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Human immunodeficiency virus- associated tuberculosis: pattern and trend in the University of Ilorin Teaching Hospital

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Summary

To define the incidence and spectrum of extra pulmonary tuberculosis (EPTB) and the trend of pulmonary tuberculosis (PTB) among human immunodeficiency virus (HIV) infected patients in the University of Ilorin teaching hospital, a tertiary care centre in Nigeria. Review of all PTB cases diagnosed by Ziehl-Neelsen staining technique and EPTB diagnosed by tissue histology and/or cytology between January 2000 and December 2004. HIV/TB co-infection occurred in 40% (297 cases) of the 744 new cases of tuberculosis (TB) seen in the last 5 years, HIV/PTB occurred in 79% and HIV/EPTB occurred in 21%. About 47 new cases of HIV/PTB and 12 of HIV/EPTB were diagnosed per year. Tuberculous pleurisy with effusion; 23%, tuberculous meningitis; 16% and genital tuberculosis; 10% as (tuberculous: orchitis, endometritis and frozen pelvis) were common form of extra pulmonary presentation. The chance of mixed presentation was 3 times higher amongst the HIV positive than HIV negative patients; 27 vs. 11: X^2= 6.99, OR 3.25; 95% CI= 1.32-8.14, p-value= 0.008. Similarly the chance of miliary tuberculosis was 4 1/2 times higher in the HIV positive group; 9 vs. 2: X^2= 4.29, OR 4.67; 95% CI= 0.90-45.93, p-value= 0.03. Both conditions recorded the lowest $CD4^+$ cells count; 88cells/ul and 93.6.6cells/ul, thus serving as features of advanced HIV illness. PTB and EPTB are common amongst the HIV infected patients; miliary spread and mixed presentation are signs of severe immunosuppression.

Keywords: *Pulmonary TB, extra-pulmonary TB, HIV, $CD4^+$ cells, Ilorin.*

Résumé

Pour définir l'incidence du spectre de la tuberculose extra pulmonaire (TBEP) et la fréquence de la tuberculose pulmonaire (TBP) parmi les patients immunodéficitaire dans le centre hospitalier universitaire d'Ilorin au Nigeria. Une étude rétrospective a été faite des cas diagnostiqués des tissues histologiques et ou cytologiques entre Janvier à Décembre 2004. La co-infection du VIH/TB était de 40% (279 cas) sur 744 nouveau cas vue dans les dernières cinq ans. Le taux du VIH/TBP était de 79% et de 21% pour le VIH/TBEP. Environ47 nouveau cas du VIH/TBP et 12 cas de VIH/TBEP étaient diagnostiqués chaque année. La pleurésie tuberculeuse avec effusion, 23% ; la tuberculose méningitique, 16% et la tuberculose génitale ,10% (la tuberculose orchite, endométrite et du pelvis) étaient la forme la plus commune de la tuberculose extra pulmonaire. Les chances des signes et symptômes mixe étaient trois fois plus élevées parmi les séropositifs que les individus sain 27 vs 11, OR=3.25, P=0.008. Semblablement la chance de la tuberculose miliaire était 4.5 fois plus élevée chez les patients séropositif a VIH que ceux négatif 9vs 2, OR=4.67, P=0.03. Ces deux conditions avaient des taux des cellules CD4 de 88 et 93 cellules/µl de sang respectivement, signe du VIH avancé. Le TBP et La TBEP sont commune parmi les patients infectés du VIH ; la distribution miliaire et des signes et symptômes mixe sont des signes sévère de l'immunosuppression.

Introduction

Pulmonary tuberculosis is prevalent in Nigeria largely because of high level of poverty and failure of the national tuberculosis control programme. Of recent HIV infection has assumed the centre stage as the most potent risk factor for acquiring the disease [1]. HIV infection causes dysfunction and depletion of the key cells of immunity which are $CD4^+$ T- lymphocytes, macrophages and monocytes [2]. These cells play a central role in anti-mycobacterial defenses [2]; their dysfunction therefore places the affected patients at a higher risk of primary tuberculosis infection or reactivation of an old focus [3]. This risk is about 8%-10% per year in HIV positive patients compare to 5% lifetime risk in HIV negative ones [4]. HIV/TB induces synergistic immune dysregulation [5] that enhance rapid progression of both conditions in the co-infected patients. One epidemiological report has estimated one third of the sub-Saharan Africans to be carrying latent *Mycrobacterial tuberculosis* infection which could be activated by HIV infection thereby increasing the pool of HIV/PTB co-infection in the region [3]. In the developed world however, it is HIV/EPTB co-association that is on the increase and tuberculous lymphadenitis is the commonest form [6]. It should be noted that EPTB though, a paucibacillary disease can affect any tissue or organ outside the lungs singly or in combinations and different types have been reported from this hospital [7-10] and from across the country [11,12] though none in HIV-infected patients. Studies from other African countries however, indicated a high incidence of HIV/EPTB in the continent [13,14] This was why we decided to define the incidence and spectrum of EPTB as well as the trend of PTB in HIV infected patients in this tertiary care centre.

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Table 1: Characteristics of patients with TB/HIV

Variable	Total	Male (%)	Female (%)	Mean age ± Std Dev	Mean CD4± Std Dev
All TB cases	744	431 (58)	313 (42)	30.9±10.1	-
PTB	627	332 (53)	295 (47)	32.1±9.3	-
EPTB	117	72 (62)	45 (38)	30.5±10.1	-
All HIV/TB	297	175 (59)	121 (41)	27.2±9.0	128.4±64.8
HIV/PTB	236	106 (45)	130 (55)	27.8±6.9	135.8±70.6
HIV/EPTB	61	37 (61)	24 (39)	24.5±9.7	111.4±45.2

Table 2: Annual distribution of HIV/TB co-morbidity

YEAR	Pulmonary TB			Extra pulmonary TB		
	HIV positive (%)	HIV negative (%)	Total (%)	HIV positive (%)	HIV negative (%)	Total (%)
2000	35(18.3)	69(17.6)	104(16.5)	10(16.4)	14(25.0)	18(15.4)
2001	44(17.9)	73(18.7)	117(18.7)	12(19.7)	11(19.6)	23(19.6)
2002	56(22.7)	84(21.5)	140(22.3)	13(21.3)	9(16.1)	22(18.8)
2003	49(20.0)	82(21.0)	131(21.0)	15 (24.6)	13 (23.2)	29(24.8)
2004	52(21.1)	83(21.2)	135(21.5)	11(18.0)	9 (16.1)	25(21.4)
Total	236(100)	391(100)	627(100)	61(100)	56(100)	117(100)

Materials and methods

The chest unit of the department of Medicine oversees the management of a sizeable number of HIV/AIDS and TB patients. Records of patients diagnosed with both conditions from 1st January 2000 to 31st December 2004, were retrieved from the unit registers for analysis. Tuberculosis cases were grouped into pulmonary (PTB) and extra pulmonary (EPTB), each of which was stratified by patient's HIV status. EPTB was later classified according to site and pattern of distribution. Each of the enlisted PTB patients had at diagnosis; a chest radiograph and 3 sputum specimens tested for acid and alcohol fast bacilli (AAFB) by Ziehl-Neelsen staining technique, 2 of which were smear positive while only EPTB diagnosed by smear study, aspiration cytology, tissue histology or autopsy report were listed for study. HIV infection was diagnosed by two enzyme linked immuno-sobent assays (ELISA) using the Wellcozyme HIV recombinant EIA (Enzyme Immuno-assay) and Murex HIV 1 and 2 kit (Murex Diagnostics, Dartford, UK). ELISA screening test was done on an automated pipetting and analysing machines with 96-well microtitre plates. It was based on the principle of HIV antigen-antibody reaction using a mixture of recombinant synthetic peptides to represent immunodominant epitopes. The viral antigen binds to the bottom of the wells in the microtitre plate and upon addition of patient serum containing HIV antibodies, antigen-antibody binding will occur. This reaction is detected by the addition of an enzyme-labeled "conjugate" which binds to the antigen - antibody complex. The enzyme contained in the bound conjugate will then act on a substrate to be added in the final step of the procedure, there will be a colour change if HIV antigen-antibody reaction had taken place earlier on in the wells of the microtitre plates. The intensity ("optical density", O.D.) of this colour reaction is measured and is proportional to the antibody activity in the sample. Patients that had paired positive tests had their $CD4^+$ cells estimated by Dynal T_4 Quant method (Dynal Biotec ASA, Oslo, Norway). This test is carried out on a fresh sample of peripheral blood at room temperature. The isolated cells were lysed and the nucleic acid counted manually on a light microscope after staining with sternheimer-Malbin solution. The result is expressed as the number of cells per microlitre of the whole blood. The average $CD4^+$ cells count for each group was determined and compared. Tuberculous meningitis was diagnosed clinically in patients with meningeal signs, confirmed tuberculosis in the lungs and cerebrospinal fluid studies suggestive of meningeal inflammation, while skeletal TB was diagnosed from clinical evaluation and radiological reports [15]

Statistics

Descriptive statistics; mean, standard deviation and range were generated where applicable using statistical package for social sciences (SPSS/PC+, version 11.0, SPSS Inc, Chicago, USA. 2002). Independent-samples T-test was used to compare the means of these variables while proportions were compared with chi-square technique.

Results

Seven hundred and forty-four cases of tuberculosis; 627 (84%) pulmonary and 117 (16%) extra pulmonary were seen in the last five years (2000 to 2004). Mean age of the patients was 30.9± 10.1 and the sex ratio was; M: F, 1.4:1, table1. HIV/TB co-infection occurred in 40% of all the cases (297 patients), 79% (236 patients) of which was HIV/PTB; and 21% (61 patients) as HIV/EPTB. Annual distribution of HIV/PTB showed a rising trend, table 2, giving an average of 47 new cases diagnosed per year. This was against 189 cases seen in the previous nine years (1991 to1999) [1], that averaged 21 new cases per year. Tuberculous pleurisy with effusion was the commonest form of extra pulmonary presentation in the HIV positive patients; 23%, though not as common as it occurred in the HIV negative cases; 34%, table 3. Other forms of HIV/EPTB presentation were; tuberculous meningitis; 16%, miliary TB; 15% and genital TB; 10% as tuberculous: orchitis, endometritis and frozen pelvis. There were however, less cases of nodal and skeletal TB in HIV positives compared to HIV negative ones; 13% vs. 20% and 11% vs. 17% respectively. Thirty–eight patients; 32.4% had mixed presentation of TB the frequency of which was 3 times higher amongst HIV positives cases; 27 vs. 11: X^2= 6.99, OR 3.25; 95% CI= 1.32-8.14, p-value= 0.008. Similarly, miliary presentation was over 4 times commoner in HIV positive group; 9 vs. 2: X^2= 4.29, OR 4.67; 95% CI= 0.90-45.93, p-value= 0.03. HIV/PTB had the highest mean CD4$^+$ count of 135.8cells/ul (range 70- 310/ul) and HIV/EPTB had a lower value of 111.4 cells/ul(range 40- 230/ul). The difference was statistically significant, p-value=0.026. Mixed cases of HIV/PTB and HIV/EPTB and miliary TB of the lungs had the lowest mean CD4$^+$ counts; 88cells/ul and 93.6cells/ul respectively.

Table 3: Spectrum of Extra pulmonary TB in HIV positive patients

Extra pulmonary TB	HIV positive No	(%)	HIV negative No	(%)	Total	(%)
Pleural	14	23	19	34	33	28.2
Meningeal	10	16	5	9	15	12.8
Skeletal	7	11	9	17	16	13.7
Lymph node	8	13	11	20	19	16.2
Miliary	9	15	2	3	11	9.4
Genital	6	10	2	3	8	6.7
Pericardial	4	7	2	3	6	5.2
*Abdominal	1	2	-	-	1	0.8
Middle ear	2	3	-	-	2	1.8
Renal	-	-	2	3	2	1.8
Orbital	-	-	1	2	1	0.8
Laryngeal (2vocal cords, 1tonsil)	-	-	3	6	3	2.6
Total	61	100	56	100	117	100

**Diagnosed at autopsy*

Discussion

The present study has demonstrated a more than two folds increase in the annual rate of HIV/PTB in our centre during the last 5 years. This confirms earlier report from Lagos and Jos, Nigeria of a rising trend of HIV/PTB in the country [16,17]. High level of poverty associated with deplorable living standard of Nigerians were the implicated factors [12,18]. Active measures that will strengthen the national tuberculosis control programme and also improve the welfare of average Nigerians are urgently required to reverse this trend.

Incidence of HIV-associated EPTB in this report was about 21% majority of the cases manifested as tuberculous pleurisy with effusion, tuberculous meningitis, miliary TB of the lungs and genital TB in a decreasing order. This was in tune with similar reports [4,14,20] in the continent that have established TB of the pleura with bilateral effusion as the commonest form of EPTB in Africa. However, the higher Mycobacterial load reported in HIV positive cases in one of the reports [14] was not found in this study, all the pleural fluid smears for AAFB in both HIV positive and negative cases turned out to be negative for tubercle bacilli. HIV/EPTB manifest commonly as tuberculous adenitis and skeletal TB in the advanced countries [6,19], but more of these cases were HIV negative in our report, this probably suggest interplay of other immunosuppressive conditions other than HIV infection in these patients. Poverty and malnutrition could readily fit in to this assumption. Mixed presentation of pulmonary and extra pulmonary TB in the same patient was observed to be 3 times more common in the HIV positive cases; 44.3% compared to the HIV negative ones; 19.6%, same for miliary TB of the lungs which was about four times more prevalent amongst the HIV positive cases; 15% vs. 3%. The location and pattern of distribution of TB in these patients was a measure of their respective level of immunity; pulmonary manifestation had the highest CD4$^+$ cells count of 135.8cells/ul while extra pulmonary cases had a lower value of 111.4 cells/ul and values less than 100 cells/ul were recorded for cases with mixed presentation and miliary disease of the lungs: 88cells/ul and 93cells/ul respectively. These values are lower compared to the suggested laboratory AIDS defining value of 163cells/ul in Nigeria [21]. However, it did confirm HIV/PTB co-infection as one of the earliest opportunistic infections that herald onset of depletion of CD4$^+$ cells, the index of a patient's level of immunity [22]. It also revealed that HIV/EPTB occurred at a much advanced level of HIV illness i.e. much lowered level of CD4$^+$ count [23].

In conclusion, the incidence of HIV-associated PTB is high and the trend is rising in this institution, HIV/EPTB are also quite common. Miliary TB of the

lungs and mixed pulmonary and extra pulmonary manifestation are common features of advanced HIV illness.

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