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CLINICAL, IMMUNOLOGICAL AND RADIOLOGICAL PROFILE OF NEWLY DIAGNOSED HIV SERO POSITIVE TUBERCULOSIS PATIENTS IN ZARIA, NIGERIA

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ABSTRACT

Tuberculosis (TB) and Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) constitute the main burden of infectious diseases in resource-limited countries. Co-infection with both organisms alters the clinical presentation, laboratory, and radiological features of TB which poses a challenge in diagnosis hence the need to profile patients to improve index of suspicion.

The study subjects were new patients who presented to Ahmadu Bello University Teaching Hospital (ABUTH) Zaria during the study period. They underwent clinical evaluation, relevant investigations and were consecutively included in the study if the diagnosis of TB/HIV was made. Seventy five (75) patients certified the study criteria. There was a high incidence of smear negative pulmonary TB, extra pulmonary involvement as well as opportunistic infections. The mean CD4+ T lymphocyte (CD4+) count of study subjects was 178 ± 116.81 cells/ul indicating severe immunosuppression. Multiple atypical chest radiological features were found in the study subjects. Oral thrush and milliary shadows best predicted advanced immunosuppression (CD4+ ≤ 200cells/l). The presence multisystem involvement and opportunistic infections should raise index of suspicion of TB/HIV co infection.

INTRODUCTION

According to the world health organization (WHO) estimates for 2007, there were 33.2million (30.6-36.1million) people infected with the human immunodeficiency virus (HIV) worldwide. An estimated 2.5 million new infections and 2.1million deaths from the infection occurred in the same year [1]. Sub-Saharan Africa accounted for 22.5milllion of these total numbers of infections and 1.7million of the deaths. [1] In the preceding year (2006) there were an estimated 9.2million new cases of tuberculosis and 1.7 million deaths from the disease worldwide. Of these new infections, 0.7million were co-infected with HIV and accounted for 0.2milllion of the deaths in the same year.[2] Tuberculosis is the commonest infectious cause of morbidity and mortality in HIV infected patients.[3] The African region accounts for 85% of HIV/TB co-infections world-wide. Nigeria being the most populous nation in the sub Saharan region bears a substantial part of the disease burden, being second only to South Africa in the absolute number of people with HIV infection and AIDS.[2] Co-infection with tuberculosis (TB) and HIV is popularly referred to as the unholy alliance or duet due to their combined devastating effect in the sufferer in terms of morbidity and mortality as HIV has been documented as the single most important cause of the increased burden of tuberculosis.[4],[5]

The Human Immunodeficiency Virus and Mycobacterium tuberculosis bacteria are both intracellular organisms, which target the $CD4^+$ cells of the monocytes/macrophage and T-lymphocytes lineages. HIV targets, destroys and impairs the function of these cells thereby suppressing cell-mediated immunity, which is necessary for protection against intracellular organisms like tuberculosis. Infected individuals are thus prone to infection with intracellular organisms including tuberculosis. [6], [7], [8] HIV infected persons have a 5-15% annual risk of developing the disease compared with 5-10% lifetime risk in HIV negative persons. [9] TB and HIV infection interfere and impact the pathogenesis phenomena of each other. Owing to atypical clinical presentations and diagnostic complications, HIV/TB co-infection continues to be a diagnostic dilemma for healthcare providers.[3] , [4], [8] The presentation of TB in HIV-negative patients conforms with the known clinical features and investigation findings of TB infection.[10],[11] However, in patients who are HIV-positive with depressed immunity (low CD4 count), the pattern of presentation is a deviation from the normal, both in clinical features and investigation findings.[10],[11] Also here, there is a rise in the extra pulmonary presentation of TB.[4] The presentation in patients with HIV who have normal CD4+ count is similar to that of HIV-negative patients.[10],[11] As immune suppression progresses, the clinical manifestations of the disease become more diverse with high incidence of extra pulmonary tuberculosis and presence of associated conditions like chronic diarrhea, herpes zoster, skin rash, oral candidiasis. Many studies in have found dyspnoea, fever, fatigue, hepatomegaly, splenomegaly, lymphadenopathy and low haemoglobin to be commoner in HIV associated tuberculosis as well as lymphopenia, and negative tuberculin skin test.[4],[12],[13]

The study was undertaken to evaluate the clinical presentation, immunological and radiological features of HIV positive tuberculosis patients at ABUTH Zaria. The findings will help in sharpening the index of suspicion of clinicians for prompt diagnosis and treatment of both diseases.

MATERIALS AND METHOD

This is a cross sectional descriptive study that was carried out at Ahmadu Bello University Teaching Hospital (ABUTH) Zaria, a tertiary health care institution in the North- western part of Nigeria from March 2007 to December 2008. The hospital draws its clientele mainly from Kaduna and the surrounding states. It was a hospital based study which utilized convenience sampling method whereby patients were enrolled as they came into the hospital and satisfied the inclusion criteria.

The study subjects were consecutive patients who presented to the Tuberculosis and HIV clinics of the ABUTH Zaria respectively, or were admitted to the medical wards of the hospital and found to be co-infected with HIV and Tuberculosis (HIV/TB). They were treatment naïve for both infections or had not used antiretroviral drugs in the preceding six months. Seventy–five (75) patients who met the study criteria during the period were enrolled. The controls were thirty five (35) age and sex matched HIV negative tuberculosis patients.

Inclusion criteria: Subjects were included in the study if they satisfied the under-listed conditions:

a. Age ≥15years.
b. Symptoms, signs and laboratory evidence of tuberculosis.
c. Double ELISA or western blot positivity to HIV-1 or 2 antibodies (or both). d.Provision of informed consent.

Exclusion criteria:

The following were excluded from the study:

a. Age <15 years
b. Presence of non-HIV related conditions likely to suppress immunity like cancers, diabetes mellitus, overt renal disease, steroid therapy and pregnancy.
c. Use of antiretroviral drugs (ARVs) or immunosuppressive therapy within the 6 months preceding diagnosis of tuberculosis.
d. Refusal to have HIV testing.

Inclusion and exclusion criteria for the HIV negative TB controls were the same except for HIV positivity.

Ethical Approval was obtained from the Ethics and Research committee of the ABUTH Zaria. All the subjects signed or thumb printed an informed consent form.

STUDY PROTOCOL

All participants were interviewed by the investigator using a drawn up protocol, which contained the biodata, major symptoms and HIV risk factors. A general and systemic physical examination was carried out and recorded. CD4+cell count estimation, chest x-rays, HIV screening, Sputum Acid Fast bacilli (AFB) were carried out along with other ancillary investigations. All the investigations were carried out in the hospital's laboratories and relevant departments by staff that were experienced in carrying out such investigations using available standard procedures.

HIV status was determined by Enzyme Linked Immunosorbent Assay (ELISA) test using the Determine HIV 1and 2 (Abbot Laboratories, Japan) and Immunocomb HIV 1 and 2 (Orgenics, Israel) test kits to double test for HIV antibodies.

Sputum AFB staining was done using Ziehl-Neelsen method and reported in the standard format. One sputum sample was collected from each study subject and control consecutively for three days for convenience after instructions by the nursing staff on the correct procedure.

CD4+ lymphocyte count estimation was carried out with the PartecCyFlow counter (Partec GmbH Munster, Germany) machine using the principle of flow cytometry.

The Chest radiographs were taken in posterior-anterior (PA) view by staff of the hospitals radiology department and reported by a Consultant Radiologist.

Diagnosis of tuberculosis was based on the WHO recommen dations for resource poor countries.[14]

STATISTICAL ANALYSIS

Data obtained comprising the Biodata, Clinical features, Radiological and Laboratory results, were analyzed using the statistical Package for social sciences (SPSS) for windows software version 11.5. All values were expressed as means ± standard deviation and qualitative data as percentages. Student's t-test and Chi-square and ANOVA were used to assess the difference between the various variables and groups as appropriate. Pearson's test of correlation was used to check association between variables and groups. Linear and multiple regressions were conducted to find out predictive values of relevant variables. A p-value of ≤ 0.05 was taken as statistically significant and confidence intervals were reported at 95%.

RESULTS

Seventy five (75) HIV/TB co-infected subjects were enrolled in the study. There were 36(48%) males and 39(52%) females. The mean age was 34.03±8.34 years. Twenty-five (69.4%) of males and 28 females (71.8%) were married, 10 (27%) and 4 (25.6%) male and females respectively were single while the rest were divorced (table1 &2). The controls were thirty five (35) HIV negative tuberculosis patients who were recruited during the study period. The mean duration of illness at time of presentation was study 5.7 months in study subjects (range 1-16 months) while that of controls was 5.4months (p=0.71).The mean BMI of study subjects was 18.3 ± 2.71kg/m^2 (range 12-26.7) compared to 18.65 ±1.97 (range 15-24), (p=0.52)in controls. Forty–eight percent (48%) of study subjects and 48.6% of the controls had BMI less than 18.5kg/m^2. (Table1)

Table 1: Data of Study subjects and controls.

Variable	Study subjects	Controls	P – value
Age (Years)	34.03 ± 8.34	32.66 ± 10.84	0.47
Male Gender: Female	36 39	19 16	0.39
BMI kg/m2	18.32 ± 2.71	18.65 ± 1.97	0.52
Mean duration of illness (months)	5.72 ± 3.27	5.40 ± 5.70	0.71
CD4+(Cells/ul)	178.96±118.81	630.22±184.96	0.01
Sputum AFB+	14(18.7%)	22(62.9%)	0.01

Clinical Features:

The commonest symptoms in both study subjects and controls were cough (p=0.54), chest pain (p=0.07), and dyspnoea (p=0.09).Weight loss and loss of appetite occurred in all subjects while fever was present in 94% of study subjects and 88.6% of controls (p=0.26). Diarrhea (61.3%),skin rash (28%) peripheral lymphadenopathy (40%) ,oral thrush (37.3%) , dermatoses (28%), hepatomegaly (13.3%) and splenomegaly (9.4%) of HIV/TB subjects showed statistically significant differences from the TB controls (table3).The most frequent auscultation findings in the study subjects were crepitations (58.7%), bronchial breath sounds (24%).There was a statistically significant difference in presence of crepitations (p=0.01)(table 4).

Table 2: Sociodemographic characteristics of study subjects and controls (TB Only)

Variable	HIV/TB		TB Only	
	Male N (%)	Female N (%)	Male N (%)	Female N (%)
Marital Status				
Married	25(69.4%)	28(71.8%)	12(63.2%)	12(75.0)
Single	10(27%)	10(25.6%)	7(36.8%)	4(25.0)
Divorced	1(2.8%)	1(2.6%)	0(0.0%)	0(0.0%)
Total	36(100%)	39(100%)	19(100%)	16(100%)
Occupation				
Trader	13 (36.1)	4 (10.3)	4 (21.1)	4 (25.0)
Student	7 (19,4)	8 (20.5)	6 (31.6)	4 (25.0)
Civil servant	6 (16.7)	2 (5.1)	1 (5.3)	1 (6.3)
Farmer	5 (13.9)	1 (2.1)	5 (26.3)	1 (6.3)
Driver	5 (13.9)	0 (0.0)	1 (5,3)	0 (0.0)
House wife	0 (0.0)	24 (61.5)	0 (0.0)	6 (37.5)
Others	0 (0.0)	0 (0.0)	2 (10.5)	0 (0.0)
Total	36 (100)	39 (100)	19 (100)	16 (100)

Table 3: Presenting symptoms in Study subjects and controls.

Symptom	Study subjects	Controls	X2	P value
Weight loss	75 (100)	32(91.4)	**	0.03*
Appetite loss	74 (100)	32(91.4)	**	0.03*
Cough	74(98.7)	34(97.1)	**	0.54
Fever	71(94.7)	31(88.6)	**	0.26
Chest pain	50(66.7)	17(48.6)	3.28	0.07
Diarrhea	46(61.3)	2(5.7)	30.02	0.01*
Dyspnoea	36(48.6)	11(31.4)	2.80	0.09
Skin rash	21(28.0)	1(2.9)	9.43	0.01*
Haemoptysis	12(16.0)	11(31.4)	3.44	0.06

Key: X^2 = (chi square); * = statistically significant;** = Fisher's exact test ; ( ) = percentages.

Table 4: Clinical Signs in Study subjects and Controls

Clinical Sign	Study Subjects	Controls	X2	P value
Peripheral adenopathy	30(40)	2(5.7)	13.60	0.01*
Oral thrush	28(37.3)	1(2.9)	14.61	0.01*
Finger clubbing	7(9.3)	7(20)	**	0.13
Pedal eodema	3(4.0)	0(0)	**	0.55
Crepitations	44(58.7)	26(74.3)	5.67	0.59
Rhonchi	2(2.7)	5(14.3)	**	0.057
Pleural effusion	11(14.7)	4(11.4)	**	0.77
Hepatomegaly	10(13.3)	1(2.9)	6.84	0.01*
Splenomegaly	7 (9.4)	0(0.0)	**	0.01*
Bronchial breath sounds	18(24)	23(66.7)	17.76	0.01*

Key— X^2= (Chi Square test; * = statistically significant; ** = Fisher's exact test; ( ) = percentages.

Laboratory Investigations:

The mean CD4+ lymphocyte count of the study subjects was 178.96±116.81 cells/mm^3 with a range of 15-500cells/mm^3 as against 630 ± 187.95 (range 241-1049) in the controls (p=0.01). Up to 61.3% of study subjects had CD4+ count less than 200cells/mm^3.There was a statistically significant difference between the groups when the study subjects and controls were matched according to their immune status (tables 1 & 5).

The sputum AFB was positive in 14 (18.7%) of study subjects and 22 (62.9%) of controls (p=0.01), (table 1).

Table 5: Distribution of study subjects and controls by Immune status.

CD4+count Cells/Ul	Study subjects n/%	Controls n/%
<200	46 (61.3)	0 (0.0)
200-350	21 (28.0)	1 (2.9)
351-500	8 (10.7)	7 (20.0)
>500	0 (0.0)	27 (77.1)
Total	75(100)	35(100)

Radiological features:

The study subjects had more atypical radiological changes than controls. Different types of lesions were found in the same radiographs in many the study subjects. The most common lesions were lower zone infiltrates (48%), milliary shadows(13.3%), and pleural effusion (16%), and mediastinal adenopathy (16%) .All showed statistically significant differences from controls.

Typical features such as upper zone cavitations and infiltrates were seen more in controls than study subjects (table 6).

Relationship of Clinical features to Cellular immunity (Cd4+):

Among the study subjects, an independent t-test was carried out to evaluate any statistically significant differences in the mean levels $CD4^+$ cell count in the presence or absence of some significant symptoms and signs. Where statistically significant differences were identified, the mean values of the relevant parameters were compared to bring out the exact nature of such differences. Thus the mean CD4+ cell counts of those with haemoptysis was found to be higher than that of those without haemoptysis (p=0.05) while that of those with oral thrush was lower than of those without oral thrush (p=0.05).

Table 6: Chest X-Ray features in Study subjects and Controls:

X-ray feature	Study subjects	Controls	X^2	P value
Atypical Features:				
Lower zone infiltrates	36(48.0)	8(22.9)	7.65	0.02*
Pleural effusion	12(16.0)	5(14.3)	0.54	0.82
Mediastinal adenopathy	12(16.0)	1 (2.9)	**	0.04*
Milliary shadows	10(13.3)	0 (0.0)	**	0.02*
Normal x ray	4 (5.3)	0 (0.0)	**	0.31
Typical Features:				
Upper lobe infiltrates	7 (9.3)	22(62.9)	35.20	0.01*
Upper lobe cavitations	6 (8.0)	16(45.7)	21.21	0.01*
Fibrosis and shrinkage	5 (6.7)	5 (14.3)	**	0.28

Key:X=(Chi Square test) * = statistically significant ** = Fisher's exact test

Table 7: Mean levels CD4+T lymphocytes and significant clinical features in the study subjects.

CD4+	Clinical Feature:	Present	Absent	T	Df	P Value
CD4+(cells/uL)	Haemoptysis	239.08 ± 137.377	137.00 ±110.02	1.98	73	0.05*
CD4+ "	Oral thrush	145.42 ±108.17	198.93 ±118.28	-1.95	73	0.05*
CD4+	CXR feature:	Present	Absent	T	Df	P value
CD4+(cells/uL)	Fibrosis and shrinkage	340.20 ±70.00	167.44 ±111.04	3.42	73	0.01*
CD4+(cells/uL)	Milliary shadows	139.80 ±64.63	184.98 ±122.12	-1.78	73	0.09

DISCUSSION

The mean age of subjects in this study was 34.02 ± 8.34 years which is similar to 35.6 ±12.4 found by Yusuph in a similar study in North-eastern Nigeria which found the ages of 25 to 44 years as most affected.[15] Awil et al and Mbatchou et al also reported a similar preponderance of the sexually active and economically productive age groups in similar studies.[16], [17] Housewives, traders and students formed the bulk of those infected with HIV and tuberculosis in this study. These groups belong to the lower socioeconomic class of the society. Most (71%) of the female study subjects were married, 62.5% of whom had no history of multiple sex partners or blood transfusion. It was also found that housewives, farmers and traders were the most affected occupational groups.[15] It has been found that married women are not protected from HIV infection despite maintaining fidelity as spouses who practice high risk behaviors, such as having a network of sexual partners, unprotected sex with sex workers and alcoholism, transmit the infection to their wives.[18]

Constitutional symptoms of HIV and TB infections such as fever, weight loss, poor appetite and feeling of ill health usually overlap making diagnosis of TB in HIV difficult. The predominance of respiratory symptoms suggest that pulmonary tuberculosis is still the commonest form of disease even in immune suppressed subjects in-spite of the increased incidence of extra-pulmonary and disseminated disease documented in several reports.[19], [20] Hepatomegaly, lympadenopathy, oral thrush, diarrhoea and dermatosis were significantly more common in the study subjects than controls. Their presence in a patient with tuberculosis should therefore raise a high suspicion of co infection. They also generally reflected the severity of immune suppression as those conditions were found predominantly in those with advanced disease (CD4+ <200cells/uL) as demonstrated by other researchers.[20], [21], [22] both study subjects and controls were late in seeking medical care. There was severe wasting in almost half of both study subjects and controls indicated by BMI <18.5Kg/m^2 . Both HIV and TB are wasting diseases as a result of fever in tuberculosis and other opportunistic infections in HIV, leading to the hyper catabolic state, as well as malabsorption. Also observed, was a delay in time of onset of symptoms to presentation and diagnosis [17], which may be explained by the low socioeconomic status of the study subjects.

Only 18% of HIV/TB subjects had AFB smear positive sputum, compared to 62.9% of TB only controls. This could be explained by the fact that most of the study subjects had severe degree of immmunosupression and as such, granuloma formation and cavitations were uncommon. Low sputum yield has also been found in other studies [19],[21].

The mean CD4+ count was significantly lower in the study subjects compared to the controls, with over 61% having $CD4^+$ count of <200cells/uL(p=0.01). Keiper et al in Philadelphia (USA) also reported 26 of 35 (74) % of patients had CD4+ count less than 200cells /uL[,23] while Teck in Malawi found that 89% of 158 HIV positive subjects with active or past TB had CD4+ count less than 350 cells/uL.[24] Advanced immune suppression poses an increased risk for tuberculosis either as a progression to disease of a new TB infection or through reactivation of a quiescent TB foci. In relation to symptoms ,the mean CD4+ counts of those with haemoptysis was significantly higher than that of those without haemoptysis (p=0.05).This can be explained by the fact that those with higher CD4+ are able to mount a more robust immune response that leads to granuloma formation, caseation and erosion into blood vessels thus leading to haemoptysis. Dermatosis, diarrhoea , adenopathy oral thrush , hepatomegaly and splenomegaly occurred mostly in study subjects with CD4+ counts less than 350cells/ul. Oral thrush had the best predictive value for advanced immunosup pression (CD4+ <200 cells/uL). Fungal infections tend to occur in the presence of very low CD4+ levels. Dissemination of TB in severe immunosupression can affect the abdominal viscera and also cause lymphadenopathy. This may explain the hepatomegaly, splenomegaly and lymphadenopathy seen in the disease though there was no histological diagnosis.

There was preponderance of atypical radiological findings in the study subjects compared to controls. Lower zone infiltrates, thoracic adenopathy, milliary shadows were strongly suggestive of HIV co-infection. Pulmonary fibrosis and shrinkage occurred only in HIV/TB subjects with CD4+ count higher than 200cells/ul. This can be explained by the fact that those with higher CD4+ counts could still mount a strong immune response to the tuberculosis antigens. [25],[26],[27],[28] Nwowu in Nnewi found on the contrary that co infected patients had more frequent cavitory lesions than tuberculosis only patients.[29] This study confirms that atypical chest radiological changes in HIV associated tuberculosis associated infection occur in the presence of severe immunosuppression. Presence of milliary shadows was the best predictor of severe immune suppression (CD4+<200 cells/uL).This is not surprising since this degree of immune suppression leads to inability of the host to localize the infection.

CONCLUSION:

HIV and TB co infection occurred in the active but low socio economic groups. Most patients presented late and with advanced immune suppression. Pulmonary disease with extra-pulmonary involvement was most frequent form of tuberculosis. Diarrhoea, dermatosis, and oral thrush were common and predictive of co-infection with HIV.

Recommendations:

The presence multisystem involvement and opportunistic infections should raise suspicion of TB/HIV co infection. There should be continuous public health education on Voluntary Counseling and Testing (VCT) for HIV and TB screening in Nigeria as well as early presentation of patients so as to ensure prompt diagnosis.

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