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Research Article

Current pattern of drug resistance in new cases of pulmonary tuberculosis at a tertiary care centre in India

Abhishek Agarwal[1]*, Shiv Sagar Gupta[1], Rajendra Prasad[1], Sudhanshu Kathuria[1], Jaswant Singh Chauhan[1], Amita Jain[2]

[1]Department of Pulmonary Medicine, Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India
[2]Department of Microbiology, King George's Medical University, Lucknow, Uttar Pradesh, India

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***Correspondence:**
Dr. Abhishek Agarwal,
E-mail: drabhishekrd@gmail.com

ABSTRACT

Background: Drug resistant tuberculosis is a major obstacle in the effective control of tuberculosis. Early diagnosis of drug resistance using drug susceptibility testing can help treat the patient effectively. Drug resistance can be monodrug resistance, polydrug resistance or multidrug resistance. The aim of the study was to determine the current pattern of drug resistance in new cases of pulmonary tuberculosis.
Methods: A prospective observational study was carried out from November 2012 to October 2014 in the Department of Pulmonary Medicine, Era's Lucknow Medical College and Hospital, Lucknow. The study consisted of 221 new cases of pulmonary tuberculosis which were sputum smear positive for AFB (Acid fast bacilli). One sputum sample from each patient was sent for culture and Drug Susceptibility Testing (DST) to first line anti-tuberculosis drugs on Lowenstein-Jensen medium. Statistical analysis was done with chi-square test.
Results: A total of 221 new sputum positive cases of pulmonary tuberculosis were diagnosed during the study period, of which 189 were culture positive for Mycobacterium tuberculosis. Drug resistance to first line anti-tuberculosis drugs among new cases of pulmonary tuberculosis was observed in 15.3% cases in our study. Multidrug resistant tuberculosis was observed to be 4.2% in these new cases.
Conclusions: Multidrug resistance seems to be on a rise in the new cases of pulmonary tuberculosis in our country.

Keywords: Pulmonary tuberculosis, New case, Monodrug resistance, Polydrug resistance, Multidrug resistance

INTRODUCTION

The development of resistance of the causative agent Mycobacterium tuberculosis (MTB) to first line anti-tuberculosis drugs is a major obstacle in the effective control of tuberculosis. Early diagnosis of drug resistance using drug susceptibility testing can help treat the patient effectively. A new case of pulmonary tuberculosis is defined as the case of pulmonary tuberculosis with no or less than one month history of anti-tuberculosis treatment.[1] Multidrug resistant tuberculosis (MDR-TB) is defined as resistance to a combination of at least rifampicin and isoniazid.

Various biological factors contribute to the development of drug resistance to first line anti-tuberculosis drugs but the most important ones are poor compliance, improper dosing, improper combination chemotherapy, poor quality drugs and inadequate duration of chemotherapy.[2,3] Resistance to first line anti-tuberculosis drugs in the new cases of pulmonary tuberculosis is due to the infection in these new cases by a resistant strain of bacteria. The determination of drug resistance to first line anti-

tuberculosis drugs in the new cases of pulmonary tuberculosis is important because standardized short course chemotherapy is less useful against the drug resistant tuberculosis[4] and hence these drug resistant cases require second line anti-tuberculosis drugs for the effective treatment of pulmonary tuberculosis. But these second line anti-tuberculosis drugs are costlier and are associated with many side effects. Hence, the initiation of second line anti-tuberculosis drugs should be guided by the Drug Susceptibility Testing (DST) results.[5]

The present study was undertaken at our institute to determine the current pattern of drug resistance of Mycobacterium tuberculosis to first line anti-tuberculosis drugs in new sputum positive pulmonary tuberculosis patients.

METHODS

A prospective study was conducted from November 2012 to October 2014 at the department of Pulmonary Medicine, Era's Lucknow Medical College and Hospital, Lucknow, a tertiary care referral centre. A total of 221 new cases of pulmonary tuberculosis which were sputum smear positive for Acid Fast Bacilli (AFB) were enrolled in the study. The new smear positive cases were differentiated from previously treated cases on the basis of a detailed past history of anti-tuberculosis treatment and radiological examination (chest X-ray). The patients were between the age group of 12-85 years of which 62% (n=137) were males and 38% (n=84) were females. Acid fast bacilli (AFB) smear examination was carried out by direct microscopy using the Ziehl Neelsen (ZN) method. AFB grading was done as shown in Table 1.

Table 1: Acid fast bacilli grading.

Number of bacilli	Grade	Number of fields to be examined
No AFB in 100 oil immersion fields	Negative	100
1-9 AFB/100 oil immersion fields	Scanty	100
10-99 AFB/100 oil immersion fields	1+	100
1-10 AFB/oil immersion field	2+	50
More than 10 AFB/oil immersion field	3+	20

Sputum sample of each patient was also sent for culture (Mycobacterium tuberculosis) and Drug Susceptibility Testing (DST) to first line anti-tuberculosis drugs by 1% proportion method on Lowenstein-Jensen (LJ) medium. The MTB culture was done in the accreditated Intermediate Reference Laboratory at the department of Microbiology, King George's Medical University, Lucknow. The LJ media was inoculated with sputum and was incubated at 37°C. The culture media was examined 72 hours after inoculation for the detection of gross contaminants. The culture media thereafter were examined weekly upto eight weeks for the appearance of the typical colonies of Mycobacterium tuberculosis which were rough, raised and non-pigmented (creamy white) and appeared gradually at least after about two weeks of inoculation. The colony was confirmed by ZN staining. A strain was labelled as drug resistant if growth on a drug containing medium was 1% or more than that on a control medium which was free of any anti-tuberculosis drug. Statistical analysis was done using the chi-square test. Informed consent was obtained from all the subjects. The approval for the study was obtained from the institute's ethical committee.

RESULTS

All the 221 patients enrolled in the study were sputum smear positive for AFB. All the patients were HIV seronegative. The most frequent age group in the present study was 21-40 years (53.4% patients) (Table 2). Sputum smear positivity grade 3+ was seen in 37.6% cases followed by grade 1+ in 33.9% cases, grade 2+ in 26.5% cases and scanty sputum positivity in 2% cases. The trend of AFB smear grades was almost similar in drug resistant and sensitive patients thereby suggesting that the level of AFB smear grading of sputum is not indicative of the drug resistance pattern of MTB. The most common symptom was cough (98.9%), followed by loss of appetite (94.7%), fever (93.7%), weight loss (83.6%), chest pain (36%) and hemoptysis (14.8%). No symptom showed any significant association with the drug resistance pattern of Mycobacterium tuberculosis. History of contact with a pulmonary tuberculosis patient was significantly higher ($p<0.001$) in resistant cases (n=17, 58.6%) as compared to sensitive cases (n=2, 1.3%). Majority of the newly diagnosed pulmonary tuberculosis patients included in the study were smokers (n=109, 57.7%) although no significant association was seen between the smoking history and the drug resistance pattern of MTB. Majority of the newly diagnosed pulmonary tuberculosis patients had non-cavitary lesions (n=146, 77.2%). The proportion of patients with cavitary lesions was higher in resistant cases (37.9%) as compared to the sensitive cases (20%) and this difference was statistically significant (Table 3).

Of the 221 patients, a total of 189 (85.5%) patients were culture positive for MTB (Table 4). Of these 189 patients, 160 (84.7%) were sensitive to all four first line anti-tuberculosis drugs while remaining 29 (15.3%) were resistant to at least one first line anti-tuberculosis drug. Among the 15.3% resistant cases, monodrug resistance was seen in 5.8%, polydrug resistance was seen in 5.3% and multidrug resistance (MDR) was seen in 4.2% cases (Table 5). Highest resistance was observed against isoniazid (13.2%) followed by ethambutol (6.3%), streptomycin (4.8%) and rifampicin (4.2%) either alone or in combination with other drugs.

Table 2: Characteristics of new cases of pulmonary tuberculosis with positive culture (MTB) included in the study (n=189).

Variable	No. of cases	Percentage
Age group (years)		
≤20	30	15.9
21-40	101	53.4
41-60	49	25.9
61 and above	9	4.8
Gender		
Males	122	64.5
Females	67	35.5
History of contact with a pulmonary TB patient		
Yes	16	8.5
No	173	91.5
Smokers		
Yes	109	57.7
No	80	42.3

Table 3: Nature of lesion on chest X-ray and its correlation with the drug resistance in the study population (n=189).

Nature of lesion	Total (n=189)		Resistant (n=29)		Sensitive (n=160)	
	No.	%	No.	%	No.	%
Cavitary	43	22.8	11	37.9	32	20.0
Non-cavitary	146	77.2	18	62.1	128	80.0

Table 4: Results of culture for Mycobacterium tuberculosis in new cases of pulmonary tuberculosis included in the study (n=221).

Outcome	No. of cases	Percentage (%)
Growth of MTB present	189	85.5
Contamination	2	0.9
No growth of M. tuberculosis	30	13.6

Table 5: Resistance pattern of *Mycobacterium tuberculosis* to four first line anti-tuberculosis drugs.

Drug resistance	No. of cases	%
Any resistance to-		
Isoniazid	25	13.2
Rifampicin	8	4.2
Ethambutol	12	6.3
Streptomycin	9	4.8
Mono-drug resistance	**11**	**5.8**
Isoniazid	7	3.6
Rifampicin	0	0
Ethambutol	2	1.1
Streptomycin	2	1.1
Poly-drug resistance other than MDR	**10**	**5.3**
Isoniazid + Ethambutol	5	2.6
Isoniazid + Streptomycin	3	1.6
Isoniazid + Ethambutol + Streptomycin	2	1.1
Multi-drug resistant	**8**	**4.2**
Isoniazid + Rifampicin	4	2.1
Isoniazid + Rifampicin + Ethambutol	2	1.1
Isoniazid + Rifampicin + Streptomycin	1	0.5
Isoniazid + Rifampicin + Ethambutol + Streptomycin	1	0.5

DISCUSSION

In the South East Asia region, a total of 90,000 MDR-TB cases were estimated to be present in 2012 which accounted for about 30% of the world's MDR-TB cases.[6] The new smear positive TB cases are mostly seen in the age group of (25-34) years in the South East Asia region with a male to female ratio of 2:1. In our study also, 53.4% cases were seen in the age group of (21-40) years with a male to female ratio of 1.8:1. Sharma *et al.*[7] also reported the mean age of the patients to be (27.8 ± 10.2) years with 73% of patients being males.

In the present study, the sputum of 221 cases was smear positive for AFB of which 189 cases (85.5%) were culture positive for MTB. The rate of culture positivity among sputum positive patients in the present study is close to that observed by Sharma *et al.*[7] Out of 189 culture positive cases for MTB, a total of 29 cases (15.3%) were found to be resistant to at least one first line anti-tuberculosis drug which is almost similar to that observed by Sharma *et al* (13%)[7], Rai *et al*. (16%)[8] and Santha *et al.* (15%)[9]. In our study, the overall drug resistance (i.e. drug resistance either alone or in combination with other drugs) was highest for isoniazid (13.2%) followed by ethambutol (6.3%) and streptomycin (4.8%). Monodrug resistance was also maximum for isoniazid (3.6%) followed by resistance to ethambutol (1.1%) and streptomycin (1.1%). The monodrug resistance pattern in our study for isoniazid, ethambutol and streptomycin is slightly higher than that reported by Sharma *et al.*[7] Monodrug resistance to rifampicin was 0% in our study which is similar to the earlier studies by Sharma *et al.*[7] and Pereira *et al.*[10] Thus the monodrug resistance to rifampicin seems to be less common in comparison to the monodrug resistance to other first line anti-tuberculosis drugs.

The polydrug resistance pattern in our study revealed a resistance of 2.6% for the combination of isoniazid + ethambutol and 1.6% for the combination of isoniazid + streptomycin. However, the resistance to isoniazid + ethambutol + streptomycin was 1.1% and the resistance to isoniazid + rifampicin + ethambutol + streptomycin was 0.5% in our study. This shows that polydrug resistance is also prevalent in our population.

Globally, in 2013, the prevalence of MDR-TB in new cases of pulmonary tuberculosis was estimated to be about 3.5%. The prevalence of MDR-TB in these new

cases of pulmonary tuberculosis has been found to be as high as 35% in countries like Belarus and as low as 1.4% in countries like Bangladesh.[11] In India, the prevalence of MDR-TB in the new cases of pulmonary tuberculosis was estimated to be about 2.2% in 2012.[12] In our study, the prevalence of MDR-TB in the new cases of pulmonary tuberculosis is found to be 4.2%, which is higher than the national data[12] and that reported by Sharma *et al*.,[7] Rai *et al*.,[8] Santha *et al*.[9] and Pereira *et al*.[10]

Limitations of the study

There might have been a selection bias because new cases of pulmonary tuberculosis were selected on the basis of past history of anti-tuberculosis treatment as given by the patient. Hence, radiological examination of the patient (chest X-ray) was also used to aid the identification of new cases of pulmonary tuberculosis and thus minimize the selection bias.

CONCLUSIONS

Thus drug resistance should be suspected even in new cases of pulmonary tuberculosis which are not responding to standard anti-tuberculosis treatment. Moreover, multidrug resistance seems to be on a rise in the new cases of pulmonary tuberculosis in our country.

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