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Research Article

Prevalence of Extrapulmonary Tuberculosis in Newly Registered HIV Patients

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A B S T R A C T

Introduction: Human Immunodeficiency Virus infection and Tuberculosis are among the ten leading causes of death worldwide. In advanced AIDS, M. tuberculosis frequently causes disseminated Extra-Pulmonary Tuberculosis (EPTB). EPTB being paucibacillary infection poses a diagnostic challenge. The emergence of Cartridge Based Nucleic Acid Amplification Test (CBNAAT) has marked an important development in the field of rapid molecular diagnostics of tuberculosis.

Aims and Objective: The purpose of this study was to determine the prevalence of EPTB in newly registered HIV patients visiting ART clinic and to find the prevalence of Rifampicin resistance using CBNAAT.

Materials and Method: 213 newly registered HIV patients were included in the study recruited over 10 months time period and followed up for six months from recruitment. Case record of each patient with detailed history, clinical examination and necessary blood, radiological and specimen sampling done to investigate for tuberculosis was maintained. The data obtained were analyzed using SPSS 20.0 software.

Result: The prevalence of EPTB in newly registered HIV patients was found to be 14.5%, with abdomen being the most common site for EPTB. Rifampicin resistance was seen in 3.2% cases.

Conclusion: The result of this study showed that the prevalence of EPTB was higher compared to PTB in HIV patients. CBNAAT sensitivity for different samples were variable. This study showed maximum sensitivity of CBNAAT for lymph node aspirate (100%) and minimum for CSF (0%). Overall the sensitivity of CBNAAT was low, yet it is a very useful investigation for detection of EPTB with high positive predictive value.

Keywords: Extra Pulmonary Tuberculosis (EPTB), HIV, CBNAAT, Rifampicin Sensitivity

Introduction

Tuberculosis is one of the most common opportunistic infection in patients living with HIV (PLHIV).[1] In advanced AIDS, M. tuberculosis frequently causes disseminated extra-pulmonary disease and mycobacteraemia. EPTB is an AIDS defining criteria since 1987.[2] The burden of EPTB is high ranging from 15-20% of all TB cases in HIV negative patients, while in HIV-positive population it accounts for 40-50% of new TB cases.[3]

EPTB being a paucibacillary infection, its diagnosis remains challenging. Emergence of Cartridge Based Nucleic Acid Amplification Test (CBNAAT) has marked an important development in the field of molecular diagnostics of Tuberculosis. It is an automated, closed system, performing real time PCR which requires only minimal technical expertise and enables diagnosis of TB with additional information on Rifampicin sensitivity within a span of 2 hours.[4]

Prioritization of this test in all HIV patients suspected of TB has been a latest initiative taken collectively by WHO, NACO and RNTCP to tackle the dual burden.[2] In India as well as other countries, there is lack of studies which can tell us the exact prevalence of EPTB in HIV patients. It is because of non availability of uniform diagnostic criteria till recently when WHO & ICMR released first EPTB diagnostic guidelines in 2016.[5] The current study was undertaken to determine the prevalence of EPTB in newly registered HIV patients visiting ART clinic and to find out the prevalence of Rifampicin resistance using CBNAAT.

Materials and Method

This cross-sectional study was conducted after clearance from institutional ethics committee and written and obtaining written informed consent from the patients. The study was undertaken in the Department of Medicine, ART Clinic, DOTS-PLUS centre at GTB Hospital &UCMS, Delhi. Subjects were recruited from ART Clinic of the hospital during the period November 2017 to April 2019. The sample size was 213, calculated based on previous 3 months records of GTB hospital where occurrence of prevalence of EPTB in newly registered HIV patients was found to be 7%. All newly registered HIV patients above 18 years were recruited with no exclusion criteria. Non-random Convenience sampling technique was used. The newly registered HIV seropositive patients were recruited in first 10 months of the study period, examined, investigated and followed up for 6 months from the time of recruitment on monthly basis. Each patient was clinically assessed by history taking and physical examination. Necessary blood and radiological investigations were done. Specimen sampling from the suspected sites were done wherever possible and subjected to CBNAAT testing as per new guidelines of NACO and RNTCP in addition to other necessary investigations of the specimen like cytology, histopathology and culture required to confirm the diagnosis of EPTB. A pretested and prevalidated case record form was used to collect the details. Finally, diagnosis of EPTB was made based on clinical, microbiological and/ or radiological evidences.

Statistical analysis was done after data entry in MS Excel. The data were analysed using SPSS 20.0 software. Categorical variables such as sites of EPTB, Rifampicin resistance, stages of HIV etc were presented in the form of percentage and continuous variables such as monthly family income, age, CD4 counts, etc were presented in the form of mean and standard deviation. Association between various categorical variables were analyzed using Chi-square test. Means were compared using the independent t-test. P-value of less than 0.05 was considered as significant.

Result

In the present study comprising 213 newly registered HIV patients, the mean age was 32.8years. 136 of them were male patients, 75 were females and 2 transgenders. The proportion of males having TB and EPTB was higher and statistically significant.

The prevalence of TB was found to be 22.5% and that of EPTB was 14.5%. Pulmonary Tuberculosis was seen in 17 cases of newly registered HIV patients. The prevalence of which was found to be 8% (17/213). The most common site of EPTB in our study was found to be abdomen constituting 54% (17/31) of the total EPTB cases, followed by pleural in 19.3% (6/31) (Table 1).

CBNAAT testing was done in 21 out of 31 EPTB cases. It could not be done in 9 abdominal tuberculosis and spinal tuberculosis cases. CBNAAT was positive in 9 (42.8 %) out of 21 cases. Rifampicin sensitivity was seen in 8 (88.9%) out of 9 cases. Prevalence of Rifampicin resistance in EPTB was found to be 3.2% (1/31). Sensitivity of CBNAAT for EPTB, considering clinical and radiological reference standard was found to be 42.8% (9/21) (Table 2).

Table 1.Sites of Extrapulmonary Tuberculosis cases in newly registered HIV patients (N=31)

Site of EPTB	Number (%)
Abdomen	17 (54.0)
Pleural	6 (19.3)
Lymph nodes	5 (16.0)
Central Nervous System	2 (6.4)
Spine	1 (3.2)

Our study showed a statistically significant association of Sex, hemoglobin, ESR and CD4 counts in EPTB patients. The mean hemoglobin level in EPTB patients was 11.3 mg/dl

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and in Non-EPTB patients it was 12.35 (± 2.09) mg/dl. The mean ESR in EPTB patients was 48 (±25.15) mm/hr and that in Non-EPTB patients was 30 (±19.89) mm/hr. The mean CD4 counts in EPTB patients was 183 (±118.08) cells/mm3 and in Non-EPTB patients it was 395 (±255.68) cells/mm3.

Table 2.Status of CBNAAT results with respect to the sites of TB pathology among EPTB cases (n=21)

Site	CBNAAT positive (n=9)		CBNAAT negative (n=12)
	Rifampicin sensitive (n=8)	Rifampicin resistant (n=1)	
Abdomen (n=8)	1	1	6
Pleural (n=6)	2	0	4
Lymph node (n=5)	5	0	0
Central Nervous System (n=2)	0	0	2

There was no significant association of age, income, platelet counts, HCV/ HBV co-infection in EPTB patients.

Discussion

HIV co-infection is one of the greatest risk factor for developing TB with 20-30 fold increased relative risk of developing TB disease from latent state compared with that in people without HIV.[6] In our study, 213 newly registered HIV patients attending the ART clinic at GTB Hospital were enrolled. The mean age was 32.8 yrs, with a range from 18 to 85 years. Out of 213 patients, 136 (64%) were male, 34 (15%) were female and 2 (1%) were transgender. In our study, the prevalence of EPTB was found to be higher in males and abdomen was found to be the commonest site of EPTB both in males and females. In a retrospective, record-based study of patients with the diagnosis of EPTB done by S Rama Prakasha et al., a total of 1267 cases in all age groups registered for treatment of all forms of tuberculosis of which 528 (41.67%) had EPTB.[7] Males (272, 51.52%) showed a bit greater number of cases than females (256, 48.48%). Lymph node TB and pleural TB cases were 28.25% (N=76) and 26.77% (N=72) in the age group of 15-44 years. The most common type of TB was pleural TB in the age group of 45-64 years and in the age group of > 65 years. The difference among male and female cases of EPTB by site was statistically significant in this study. In this study, the HIV status of patients studied was not taken into consideration.

A systematic review and meta-analysis of EPTB in PLHIV in sub-Saharan African population, done by Mohammed H, et al. included 31 studies with 28,659 HIV/AIDS patients, published from 1990 to 2017.[8] There was high and diverse prevalence of EPTB among PLHIV in Sub-Saharan Africa, ranging from 6.4% (95% CI: 3.8, 9.0) in Nigeria to 29-36.8% (95% CI: 28.6, 45.0) in Ethiopia. The overall pooled estimate prevalence of EPTB among PLHIV was 20% (95% CI: 17, 22). Similar results were found in our study.

Another systematic review and meta-analysis of multiple databases till October 15, 2013 done by Denkinger Claudia M et al. gave the pooled sensitivity and specificity of CBNAAT/ Xpert MTB/RIF testing in various samples.[9] The pooled sensitivity across studies for Lymph node aspirate was 83.1% (95% CI 71.4-90.7%) and pooled specificity was 93.6% (95% CI 87.9-96.8%). The pooled sensitivity for pleural TB was 46.4% (95% CI 26.3-67.8%) and the pooled specificity was 99.1% (95% CI 95.2-99.8%). For CNS TB pooled sensitivity was 80.5% (95% CI 59.0-92.2%) and pooled specificity was 97.8% (95% CI 95.2-99.0%). In our study the sensitivity of the test was found to be 25% for abdominal TB, 33% for pleural TB, 100% for lymphnode TB and 0% for spine TB.

In the present study, Rifampicin resistance was found to be 3.2% in EPTB patients. In a systematic review and meta-analysis done by Vishal Goyal et al. on prevalence of drug-resistant pulmonary tuberculosis in India, various studies done countrywide which were fitting into their inclusion criteria were analyzed.[10] This study was sponsored by the pharmaceutical company Janssen, the manufacturer of Bedaquiline drug. The review gave following results: (1) Pooled estimates for the countrywide prevalence of DR-TB and MDR-TB revealed increasing prevalence of drug resistant TB during the time period 1995 to 2015; (2) the prevalence of MDR-TB was found to be 37.7% from 1995- 2005, 46.1% from 2006-2015 and 42.6% for overall 20 years period; (3) the prevalence of MDR-TB in previously treated cases was found to be 33.7% and in newly diagnosed TB patients it was found to be 4.8%. The results were higher compared to national RNTCP statistics 2015 (15% in previously treated cases and 2.2% in newly diagnosed TB patients) and WHO estimates for India which was 16% in previously treated cases and 2.5% in newly diagnosed cases.[11,12] This discrepancy was because of difference in the population selected. The prevalence of Rifampicin resistance in EPTB patients in present study was comparable to the National data. In our study CBNAAT detected 2% of cases which were not detected by other investigations and Rifampicin resistance was seen in 3.2% of EPTB cases. A study done by Sunil Kumar et al. to look for role of CB-NAAT in diagnosing extra pulmonary tuberculosis in correlation with FNA in a tertiary care center during 2017-18 showed similar results.[13] A total number of 289 cases with presumptive diagnosis of EPTB were identified. Majority of them were lymph node TB. CBNAAT detected 6.5 % of cases (19/289) which were not detected by FNA and other investigations. Resistance to Rifampicin was identified in 2.1% (3/142 cases) of CBNAAT positive cases.

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The values of Rifampicin resistant was very high in the study done by Rajneesh Tripathi et al. 207 PLHIV patients having pulmonary tuberculosis were tested for Sputum CBNAAT.[14] A total of 59/207 (28.5%) HIV positive cases were detected as positive for Mycobacterium tuberculosis by CBNAAT. Out of 59 HIV-TB co-infected cases, 45 were male and 14 were female. Rifampicin resistance was seen in 15/59 (25.4%) of TB confirmed cases. Male predominance was seen in this study similar to our study but the prevalence of Rifampicin resistance was far greater in comparison to our study.

Another study conducted by Mahesh Gupta et al. on prevalence of positivity of CBNAAT in EPTB patients included 300 patients (203 pleural fluid, 58 lymph node aspirate, 18 empyema, 9 ascitic fluid, 9 CSF, 3 pericardial fluid) and diagnosed EPTB on history, clinical and radiological basis.[15] Out of these 28 (13.8%) patients of pleural fluid, 35 (60.3%) patients of lymph node aspirate, 8 (44.4%) patients of empyema, 1 (11.1%) patient of ascitic fluid and none of the CSF and pericardial fluid were CBNAAT positive and out of 72 positive patients 12 (16.7%) were rifampicin resistant. This study concluded that Gene Xpert assay has the potential to significantly improve and escalate the diagnosis from smear negative body fluids in the regions with not only high TB burden but also with overlapping HIV. The same conclusion was drawn in our study.

Our study found higher prevalence of EPTB in PLHIV with a significant predominance in males and patients with low CD4 counts. CBNAAT seems to be a sensitive investigation for detecting EPTB with high positive predictive value.

Conclusion

Our study showed that the prevalence of EPTB was higher compared to PTB in HIV patients. Abdomen was found to be the commonest site of EPTB. CBNAAT sensitivity was variable. Our study showed maximum sensitivity for Lymph node aspirate and minimum for CSF. Overall the sensitivity of CBNAAT was low, yet it is a very useful investigation for detection of EPTB with high positive predictive value.

Conflict of Interest: None

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