 01st April 2007 at Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, New Delhi. Twenty MDR-TB patients in the case group and forty patients matched by age, sex and subtype of re-treatment regimen were enrolled in the control group. Patient's demographical, clinical, bacteriological, and radiological profile was recorded.

Conclusions Statistically significant risk factors for Multidrug resistance were Prior history of Anti Tuberculosis T/T more than twice, Prior TB treatment for more than 11 months, presence of cavitation, bilateral and far advanced disease on the chest radiograph. Factors like smoking, alcoholism and treatment interruptions were not associated with development of MDR-TB.

KEYWORDS

MDR-TB, retreatment regimen, Cat.II, risk factors

INTRODUCTION

The standardized drug regimens used by RNTCP are highly effective, with low failure rates of around 2% and 6% amongst Category I and II (re-treatment) cases respectively.[1] However, clearly not all such patients have MDR-TB, their previous treatment history, outcome and clinico-radiological profile may provide hints as to who are most likely to have MDR-TB. In the current study an effort has been made to identify significant risk factors which, if present in a patient registered for retreatment regimen (CAT II), can be suspected as having Multidrug resistant Tuberculosis.

MATERIAL AND METHOD

The study was conducted from 1st April 2007 to 31st March 2008 at Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, New Delhi. The LRS-RNTCP area covers a population of around one million. It was a prospective case control study, conducted on all patients who were sputum smear positive after extended intensive phase of retreatment regime (category II) and diagnosed to have MDR pulmonary TB.

The case group consisted of patients who were sputum smear positive at any time after completion of extended intensive phase of retreatment regime (category II)and were found to have bacteriologically confirmed MDR-TB (resistance to both isoniazid and rifampicin). 'Relapse', 'Treatment after Default' and 'Failure' of CAT-I were included in the study whereas, 'Others' were excluded.

The Control group consisted of the randomly selected patients who achieved, smear conversion by the end of intensive phase. Two patients from the control group were matched to one patient from the case group in terms of age, sex and subtype of retreatment regime (category II).

The retreatment regime (category II) consisted of thrice weekly streptomycin (S), rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z) for 2 months followed by RHEZ for another month. If patient still sputum smear positive by 3 months, the intensive phase was extended by one more month. The continuation phase consisted of thrice weekly RHE for 5 months.

Sputum samples of the patients were processed for culture and drug sensitivity testing at National Reference Laboratory of LRS Institute on BACTEC 12B medium. Drug sensitivity testing was carried out for isoniazid, rifampicin, streptomycin and ethambutol using the modified 1% proportional method. After drug sensitivity testing the patients confirmed as having MDR-TB bacilli (resistant to both isoniazid and rifampicin) were included as cases.

After patient's informed consent, their demographical, clinical, bacteriological, radiological profile and detailed history of previous anti tubercular treatment were recorded in a standardized pre-tested form. The patients' adherence to treatment, number of doses missed, results of initial and follow-up sputum examinations were also recorded from the treatment cards.

The chest x-rays were reviewed and classified into two groups on the basis of presence or absence of cavitation and extent of disease weather unilateral or bilateral. The radiological extent of disease was assessed on the basis of the guidelines of the National Tuberculosis Association of the USA.[2]

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 12.0 (SPSS inc., Chicago, IL) and Epi Info version 6.0 software. Mean and standard deviation (SD) for the different variables in the overall group of cases and controls was determined. Comparisons of difference of mean were made with Independent-samples T-test. The data was further analyzed using Chi-square test and Fisher's exact test. Odds ratios (OR) and 95%CI were calculated to measure the association between variables at the univariate and multivariate level. A value of $p<0.05$ was considered statistically significant.

RESULTS AND OBSERVATIONS

Twenty patients in the case group and forty patients matched by age, sex and subtype of retreatment regime in the control group were enrolled. The case population consisted of 12 (60%) males and 8 (40%) females. The control group had 24 (60%) males and 16 (40%) females. The age of the patients in the case group ranged from 19 to 60 years with a mean (SD) of 30.05 10.36 while that of control group ranged from 15 to 56 years with a mean (SD) of 28.53 9.74. Eighty percent cases were in the age group of 15-34 years. Age and sex distribution given in Table-1.

Table-1: Age & Sex Distribution

AGE GROUP	CASES (n = 20)			CONTROLS (n=40)		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
15 - 24	3	4	7	8	8	16
25 - 34	6	3	9	9	5	14
35 - 44	2	-	2	5	1	06
45 - 54	-	1	1	-	2	02
55 – 64	1	-	1	2	-	02
TOTAL	12	8	20	24	16	40

Out of 20 patients of case group, 11 (55%) were Relapse, six (30%) were Treatment After Default and three (15%) patients were CAT-I failure. In 40 patients of control group, 22 (55%) were Relapse, 12 (30%) were Treatment After Default and 6 (15%) patients were CAT-I failure. The difference in type of patients among cases and controls was not studied as they were matched at intake.

Smoking habit was seen in 7 (35 %) patients in the case group and 13 (32.5%) patients in the control group. Alcoholism was seen in 25% of patients each in case and control group. These differences in the personal habits between the two groups was not statistically significant (p>0.05).

Three patients (15 %) in the case group had any co-existent disease. two patients were diabetic on oral hypoglycaemic and one patient was of COPD, on bronchodilators. Among the controls only three patients (7.5 %) had co-existent disease. All of 3 were patients of COPD and on bronchodilators. This difference in the co-morbidities between the two groups was not statistically significant (p>0.05).There was no HIV positive in the case group and only one patient from the control group found to be positive for the Human Immuno-deficiency virus.

Majority of patients had no history of contact with MDR-TB patients. Only one patient (5%) among case group and no patient among controls had history of contact with MDR-TB patient. Hence, this factor could not be analyzed.

Patients in the case group had history of total number of anti tubercular treatments received, ranging from two to six times as compared to ranging from two to three times in control group. Eleven (55%) patients among cases and only four (10%) patients among controls had received treatment more than two times. This difference was found to be highly significant on univariate (p=0.000) as well as multivariate analysis (p<0.05).

Total duration of anti tubercular treatment received, ranged from nine months to 44 months in the case group and from nine months to 26 months in control group. Fifteen (75%) patients among cases and 19 (47.5%) patients among controls had received anti tubercular treatment for a total duration of more than 11 months. This difference was found to be significant on univariate analysis (p<0.05).

Interruption to treatment was seen in 8 (40%) patients in the case group and 18 (45%) patients in the control group (p>0.05).

On radiological examination presence of cavitation was seen in fourteen (70%) patients among the cases group and 13 (32.5%) patients among control group. The remaining six (30%) cases and 27 (67.5%) controls showed no cavity. On univariate analysis this difference between case and controls was found to be statistically significant (p<0.05). The chest x-rays showing the presence of cavity were further classified on the basis of single or multiple cavities. In the cases group, 02 (14.2%) and 12 (85.7%) patients had single and multiple cavities respectively. In the control group, 06 (46.1%) patients had a single cavity and 07 (53.8%) patients had multiple cavities. This observation was not statistically significant (p>0.05). Thus, although presence of cavitating disease was associated with development of MDR-TB among retreatment cases, the number of cavities present did not have an influence on it.

Bilateral disease was seen in Eighteen (90%) patients among the cases group and 24 (60%) patients among control group. The remaining two (10%) cases and 16 (40%) controls showed unilateral disease. On univariate analysis this difference was found to be statistically significant (p<0.05) indicating that bilateral disease on chest X-ray was a risk factor for development of MDR-TB among retreatment cases. Among the 20 patients in the case group, 17 (85%) had far advanced disease and only three patients (15%) had less advanced disease. Among the 40 patients in the control group, 12 (30%) had far advanced disease and 28 (70%) had less advanced disease. This difference in the extent of disease was highly significant (p=0.000). Hence, far advanced disease on chest X-ray is associated with a high risk for development of MDR-TB among retreatment cases. On multivariate analysis only far advanced disease was found to be statistically significant (p<0.05). This univariate and multivariate analysis of the various factors studied is given in Table-2 and Table-3 respectively.

Table-2: Results of univariate analysis of Different parameters

Variables	Cases (n=20)	Controls (n=40)	OR (95% CI)	p value
No. of t/t received =2 >2	9 (45%) 11 (55%)	36 (90%) 4 (10%)	11.0 (2.42, 54.71)	**< 0.001***
Interruption No Yes	12 (60%) 8 (40%)	22 (55%) 18 (45%)	0.81 (0.24, 2.76)	0.926
Total duration of t/t Upto 11 months > 11 months	5 (25%) 15 (75%)	21 (52.5%) 19 (47.5%)	3.32 (0.89, 12.98)	**< 0.05***
Cavity No Yes	6 (30%) 14 (70%)	27 (67.5%) 13 (32.5%)	4.85 (1.33, 18.47)	**< 0.01***
No. of cavity Single Multiple	2/14 (14.2%) 12/14 (85.7%)	6/13 (46.1%) 7/13 (53.8%)	5.14 (0.63, 51.25)	0.164
UL / BL disease Unilateral Bilateral	2 (10%) 18 (90%)	16 (40%) 24 (60%)	6.00 (1.09, 43.28)	**< 0.04***
Extent of disease Less advanced Far advanced	3 (15%) 17 (85%)	28 (70%) 12 (30%)	13.22 (2.84, 70.41)	**< 0.001***

*t/t – treatment, UL – Unilateral, BL – Bilateral,

Table-3: Multivariate analysis using Logistic Regression of Different parameters

Variables	Reference Catogery	Odds Ratio	95% Confidence Interval	P Value
Total No. of ATT received	= 2	6.949	1.540, 31.351	**0.012**
Total duration of ATT received	Up to 11 Months	1.525	0.326, 7.140	0.592
Cavity	No	1.888	0.260, 13.721	0.530
Unilateral / Bilateral disease	Unilateral	0.357	0.023, 5.441	0.459
Extent of disease	Less advanced	9.338	2.123, 41.080	**0.003**

- *ATT – Anti Tubercular Treatment

DISCUSSION

In previous studies younger age has been found to be associated with emergence of multi-drug resistance. [3,4,5,6,7,8,9] In the present study, both cases and controls were in the younger age group which is in accordance with the epidemiological findings that, tuberculosis usually affects people in the age group of 15-45.[10] Further, sixty percent patients were male and forty percent were female amongst, cases which is in accordance with the epidemiological gender trends in most settings.[11] The reason for the higher male prevalence and incidence are poorly understood, and need further research to identify associated risk factors. *Faustini A et al[4] found male sex whereas, Lomtadze n et al[12] and Helen Suzanne Cox et al[13] found female sex to be significantly associated with MDR-TB in previously treated cases.* Because the control group was matched for age and sex with the case group, hence these issues could not be studied as risk factor in our study.

Elizabeth Clara et al[14] found alcoholism and smoking as a significant risk factor for acquired MDR-TB. In another study *A. Moniruzzaman et al[5]* could find only alcoholism but not smoking as a significant risk factor for acquired drug resistance. We found neither smoking nor

alcoholism associated with development of MDR-TB among retreatment cases. This was similar to the studies done by Reuben M. Granich et al[3] and *Faustini A et al*[4] who found no association of alcoholism with MDR-TB.

In a study by *A. Moniruzzaman et al*[5] drug resistance was not influenced by diabetes. In contrast Bashar M et al[15] calculated the relative risk of 8.6 to develop MDR-TB in the diabetic group compared to the control group. We could not calculate the relative risk to develop MDR-TB in the diabetic group because of small sample size.

In a study conducted by *M. A. Espinal*[6] *et al*, having received TB drugs for an overall period of time totalling 6 –11 months or > 12 months was associated with MDR-TB. Similarly in our study total duration of anti tubercular treatment received for more than eleven months was found to be significant as a risk factor for development of multi-drug resistance among retreatment cases.

In our study total no. of anti tubercular treatment received more than two times was significantly associated with development of multidrug resistance among retreatment cases. This observation was similar to that made by Elizabeth Clara et al[14] who found that, the risk of development of acquired multidrug resistance was 4.58 times higher in patients, who had received antitubercular treatment for over two times. In our study the risk of development of acquired multidrug resistance was 6.94 times higher in patients, who had received antitubercular treatment for more than two times.

No significant difference in the treatment adherence between the cases and controls was observed in the study. This is in contrast to reports by by Elizabeth Clara et al[14] and *Oguz Karabay et al*[16] who showed that development of acquired MDR-TB was significantly associated with irregular treatment.

In our study, cavitating disease on chest X-ray was observed to be significantly associated with development of multidrug resistance among retreatment cases. Similarly, in various studies conducted by *Reuben M. Granich et al*[3], Elizabeth Clara et al[14], *Oguz Karabay et al*[16], *Aguiar F. Vieira et al*[17] and *S. K. Sharma et al* [18], cavitating disease on the chest x-ray was significantly associated with development of multidrug resistance among previously treated cases. Further, bilateral and far advanced disease on chest X-ray was observed to be significantly associated with development of multidrug resistance among retreatment cases which is in accordance with the observations made by Elizabeth Clara et al[14]. The risk of development of multidrug resistance was increased 9.33 times if patient had far advanced disease on chest X-ray.

The limitation of our study is small sample size. Large scale multicentre studies with a bigger sample size are required in order to validate these results.

CONCLUSIONS

Patient with significant previous history of Anti Tuberculosis treatment, especially in context of duration and number of treatments and patients with far advanced disease on Chest X-Ray should be considered as suspected case of multi-drug resistant Pulmonary TB. Therefore Culture and drug sensitivity testing of sputum at the beginning of retreatment regimen should be considered in all these suspected MDR-TB patients.

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