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STUDY OF HIV-TB COINFECTION: A PERSPECTIVE FROM EASTERN INDIA

Medicine

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ABSTRACT

Background: TB is the commonest opportunistic co-infection among PLHIV. The study was designed to determine the significantly susceptible cohort of PLHIV to TB based on their CD4 count and the distribution of PTB and EPTB among them.

Methodology: 140 HIV infected admitted patients aged 18 years and above were included in the study. PTB and EPTB were diagnosed based on RNTCP criteria and CD4 count was determined using Flow cytometer.

Result: Out of 140 study populations, 86 patients (61%) were co-infected with TB which includes 73 (85%) patients with CD4 count <250 cells/μL. 60% (52) patients presented with EPTB and the commonest site was lymph node.

Discussion: CD4 count <250 cells/μL were the demarcation for susceptibility of MTB co-infection and EPTB.

Conclusion: Identification of the most susceptible cohort of PLHIV for TB co-infection is essential to decrease the mortality rates and to avoid therapeutic complications of the two monsters.

KEYWORDS

Tuberculosis, People Living with Human Immunodeficiency Virus, CD4 count, pulmonary TB, extra-pulmonary TB.

INTRODUCTION

Tuberculosis (TB) is one of the oldest diseases of human being. It is distributed worldwide and according to 2004 WHO report, it is the seventh leading cause of death worldwide accounting for 2.5% of all deaths. India has the highest burden of TB in terms of absolute numbers of incidence cases worldwide. Total number of People Living with HIV (PLHIV) in India in the year 2015 is estimated to be 21.17 lakhs.

Most common opportunistic infection among PLHIV (People Living with Human Immunodeficiency Virus) is TB and the same is responsible for about 24% of all HIV related mortality. HIV infected persons have greater risk of acquiring TB infection, about 8 times higher than HIV non infected persons ("*Revised National Tuberculosis control programme, technical and operational guidelines for tuberculosis control in India", 2016*) and more likely to have active TB by about 100 times greater than HIV non infected persons (Raviglione MC, 2015).The risk of TB infection increases among HIV infected persons with disease progression and CD4 count deterioration. TB infection can occur in any stage of HIV infection and presentation may vary with degree of immune suppression.

In early stage of disease, when CD4 cell count is higher, pulmonary TB presents in typical manner as HIV non infected person. But when HIV disease progresses, extra-pulmonary TB infection or smear negative pulmonary TB infection is more than HIV non infected persons.40-60% of all HIV-TB co-infected persons have extra-pulmonary TB along or with pulmonary disease. Most common forms of extra-pulmonary TB in HIV infected persons are lymphatic, disseminated, pleural, and pericardial. Our study was designed to elucidate the significantly susceptible cohort of hospitalised patients with HIV infection based on their CD4 count, in eastern India. We also tried to find out the critical level of CD4 count below which patients are significantly susceptible to EPTB.

AIMS AND OBJECTIVE:

To detect the distribution of TB-HIV co-infections in relation to CD4 count among the patients aged >18 years admitted in a tertiary care hospital and also to determine the distribution of pulmonary and extra pulmonary TB among the co-infected cohort.

METHODOLOGY:

The study was performed at Calcutta School of Tropical Medicine, a tertiary care hospital over a period of two years. 140 hospitalised known HIV infected patients aged 18 years and above were included in the study. All Immunocompromised patients admitted during the study period fulfilling the inclusion criteria were included in the study after taking proper consent, which included 140 patients. The baseline demographic data of every patient was taken based on predesigned pro forma. Physical examination was done including general survey and systemic examination. Repetition of patients in the study was not done for patients being admitted for subsequent times during the study period. All presumptive pulmonary TB patients that is a person with any of the symptoms and signs suggestive of TB including cough >2 weeks, fever >2 weeks, significant weight loss, haemoptysis, any abnormality of chest radiography, undergone sputum smear examination by Zeihl Neelsen staining.

Two sputum specimens collected (spot-early morning or spot-spot).If first smear was positive, patient categorized as microbiologically confirmed TB. If first smear was negative, chest x-ray (CXR) was considered and if reported as suggestive of TB, the second sample was subjected to smear and CBNAAT (Cartridge Based Nucleic Acid Amplification Test) simultaneously.

Based on CBNAAT result, patients were categorized as microbiologically confirmed drug sensitive TB or Rif resistant TB. In case of all presumptive EPTB, that is the presence of organ specific symptoms and signs like swelling of lymph node, pain and swelling in joint, neck stiffness, disorientation, etc and/or constitutional symptoms like significant weight loss, persistent fever >2 weeks, night sweats, appropriate specimens from presumed sites of involvement were collected for CBNAAT/ smear microscopy/ culture / histo-pathological examinations, based on type of specimen and availability of facilities. CXR, Ultrasonography (USG), Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI) are other investigations used as supporting tools for diagnosing EPTB. CD4 count of the HIV infected patients were determined using flow cytometry assay.

RESULTS:

Table 1 shows that out of the 140 hospitalised HIV infected patients included in our study, 112 patients were male and 28 patients were female (Male:Female 4:1) with mean age 39 years. 138 patients were in the age group of 18-59 years while only two were above 60 years. Details of other demographic characteristics and transmission categories are presented in Table-1. Labourers were the most common groups followed by the truck drivers. Percentage of HIV infection was

also much common among the housewives and most of these patients denied any extramarital affairs. However their husbands could not be traced for further investigations. The disease was found to be most commonly transmitted by heterosexual route. Only two patients reported of homosexual practices and three patients were injectable drug users (IDU). 46% of the study group had no high risk behaviour.

Table 1: Demographic characteristics of all the study participants

PARAMETERS	NUMBER OF PATIENTS, n (%)	
Age in years (mean ± SD)	39 ± 10	
Males	112 (80)	
Occupation	Labourer	49 (35)
	Driver	31 (22)
	Housewife	18 (13)
	Professional	17 (12)
	Unemployed	8 (6)
	Businessman	7 (5)
	Clerk	4 (3)
	Sex worker	4 (3)
	Student	2 (1)
Route of infection	Heterosexual	84 (60)
	Homosexual	3 (2)
	Blood transfusion	4 (3)
	IDU	3 (2)
	Unknown	46 (33)
Duration of disease, in years (mean)	3	
CD4 count, in cells/µl median (IQR)	88.5 (3-1052)	

*IDU- Injectable Drug Users
#IQR- Inter Quartile Range

Total study population was divided into three cohorts based on the CD4 count (table 2). CD4 count <50 included 57 patients (41%) while CD4 count 50-250 included 49 patients (35%) and CD4 count >250 included 34 patients (24%). Out of the total study populations of 140, 86 patients (61%) were co-infected with Mycobacterium tuberculosis (MTB). Co-infections were found to be significantly high among the patients with CD4 count less than 50 cells/µL (44%) and CD4 count 50-250 cells/µL (41%).

Table 2: Shows distribution of HIV-TB co-infected patients and HIV infected patients based on CD4 count

CD4 COUNT (cells/µL)	HIV-TB CO-INFECTED n (%) N=86	HIV INFECTED n (%) N=54	p-value
*<50	38 (44)	19 (35)	0.0007
# 50-250	35 (41)	14 (26)	0.0001
$ >250	13 (15)	21 (39)	0.0896

Among the 86 HIV-MTB co-infected cohorts, 34 patients (40%) had pulmonary TB (PTB) while 52 patients (60%) had extra-pulmonary TB (EPTB). Patients having both pulmonary and extra-pulmonary TB were included in PTB group. We further studied the proportion of PTB and EPTB in HIV infected patients based on CD4 count (table 3) and found that EPTB was significantly high among the patients having CD4 count <250 cells per microliter while patients with CD4 count above 250 cells per microliter were significantly susceptible to PTB.

Table 3: Distribution of CD4 counts and percentage of PTB & EPTB infected patients.

CD4 COUNT (cells per µL)	PTB n (%) N=34	EPTB n (%) N=52	P value
*<50	13 (38)	25 (48)	0.0116
# 50-250	11 (32)	24 (46)	0.0041
§ >250	10 (30)	3 (6)	0.0186

Further the sites of EPTB among the co-infected patients were investigated (figure 1) and we found that most commonly involved site was lymph node (22 cases), cervical lymph node followed by retro-peritoneal lymph node. 8 cases had pleural effusion while another 7 cases had central nervous system involvement that included tubercular meningitis (5 cases) and tuberculoma (2 cases). Disseminated TB was diagnosed among 6 cases and only 2 cases had spinal TB involving the thoracic spine. Among the co-infected cohort, only two patients having PTB expired in the hospital.

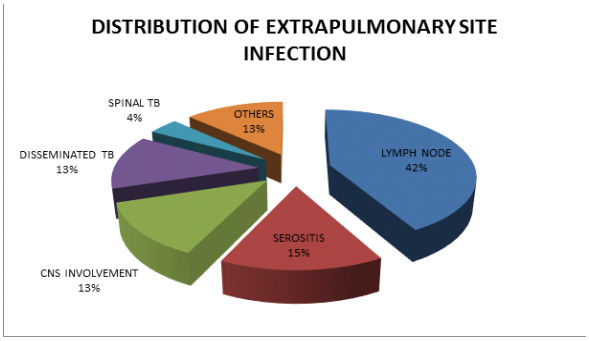

Fig 1: Pie diagram showing frequency of sites involved in EPTB patients.

DISCUSSION:

Total number of PLHIV in India in the year 2015 is estimated to be 21.17 lakhs and co-infection of TB among them is the leading cause of their mortality ("*National AIDS control organisation, Annual report 2016-2017",* 2017). Screening of TB among PLHIV is thus essential for early detection and initiation of treatment of TB to decrease the morbidity and mortality rate of the HIV infected patients. Our study aimed to detect the distribution of TB-HIV co-infections in relation to CD4 count among the patients aged >18 years admitted in a tertiary care hospital. We found increased chances of HIV-TB co-infection with drop in CD4 count among the PLHIV and the co-infection was significantly high among the patient with CD4 count <250 cells/ µl. Further, the distribution of pulmonary and extra pulmonary TB was detected among the co-infected cohort.

Demographic data of the total 140 hospitalised HIV positive patients showed that males were predominant in our study group and 25-49 years age group were mostly affected. Males were more predominant probably because the females avoid seeking medical care in the fear of social outcast and loss of family support. 25-49 years of age group was mostly affected because it is the sexually active group. Labourer was the most common group (35%) followed by driver (22%) among our study population. Housewives were also common among our cohort and included 13% of the study population but none of them had any high risk behaviour. Heterosexual route was found to be the commonest route of transmission. Only three patients were injectable drug users, the finding corroborates with the study done by Sharma SK, Kadhiravan T, Banga A, Goyal T, Bhatia I and Saha PK, (2004). However, 46% of the patients had no history of high risk behaviour or exposure to HIV infection.

In our study, 86 (61%) patients had HIV/TB co-infection, the finding corroborates with the study done by (S.K.Sharma et al., 2004) at AIIMS Delhi, a tertiary care hospital of North India, among 135 hospitalised patient which showed that the commonest opportunistic infection was TB (71.1%) among the HIV infected patients. Another study done by Giri PA, Deshpande JD, and Phalke DB, (2013) carried out at the ART clinic of Pravara Rural Hospital, Loni among the outpatient showed a different picture. According to the study out of the total 1012 HIV positive patients, who attended the ART clinic and received treatment, 172 (17%), had HIV/TB co-infection and remaining 480 (83%) were without HIV/TB co-infection. The higher percentage of co-infection in our study could be explained by the fact that we included only the admitted patients in our study populations most of which were admitted due to manifestation of opportunistic infections. The risk of developing disease after acquiring TB infection actually depends on the endogenous factors, such as individual's innate immunologic and non-immunologic defences and the level at which individual cell mediated immunity (CMI) is functioning. Cell mediated immunity (CMI) confers partial protection against MTb. Among CMI, activation and proliferation of CD4+ T cells to produce cytokines especially Interferon-gamma (IFN-y) is crucial for the host's defence against MTb (Raviglione MC, 2015). So with qualitative and

quantitative defects in the CD4+ T cell, capability to contain MTb proliferation decreases. This explains the increased rate of MTb infection with the drop in CD4+ T cells count among PLHIV, precisely below <250 cells/µl. We found EPTB to be the more prominent presenting features (60% cases) among the co-infected patients than the PTB. This was also the finding of Manjareeka SN (2013). According to a review article by SK Sharma and Mohan A (2004) in HIV-positive patients, EPTB accounts for more than 50 per cent of all cases of TB. In studies reported from India, EPTB constituted 45 to 56 per cent of all the cases of tuberculosis in persons with AIDS (Kumar P, 2002; Sharma SK, 1997) The little higher percentage of EPTB cases in our study could be explained by the fact that we included only admitted patients and higher percentage of our study populations were having CD4 count <250 cells/µL who were significantly susceptible to EPTB. According to QM Trinh, HL Nguyen, TVA Nguye, V Sintchenko, and BJ Marais, (2015), more severely immunocompromised individuals have more chances of extra-pulmonary and disseminated TB. Our study also showed that EPTB was significantly high among the seropositive patients having CD4 count <250 cells/µL as compared to PTB. However PTB was significantly high among patients having CD4 count > 250 cells/µL. The most common extrapulmonary site in HIV-positive individuals is the lymph node. The lymph node involvement in MTB is usually the local manifestation of the systemic disease. The TB bacilli enter through the respiratory system and spreads via haematogenous and lymphatic routes to involve the hilar and mediastinal lymph nodes. Sometimes, tonsil may be the route of entry and from there the bacilli spread via lymphatics to involve the cervical lymph node. However, neurological, pleural, pericardial, abdominal involvement has been described and virtually every site in the body can be involved in HIV-positive patients (Barnes PF, 1993; Fanning A, 1999; Iscman MD; Jones BE, 1993; Raviglione MC, 1992). We found most commonly involved extra-pulmonary site was lymph nodes (cervical lymph nodes most common) followed by pleural effusion. This finding also corroborates with the study done by Prakasha SR, Suresh G, 'Dsa IP, Shetty SS, and Kumar SG, (2013) which showed that lymph node and pleural TB were the common EPTB cases in the age group of 15–44 years.

CONCLUSION:

A slowly emerging prevalence of HIV infection in a TB endemic country like India is a potential threat to the mankind. TB, the commonest life-threatening opportunistic infection in PLHIV increases the morbidity and mortality of PLHIV and also complicates the management of the double burden. Thus early diagnosis and treatment of TB among susceptible cohort of PLHIV is essential to combat the emerging threat of HIV-TB co-infection and to improve the epidemiology of TB in the endemic countries.

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