ORIGINAL RESEARCH PAPER

Pulmonary Medicine

PREDICTORS OF MULTIDRUG RESISTANCE IN PULMONARY TUBERCULOSIS PATIENTS WHO FAILED ON CATEGORY II DOTS TREATMENT UNDER RNTCP

KEY WORDS: MDR-TB, DOTS Plus, Category II failures, predictors

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ABSTRACT

Introduction-Patients failing on CAT(category) II treatment for Pulmonary tuberculosis may not develop multi drug resistant TB (MDR-TB) in all cases. Their previous treatment history and profile may provide clues as to who are most likely to develop MDR-TB.
Aims and Objectives-The aim of study was to determine risk factors which might predict possibility of development of Multidrug resistance in the sputum positive pulmonary tuberculosis patients who failed on category II treatment under Revised National Tuberculosis Control Programme (RNTCP).
Material and Method-The study was a prospective case control study conducted from 01st April 2007 to 31st March 2008 at Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, New Delhi. Patients were enrolled from the DOTS Centres under the domiciliary areas of the Institute. Twenty MDR-TB patients in the case group and forty patients matched by age, sex and subtype of CAT-II were enrolled in the control group. Patient's demographical, clinical, bacteriological, radiological and haematological profile was recorded as per the protocol.
Result- It was observed that the total number of antitubercular treatment courses more than two, total duration of anti tubercular treatment more than 11 months, presence of cavities, bilateral and far advanced disease on the chest X-ray were statistically significant factors. Factors like high initial sputum grade, treatment interruptions, low education, smoking, alcoholism and low BMI were not associated with development of MDR-TB.
Conclusion- The detailed past history regarding antitubercular treatment courses and radiological findings at the beginning of category II treatment, may provide clues as to who are most likely to develop MDR-TB. However as the number of patients is small, more detailed study is required.

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 cases respectively but the issue of the treatment of these has previously not been well addressed by the RNTCP.[1] However, clearly not all such patients develop MDR-TB, and their previous treatment history and outcome may provide clues as to who are most likely to develop MDR-TB. In the current study an effort has been made to identify significant risk factors which, if present in a patient registered for CAT II treatment, can be considered as a high risk for development of Multidrug resistance to Anti tuberculosis drugs.

MATERIAL AND METHOD

The study was conducted at Lala Ram Sarup Institute of Tuberculosis and Respiratory Diseases, New Delhi. The study area has 11 designated microscopy centres and 15 DOTS centres, covering a population of one million. It was a prospective case control study, conducted on all category II treatment failure MDR pulmonary TB cases diagnosed between 1st April 2007 to 31st March 2008 from the LRS-RNTCP area.

The case group consisted of patients who were sputum smear positive at or after four months of Category II treatment and were found to be bacteriologically confirmed MDR-TB (resistance to both isoniazid and rifampicin). Of the various sub-types in Category II 'Relapse', 'Treatment after Default' and 'Failure' of category I were included in the study whereas, 'Others' were excluded.

The Control group was randomly selected and consisted of the 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 category II.

The Category II treatment 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 failed to convert 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, a standardized pre-tested form was filled out which included their demographical, clinical, bacateriological, radiological and hematological profile. The patients' regularity and adherence during treatment, number of doses missed, results of initial and follow-up sputum examination were assessed from the treatment cards and patient interaction by the researcher. The modified Kuppuswamy scale was used to segregate the patients into their respective socio-economic classes.[2]

The patients were classified as BMI less than 18.5 kg/m^2 ('low BMI') and those with BMI more than 18.5 kg/m^2 ('normal BMI').[3] The chest x-rays were reviewed and classified into two groups on the basis of presence or absence of cavities and unilateral or bilateral disease. The radiological extent of disease was assessed on the basis of the guidelines of the National Tuberculosis Association of the USA.[4]

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 CAT-II in the control group were enrolled. The case population consisted of 12 (60%) males and 8 (40%) females. 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

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. The BMI of the patients in the case group and control group varied from 10.80 to 27.55 kg/m2 (mean 17.05) and 12.32 to 24.24 kg/m2 (mean 18.09) kg/m2 respectively which was not statistically significant. Among cases 14 patients were underweight, 5 were normal weight and only 1 patient was overweight. Among controls 24 patients were underweight, 16 were normal weight and none was overweight.

Education level was low (below High school) in 70% of cases and 80% of controls. The difference in socio-economic status among cases and controls was not statistically significant because maximum no. of cases as well as controls belonged to lower socio-economic class.

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.

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).

No patient was positive for HIV in the case group and only one patient from the control group turned out to be positive for the Human Immuno-deficiency virus.

Non adherence to treatment was seen in 8 (40%) patients in the case group and 18 (45%) patients in the control group. This difference was not 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)	0.000 *
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)	0.042 *
Cavity No Yes	6 (30%) 14 (70%)	27 (67.5%) 13 (32.5%)	4.85 (1.33, 18.47)	0.005 *
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)	0.036 *
Extent of disease Less advanced Far advanced	3 (15%) 17 (85%)	28 (70%) 12 (30%)	13.22 (2.84, 70.41)	0.000 *
Initial sputum grading 1+ / 2+ 3+	8 (40%) 12 (60%)	25 (62.5%) 15 (37.5%)	2.50 (0.73, 8.73)	0.168
Type of patient Relapse TAD Failure	11 (55%) 6 (30%) 3 (15%)	22 (55%) 12 (30%) 6 (15%)	X22 - 0.00	1.000

*t/t – treatment, UL – Unilateral, BL –Bilateral, TAD- Treatment After Default

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

VARIABLES	REFERENCE CATOGERY	ODDS RATIO	95% CONFIDENCE INTERVAL	p Value
Total No. of ATT courses received	= 2	6.160	1.444, 33.175	0.034
Total duration of ATT received	Up to 11 Months	1.452	0.310, 6.796	0.636
Cavity	No	1.633	0.231, 11.536	0.623
Extent of disease	Less advanced	13.241	1.722, 101.846	0.013

*ATT- Anti tubercular treatment

Total number of anti tubercular treatment courses received ranged from two to six in the case group and from two to three in control group. Eleven (55%) patients among cases and only four (10%) patients among controls had received treatment courses 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).

X-rays of all patients were reviewed and it was seen that fourteen (70%) patients among the cases group and 13 (32.5%) patients among control groups showed the presence of cavitating diseases. 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 x-rays which showed the presence of cavity were further classified on the basis of having 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 category II failures, the number of cavities present did not have an influence on it.

Eighteen (90%) patients among the cases group and 24 (60%) patients among control groups showed the presence of bilateral diseases. 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 category II failures. 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. On univariate analysis 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 category II failures. During multivariate analysis unilateral Vs. bilateral disease was excluded as unilateral Vs. bilateral and disease severity both indicate almost same thing and may nullify the result. On multivariate analysis far advanced disease was found to be statistically significant (p<0.05).

Eight (40%) and 25 (62.5%) patients from the case group and control group respectively, had initial sputum grading of 1+ and 2+. Twelve (60%) patients from the case group and 15 (37.5%) patients from the control group had initial sputum grading of 3+. Even though the difference is indicative but initial sputum grading was not a statistically significant (p>0.05) factor.

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.

DISCUSSION

In previous studies younger age has been found to be associated with emergence of multi-drug resistance.5,6,7,8,9,10,11 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 15-45.12 However, because the control group was matched for age with the case group hence this issue could not be studied as risk factor for MDR-TB.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.13 Because the control group was matched for sex with the case group, hence this issue could not be studied as risk factor in our study.

In present study education level was low in 70% (35% illiterate+ 35% primary and middle) of cases and 80% (45% illiterate+ 35% primary and middle) of controls. The difference was not statistically significant. This finding was similar to that of A. Moniruzzaman et al6 who could not find low education level as a significant risk factor for antitubercular drug resistance. In other studies Faustini A et al7 and Elizabeth Clara et al14 also could not find low education level as a significant risk factor for multi-drug resistance in previously treated cases. In contrast Tanrikulu AC et al15 found low education level as an important risk factors for the development of MDR-TB in previously treated cases. In our study the difference in educational status among cases and controls was not statistically significant because maximum number of cases as well as controls belonged to lower socio-economic class, as the institute caters primarily to such patients.

Elizabeth Clara et al14 found alcoholism and smoking as a significant risk factor for acquired MDR-TB. In another study A. Moniruzzaman et al6 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 CAT-II Failures. This was similar to the studies done by Faustini A et al7 and Reuben M. Granich et al9 who found no association of alcoholism with MDR-TB.

In a study conducted by M. A. Espinal et al 5, 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 CAT-II Failures.

In our study total no. of anti tubercular treatment courses received more than two times was significantly associated with development of multidrug resistance among CAT-II Failures. This observation was similar to that made by Elizabeth Clara et al14 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 6.16 times higher in patients, who had received antitubercular treatment courses 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 al14 and Oguz Karabay et al16 who showed that development of acquired MDR-TB was significantly associated with irregular treatment.

Our study also showed that cavitating disease on chest X-ray was observed to be significantly associated with development of multidrug resistance among CAT-II Failures. Similarly, in various studies conducted by S. K. Sharma et al17, Reuben M. Granich et al9, Elizabeth Clara et al14, Oguz Karabay et al16 and Aguiar F. Vieira et al18, 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 CAT-II failures which is in accordance with the observations made by Elizabeth Clara et al14. The risk of development of multidrug resistance was increased 13.24 times if patient had far advanced disease on chest X-ray.

No significant association could be seen between initial bacillary load and multi-drug resistance in CAT-II Failures. This finding was similar to the study conducted by Suheyla Surucuoglu et al19 in which sputum smear positivity was unrelated to the development of resistance.

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.

Conclusion

Present study concludes that the past history regarding antitubercular treatment, should be taken carefully, when starting a patient on category II treatment, especially in context of duration and number of treatments. The X-ray chest of all patients should be advised at the beginning of category II treatment and patients with far advanced disease could be considered as high risk for development of multi-drug resistance and culture and drug sensitivity testing of sputum at the beginning of category II treatment of patients, suspected as high risk for development of multi-drug resistance should be considered.

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