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Pulmonary Medicine

PREVALENCE OF RIFAMPICIN RESISTANCE BY CBNAAT IN HIV SERO-POSITIVE PATIENTS CO-INFECTED WITH PULMONARY TUBERCULOSIS, ATTENDING TERTIARY CARE CENTRE OF SOUTHERN PART OF RAJASTHAN, UDAIPUR.

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ABSTRACT HIV and MDR-TB have emerged as threats to TB control. The association between MDR-TB and HIV infection has not yet been fully investigated however chance of developing tuberculosis disease is 10-15 times higher than non HIV.

Aim: - to know prevalence of MDR-TB in HIV TB co-infected patients.

Methods:- HIV positive patients with chest symptoms attended dept. of Pulmonary medicine and Internal Medicine were included. After detail history and examination, chest X-ray and routine investigations were ordered. Sputum were also sent for AFB and CBNAAT.

Results: - Out of 58 new PTB case, CBNAAT detect MTB in 35 patients, in which, 34 patients were 'R' sensitive, whereas, 1 patient was 'R' resistance. The prevalence of 'R' resistance in newly treated patient was 2.85% (1/35). Out of 22 previously treated patients, CBNAAT detect MTB in 16 patients, of which 13 were 'R' sensitive whereas 3 were 'R' resistance. Prevalence of 'R' resistance in previously treated patients was 18.75 (3/16). Overall prevalence of 'R' resistance in newly treated and previously treated patients was 7.84% (4/51).

KEYWORDS : cartridge based nucleic acid amplification test (CBNAAT), pulmonary tuberculosis (PTB), rifampicin resistance ('R' resistance).

INTRODUCTION

In 2015, an estimated 1.1 million (12%) of the 10.4 million people who developed TB worldwide were HIV-positive.[1] TB is the leading cause of death among people living with HIV, accounting for 25 % of HIV-related death. Person co-infected with TB and HIV is more likely to develop active TB disease than persons without HIV infection.[2] In recent years, the prevention, diagnosis and treatment of TB has become more complicated because of two factors changing the epidemics; HIV-associated TB and multidrug - resistant (MDR) TB.[3] Sputum smear microscopy remains the most common way to diagnose pulmonary TB, can accurately detect TB in 20% to 80% of TB case.[4] Sputum smear microscopy has significant limitations because it can only be used to diagnose TB when sputum has sufficient bacillary load, and it cannot detect drug resistance. Thus, HIV-associated TB often goes undetected because people living with HIV (PLHIV), especially those with severe immune-suppression generally have very low number of bacilli due to paucity of pulmonary inflammation and decreased cavitation.[5] A more sensitive approach to diagnosis of TB is culture, which includes testing for drug resistance also. However, such techniques require expensive and sophisticated laboratory infrast ructure and skilled staff.[3] Even where accessible; culture results are typically not available before [2-6]weeks. Realistically, most people who need culture tests to diagnose TB will not have access to the test results in time to save their lives or to prevent transmission to others. Thus, for rapid identification, which is essential for the earlier initiation of treatment and improved outcomes, more effective public health interventions and newer methods of detection are required.[6], [22] With the advent of new molecular diagnostics, a rapid and sensitive test to diagnose TB, including HIV associated TB and MDR-TB, is within reach. The X-pert MTB/RIF assay from Cepheid, Inc. is a molecular-based rapid test with potential to revolutionize TB diagnosis. In December 2010, the World Health organization (WHO) endorsed gene X-pert for the rapid and accurate detection of TB, particularly among PLHIV and people suspected of having MDR-TB.[7] (23 Results from 12 single centre evaluation studies with varying design and study population and reviewed by WHO reported the sensitivity in detecting TB from 70%-100% in culture positive patients and around 60% in those with smear negative disease and specificity ranging from 91%-100% and average 'Rifampicin' sensitivity and specificity around 98% and 99%.[8]

AIM

To find out the prevalence of 'Rifampicin' resistance in HIV-TB co-infected patients attending department of Respiratory medicine and Internal Medicine, R.N.T. Medical College, Udaipur.

MATERIALAND METHOD

This was a prospective study and was conducted in attached hospitals of R.N.T. Medical College, Udaipur (Raj.). 80 HIV-TB co-infected patients who were attended in the department of pulmonary medicine and internal medicine were included in this study. An informed and written consent was taken from all patients prior to study. HIV positive patients who attended and referred from ART center in these department were the study population. Their demographic profile, socio-economic status, anthropometric data and past history of tuberculosis was recorded. There clinical history, physical exami nation as well as systemic examination was carefully assessed and documented. All study subjects were subjected to digital chest radiograph for better interpretation. Radiological extend of disease was classified as minimal, moderately advanced and far advanced, according to National TB association of USA (1961). Early morning and spot, sputum samples were send in broad mouth container for AFB examination under RNTCP. Sputum was induced by nebulization with hypertonic saline (3-5%) in patients who had less expectoration or unable to expectorate out. Early morning, deep coughed sputum specimen in falcon tube were also sent for CBNAAT test. Reports were collected electronically or manually on same day. The entire patient's data were collected and entered in performed proforma for final analysis. **Exclusion criteria:** Active hemoptysis, unstable angina or arrhythmias, fractured rib or other chest trauma, moribund patients and severely ill patients, patients with extra-pulmonary tuberculosis without chest symptoms.

RESULTS

In this present study there were 57 (71.25%) male and 23 (28.75%) female. Male to female ratio was 2.47:1. Mean age for male was 37.56±9.86 years whereas mean age for female was 35.87±7.93 years (overall mean age 37.07±9.33). 90% patients were from rural area and 10% patients were from urban area, 47 (58.75%) patients were literate and 33 (41.25%) were illiterate, 58 (72.5%) patients were newly treated whereas 22 (27.5%) has past history of ATT and 75 (93.75%) patients had BMI<18.5kg/m^2. Cough was the commonest respiratory symptom followed by expectoration and dyspnea in 95%, 81.25% and 48.75% patients respectively. (Table-1) On radiological examination, 72 patients had parenchymal lesion. Out of these, bilateral disease was seen in 42 (52.50%) patients and unilateral disease seen in 30(37.5%) patients. Among 8 patients in which no parenchymal lesion was seen, three patients had pleural effusion, one patient had bilateral hilar enlargement and 4 patients had normal chest x-ray but had chest symptoms. Infiltration was the most frequent radiological finding and was present in 37 (46.25%) study subjects. Only 8 (10%) patients had cavitary disease. In chest x-ray, 28 (38.38.89%), 30 (41.67%) and 14 (19.44%) patients were identified as minimal disease, moderately advanced and far advanced respectively. (Table-2) Three patients with moderately advanced disease were diagnosed as 'Rifampicin' resistance and one patient with minimal disease was 'Rifampicin'

resistance by CBNAAT. In this study, 58 patients were newly treated and 22 patients were previously treated. Out of 58 newly treated patients CBNAAT was able to detect MTB in 35 patients, in which, 34 patients were 'Rifampicin' sensitive, whereas, 1 patient was 'Rifampicin' resistance. The prevalence of 'Rifampicin' resistance in newly treated patient was 2.85% (1/35). CBNAAT was not able to detect MTB in 2 patients, though they were positive by sputum microscopy, suggestive of atypical mycobacterium infection. Out of 22 previously treated patients, CBNAAT detect MTB in 16 patients, of which 13 were 'Rifampicin' sensitive whereas 3 were 'Rifampicin' resistance. Prevalence of 'Rifampicin' resistance in previously treated patients was 18.75 (3/16). Overall prevalence of 'Rifampicin' resistance in newly treated and previously treated patients was 7.84% (4/51). (Table-3)

DISCUSSION

Globally, an estimated 3.3% (95% CI: 2.2–4.4%) of new cases and 20% (95%CI: 14–27%) of previously treated cases have MDR-TB. From India, though drug resistance in TB has frequently been reported, most of the available information is localized, sketchy or incomplete and most studies have used non-standardized methodologies to assess drug resistance.[9] A large scale population based in the states of Gujarat and Maharashtra has indicated multidrug resistance level of <3% among new TB cases and 12-18% among previously treated TB patients.[10] The dual burden of HIV and TB/ DRTB in India is significantly high with a combined rate of 5.2% ranging from 0.4% to 28.8% in various studies, with increasing trends noted in states having a higher burden of HIV infection.[11-13] In this study male were 2.5 time more frequently involved than female. Same male predominance was also reported by Purohit S.D. et al,[14] Pratima Gupta et al[15]., Praveen Kumar et al,[16] et al., Deshwal et al,[17] Anand K Patel et al and Deswal. The male preponderance might have been due to the fact that in the existing social milieu, females do not seek medical care fearing ostracism, gender bias, and social stigma of TB and neglected attached with the disease which decreases the number of females attending to the chest hospital. So the low number of the females may not be the true representative of the community with HIV-TB co-infection. In this study, number of the patients with HIV-TB co-infection were belongs to rural area than the urban area which is similar to Pratima Gupta et al,15 but contradicted to Jaiswal Rishi K et al,[18] in which they reported that the number of study subjects belongs to urban areas than rural and slums. The rural preponderance of HIV-TB patients is believed to be an indication of spread of HIV-TB infection from the urban to the vast rural areas. This type of distribution in the present study might be due to the diagnostic facility for both HIV &TB made available at PHI level under "Mukhya Mantri Nishulk Janch Yojna" and RNTCP. Diagnosis of HIV-TB in rural areas also might be due to the HIV-TB collaborative activities in which each HIV confirmed patient with chest symptoms should be tested for TB and all TB patients should be tested for HIV as well. In our study and study done by Jaiswal Rishi et al,[18] and S K Jain et al,[19] reported that TB-HIV co-infection amongst the study cases were significantly associated with the literacy status. People with low health literacy may have access to health information but they often fail to use the information properly. In a series by S.D. Purohit (1996) et al,[14] Praveen Kumar (2002) et al,[16] Thanasekaran (1994) et al,20 Bharat Bhushan (2013) et al,[21] and Deivanayagam (2001) et al,[22] cough was the frequent complaint in HIV-TB patients whereas Pratima Gupta et al,[15] Bhagyawati devi et al,[23] and Zuber et al,[24] they reported fever as common symptom. HIV positive people with Pulmonary TB may have the classic symptoms of TB, but many people with both TB and HIV infection have symptoms of TB or even less specific ones. Cough, expectoration, dyspnoea, chest pain and hemoptysis were the respiratory symptoms in HIV-TB co-infected patients, although the percentages were different in the above mention studies. The respiratory symptoms in HIV-TB co-infected patients depends on, to which extent lung parenchyma had involved, extra-pulmonary involvement, type of the lesion in Chest X-ray, immune-compromised status and involvement of tracheo-bronchial tree. As our aim was to find out 'Rifampicin' resistance in pulmonary tuberculosis patients co-infected with HIV, so we focused more on chest symptomatic PLHIV patients. This could be the reason for cough and expectoration as a common presenting symptom. Secondly, this institute is famous as a TB sanatorium, so PLHIV patients who were chest symptomatic and suspected to be a case of tuberculosis were selectively referred. In our study we found bilateral disease in more than half of patients. Mahesh Padayana et al,[25] Anand Patel et al,[26] found bilateral disease more frequently whereas Mehrdad et al,[27] and Maniar et al,[28] found unilateral disease more frequently. Radiological manifestations of PTB depend on immune status of the individuals. In this study 41.67% had moderate disease, 38.89% had minimal disease and 19.44% had advanced disease which is similar to Assefa Getachew et al,[29] Nodular infiltration was the common radiological finding in this present study. Exudative nodular tuberculous lesion with or without hilar mediastinal glandular involvement was seen by Deivanayagam (2001) et al.10 Pulmonary infiltrate were also common in study by Purohit S D (1996) et al,[14] and seen in 7 study subjects. The prevalence of 'Rifampicin' resistance was 2.85% (1/35) and 18.75% (3/16) respectively. Overall prevalence was 7.84% (4/51). Prevalence of rifampicin resistance in our study was almost similar to study by Neeraj Raizada et al,[30] they found rifampicin resistance in 73 out of 770 patients (9.48%) but lower than reported by Sunil Sethi et al,[31] from north India (27.3%). Joydeep Ganguly (2015) et al[32] from Eastern part of India found Rifampicin resistance in 29.87% (96/328) patients using molecular diagnostic method (Gene- X pert) and HIV sero-positivity was in 3.06% patients. Deepak Arora (2015) et al,[33] from Punjab, studied 733 MTB positive patients. Out of these, 19 were HIV TB co-infected, among 19 co-infected patients, 3(15.78%) were 'R' Resistant. Dewan R (2015) et al, [34] found Rifampicin resistance by CBNAAT in 10 HIV-TB co-infected patients and the prevalence was 25% (10/40). Dagnra A. Y. (2015) et al,[35] found Rifampicin resistance in 2 HIV TB co-infected patients, out of 10 patients in whom Gene X-pert was performed. So the prevalence was 20 % (2/10) and both patients were retreatment cases. Cartridge based nucleic acid amplification testing is a new operational system recommended by WHO, so there were only a few studies available in literature to find out prevalence of Rifampicin resistance by using this technology. Various authors from different part of World have different experience on drug resistant TB in HIV using different culture methods.

CONCLUSION

CBNAAT is new diagnostic tool gaining popularity for the diagnosis of pulmonary as well as extra-pulmonary tuberculosis. WHO recommended use of this test in non HIV and HIV infected patients. In HIV co-infected patients it is also recommended in new pulmonary tuberculosis cases. CBNAAT detects pulmonary TB in PLHIV with greater efficacy than sputum microscopy, also helping in early diagnosis in 2 hours. It also detects rifampicin resistance with high specificity and can be used for screening for MDR-TB so that early therapy can be started, thus decreasing the incidence of MDR-TB.

Table-1. Characteristic of the study subjects

Characteristics	Number (%)
Male	57 (71.25%)
Female	23 (28.70%)
Male to female ratio	2.47: 1
Mean age male	37.56±9.86
Mean age female	35.87±7.93
Rural	72 (90%)
Urban	8 (10%)
Literate	47 (58.75%)
Illiterate	33 (41.25%)
History of ATT	
Yes	22 (27.5%)
No	58 (72.5%)
BMI (kg/m^2)	
< 18.5	75 (93.75%)
> 18.5	5 (6.25%)
Radiological extension of disease (n=72)	
Minimal	28 (38.89%)
Moderately advanced	30 (41.67%)
Far advanced	14 (19.44%)

Table-2. Distribution of study population according to sputum microscopy and CBNAAT result

Sputum microscopy result	MTB detected by CBNAAT			MTB not detected by CBNAAT	Total
	'R' Sensitive	'R' Resistant	Total		
Sputum positive (n=38)	33	3	36	2	38
Sputum negative (n=42)	14	1	15	27	42
Total	47	4	51	29	80

Table-3. Distribution of study population according to CB-NAAT results and history of anti-tuberculosis drugs

H/o ATT	MTB detected by CBNAAT			MTB not detected by CBNAAT	Total
	'R' Sensitive	'R' Resistant	Total		
Newly treated (n=58)	34	1	35	23	58
Previously treated (n=22)	13	3	16	6	22
Total	47	4	51	29	80

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