Baseline chest radiographic features among antiretroviral therapy naïve human immuno-deficiency virus positive children in a pediatric care program

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ABSTRACT

Background: Pulmonary diseases are commonly seen in children with HIV infection, and their etiology is often unclear. The radiological appearances of these conditions are often non-specific. Conventional radiographs play an important role in the management of chest conditions especially in resource poor settings. **Objective:** This retrospective study was carried out to determine the chest radiographic pattern in children with HIV infection. **Materials and Methods:** The baseline chest X-ray of 150 HIV-positive but antiretroviral drug naïve children were analyzed between July 2008 and December 2009 at the University College Hospital in Ibadan, south-west Nigeria. All children were screened for tuberculosis (TB) by one or combination of mantoux, acid-fast Bacilli (AFB) sputum, and erythrocyte sedimentation rate. The CD4 count was also taken as part of baseline laboratory test. Chi-squared test was used to determine association between the pattern of chest X-ray findings, and sex, age, and CD4 counts. **Results:** The mean age of the study group was 51.6 months, with children older than 5 years dominating and there was no statistical difference in the sex distribution. A total of 115 children (76.7%) had abnormal chest X-ray, with lymphadenopathy accounting for 45.3% followed by parenchymal lesions with 37.3%, miliary shadows, and cavities accounted for 6.7% and 2.6%, respectively. Cavities were found to be common in patient who tested positive to AFB than AFB-negative patients. Other findings like reticulonodular or diffuse patterns, lymphadenopathy, pleural effusion, or soft tissue swelling were also commoner in the AFB-positive patients. The CD4 count was available for 42% of the patient and there was no significant association between the chest radiographic changes and the CD4 count. **Conclusion:** Definitive diagnosis of pulmonary disease might be difficult based on chest X-ray alone, however, chest X-ray is a basic radiological test and almost the easiest to perform in both resource poor or rich setting and it is still recommended that routine chest X-ray should remain part of investigation of HIV-positive children to serve as adjunct to other investigations in early detection of TB.

Key words: Chest X-Ray; HIV; pediatrics

Introduction

Human immuno-deficiency virus (HIV) infection has generated lot of interest in the past three decades and still remains a serious health problem. The first diagnosed case of acquired immune deficiency syndrome in Nigeria was diagnosed in 1986.[1] Since then both the incidence and prevalence have been on the increase[1] and by 2008, it had caused over 25 million deaths worldwide with profound demographic changes especially in sub-Saharan Africa. Globally, the number of children younger than 15 years living with HIV increased from 1.6 million (1.4-2.1 million) in 2001 to 2.0 million (1.9-2.3 million) in 2007 with about 1000 new infections per day in children under 15 years. Almost 90% of these children live in sub-Saharan Africa.[2,3]

Pulmonary diseases are commonly seen in children with HIV infection, and the etiology is often unclear. Therefore treatment decisions are frequently based on the clinical findings and those of chest radiographs.[4,5] Chest infections are the commonest causes of pulmonary abnormalities seen on chest X-ray in children with HIV infection[6] and most of these patients succumb to the respiratory infection during the course of their illness.[3,6,7] The radiological appearance of pulmonary infection in HIV-infected children is often

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non-specific and variable.[8] Common pulmonary infections encountered include *Mycobacterium tuberculosis* (TB), bacterial pneumonia, pneumocystis jiroveci pneumonia, and lymphocytic interstitial pneumonitis.[9,10] Others include mycobacterium avium complex, cytomegalovirus, respiratory syncytial virus, para influenza virus, and fungal infections (Cryptococcus, Aspergillus SPP, Ibadan).

Conventional chest radiography plays an important role in the diagnosis, management, and monitoring of response to treatment especially in resource poor settings.[4,5,10,11] In addition, proper interpretation of radiographic findings could assist in narrowing the list of potential pathogens and determining appropriate diagnostic procedures such as broncho-alveolar lavage, transbronchial biopsy, or open biopsy.[8,12]

This study evaluated the baseline chest radiographic features seen among antiretroviral therapy (ART)-naïve HIV-positive children and compared these findings with their ages, acid-fast Bacilli (AFB) status, and CD4 percentages.

Materials and Methods

Chest X-rays performed at the Department of Radiology as part of the routine baseline investigation for children who were presented at the Pediatric Infectious Diseases unit of the University College Hospital, Ibadan between July 2009 and December 2010 were reviewed. The hospital being a tertiary referral referral center for many states in the south west as well as other parts of Nigeria is one of the treatment centers for HIV, funded by the Nigerian Government and the President's Emergency Plan for AIDS Relief (PEPFAR).

HIV diagnosis was based on positive rapid diagnostic tests confirmed by positive HIV DNA polymerase chain reaction in children less than 18 months and a positive Western Blot in children older than 18 months. Caregivers had HIV pre-test counseling. History and clinical examination were conducted in all patients followed by laboratory investigations which included CD4 count and routine screening for TB in accordance with the National Pediatric ART guideline (Federal Ministry of Health. National Guidelines for Pediatric HIV and AIDS Treatment and Care 2007 Abuja).

Antero-posterior or postero-anterior (as appropriate for age) radiographs were obtained by experienced radiographers with General Electric MS-185 basic machine (Waukesha, WI, USA) in the antero-posterior projections using a range of 65-74 kVp and 8-16 mAs, depending on patient age, with a film focus distance of 150 cm. The radiographs were interpreted independently by two radiologists who already agreed on the mode of reporting using a data collection form. A kappa agreement of 0.95 was obtained during the pilot reporting exercise. Where there were discrepancies in the report, the two radiologists came together to reach a consensus.

All the patients were ART-naïve and were screened for TB by combination of clinical features, Mantoux test, and gastric washing or sputum microscopy for AFB and erythrocyte sedimentation rate (ESR). Mantoux test result of ≥5 mm was interpreted as positive. The biodata indication for chest X-ray and its findings were documented. Ethical approval was obtained from the joint University of Ibadan and University College Hospital Ethical committee and consent was obtained from the parents/caregivers. Data were analyzed using SPSS software version 16.0 by SPSS Inc. Chicago, Il, USA. Simple frequency distribution was performed for the social characteristics of patients. Chi-squared test was used to determine association between the pattern of Chest X-ray findings and sex, age, AFB, and CD4 counts. The level of statistical significance was set at 0.05.

Results

A total of 150 children were studied. Their ages ranged between 3 months and 14 years with a median of 36 months.

Socio-demographic characteristics

Table 1 shows the age and sex distribution of the children studied. There were 89 males and 61 females (1:1.5). The proportion of children less than 1 year was 16.7%, those aged 1-3 years was 24.7%, 3-5 years was 22.7% and those above 5 years was 36%. The age distribution for males and females appeared similar.

Pattern of chest radiographic features

There were 115 patients (76.7%) with abnormal radiographs. The pattern of radiographic findings is shown in Table 2.

Parenchymal lesions were found in 56 patients (37.3%), of these 17 patients (11.4%) had reticulonodular lesions on one side only, whereas 11 (7.3%) had bilateral lesions. Patients who (13.4%) had homogenous opacities were 20 out of which 13 (8.7%) had on the right side. None of the children had bilateral homogenous lesions. Patients who had widespread diffuse lesions were 10 (6.7%) of which 7 (4.7%) had unilateral and 3 (2.0%) had bilateral lesions. Bilateral perihilar lymphadenopathy was the most frequent pattern of adenopathy seen on X-ray, which was present in 32 (21.3%) children. Hilar lymphadenopathy was found in 30 children (20.1%) of which 7 of them exhibited bilateral adenopathy [Figure 1]. Mediastinal lymphadenopathy was found in only 5 (3.3%) children. A miliary pattern and soft

Table 1: Age and sex distribution of children studied

Age group (years)	Male (%)	Female (%)	Total
<1	16 (18.0)	9 (14.8)	25 (16.7)
1-<3	21 (23.6)	16 (26.2)	37 (24.7)
3-<5	19 (21.3)	15 (24.6)	34 (22.7)
≥5	33 (37.1)	21 (34.4)	54 (36.0)
Total	89 (100.0)	61 (100.0)	150 (100.0)

tissue wasting was found in 6.7% and 8% of all children, respectively, whereas the least common findings were cavitations (4, 2.6%) and pleural effusion (3, 2%) [Figure 2].

Comparison of radiographic features with age

The differences in proportions of different age groups with the radiographic findings are shown in Table 3. Generally, chest abnormalities were less frequent within the first year of life. Infants who had an abnormal chest radiograph were 60% compared to 82% among those aged between 1 and 5 years and 77.8% among those aged ≥5 years. The difference was not significant at 5% but it was at 10% level (P=0.085). There was a significantly higher proportion with lymphadenopathy at older ages. Infants who had lymphadenopathy on chest radiograph (P=0.042) were 4% compared to 28.2% of children between the age of 1 and 5 years and 25.9% of children above 5 years The proportion with soft tissue wasting was about 4.2% in subjects less than 5 years but greater than a year, and 16.7% among those who were 5 years and above. Soft-tissue wasting was not noted in those less than 1 year.

Table 2: Pattern of radiographic findings among children studied

Radiographic finding	Frequency	%
*Parenchymal n=56 (37.3%)		
Reticulonodular		
Right only	13	8.7
Left only	4	2.7
Bilateral	11	7.3
Homogenous		
Right only	13	8.7
Left only	7	4.7
Bilateral	0	0.0
Widespread or diffuse		
Right only	0	0.0
Left only	7	4.7
Bilateral	3	2.0
*Lymphadenopathy n=68 (45.3%)		
Hilar		
Right only	13	8.7
Left only	10	6.7
Bilateral	7	4.7
Perihilar opacities		
Right	4	2.7
Left	2	1.3
Bilateral	32	21.3
Mediastinal	5	3.3
Pleural effusion		
Right only	1	0.7
Left only	2	1.3
Bilateral	0	0.0
Cavities/Cystic changes	4	2.6
Miliary TB	10	6.7
Soft tissue wasting	12	8.0

*More than one pattern was found in some children hence the frequencies of the subtypes exceeds the total for this group

This difference was statistically significant (P=0.011). No significant differences were found for the other radiographic findings.

Mantoux test results

Mantoux test was carried out on 126 patients out of which 4 (3.1%) were positive.

Radiological features versus AFB status

A total of 30 children (20%) were found to be AFB positive. Table 4 shows the difference in the pattern of radiological findings between those with positive results on AFB and those who tested negative. There was a significantly higher proportion of patients with cavitations among those with positive AFB results compared with those who tested negative (P=0.005). In addition, the proportions of children with reticulonodular or diffuse patterns, lymphadenopathy, pleural effusion, or soft tissue swelling were more common among those with positive AFB results but these differences were not statistically significant at 5% level.

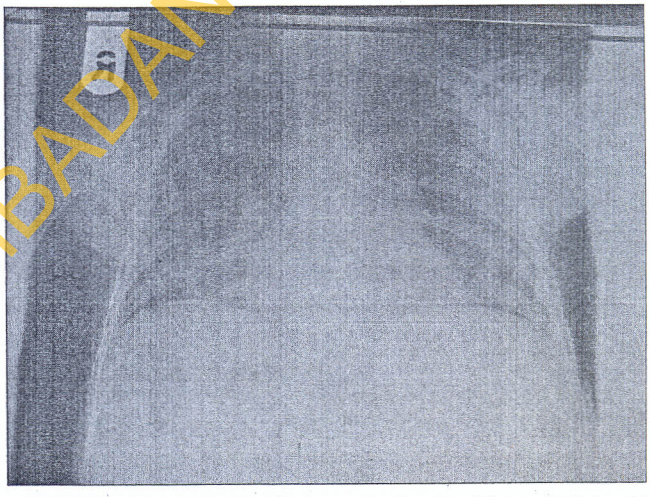

Figure 1: Postero-anterior radiograph showing bilateral hilar and axillary lymphadenopathy

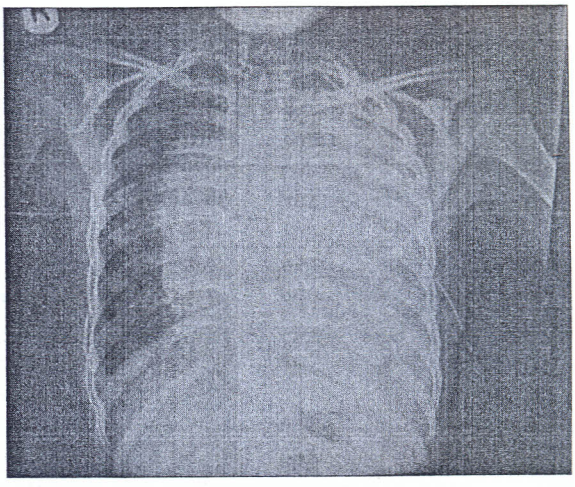

Figure 2: Postero-anterior chest X-ray showing right lung collapse with left pleural effusion

Radiological features and CD4 levels

The differences in pattern of radiograph findings at different CD4 levels are shown in Table 5. CD4 counts were available for only 63 children. There were no significant differences in any of the pathologies at 5%.

Discussion

In the cohort of the HIV-positive children studied, the median age was 36 months and 64% was aged less than 5 years. This may be as a result of an increasing awareness about HIV resulting in more cases being diagnosed in very young children. In addition, treatment and care have become more readily available so that caregivers may be coming out more readily for medical care of their children. In studies carried out by Balogun *et al.*[13] in Lagos and Bugaje and Aikhionbare[14] in Northern Nigeria, there were many more children over 5-year age group. The difference in the age distribution between children in their studies and the present study could be as a result of the fact that those studies were carried out many years before organized pediatric HIV care programs commenced in the country. Similarly, some other studies in India reported a smaller proportion of younger children in their cohorts of HIV-positive children.[15-17] HIV infection in children may also be misdiagnosed as its manifestation may be similar to other diseases that are endemic in the developing countries and young children with perinatally acquired HIV infection without intervention have a short survival period.[2,18] There was no statistical difference in the sex distribution of the patients in this study as the male: female ratio was 1:1.45. This is in agreement with other studies carried out elsewhere,[13,19-21] but at variance once again with the study by

Table 3: Age differences in the proportions with the radiographic findings

Lesion	Age (years)			Chi-square	*P* value
	< 1yr (%) N=25	1 – < 5 yrs (%) N=71	≥5 yrs (%) N=54		
Abnormal chest X-ray	60.0 (15)	81.7 (58)	77.8 (42)	4.921	0.085
Reticulonodular	8.0 (2)	15.5 (11)	31.5 (17)	5.297	0.071
Homogenous	8.0 (2)	19.7 (14)	7.4 (4)	4.761	0.092
Diffuse	4.0 (1)	8.5 (6)	5.6 (3)	0.756	0.685
Lymphadenopathy	40.0 (10)	50.7 (36)	50.0 (27)	0.842	0.657
Pleural effusion	0.0	2.8 (2)	1.9 (1)	0.758	0.685
Cavities	0.0	1.4 (1)	5.6 (3)	2.854	0.240
Miliary TB	0.0	11.3 (8)	3.7 (2)	4.963	0.084
Soft tissue wasting	0.0	4.2 (3)	16.7(9)	9.059	0.011

Table 4: Comparison of radiograph findings among children with HIV based on AFB status

Lesion	AFB result		Chi-square	*P* value
	Positive N=30 (%)	Negative N=120 (%)		
Abnormal chest X-ray	26 (86.7)	89 (74.2)	2.096	0.148
Reticulonodular	7 (23.3)	23 (19.2)	0.538	0.463
Homogenous	3 (10.0)	17 (14.2)	0.361	0.548
Diffuse	3 (10.0)	7 (5.8)	0.670	0.413
Lymphadenopathy	17 (56.7)	54 (45.0)	1.944	0.163
Pleural effusion	1 (3.3)	2 (1.7)	0.340	0.560
Cavities	3 (10.0)	1 (0.8)	7.770	0.005
Miliary TB	1 (3.3)	9 (7.5)	0.670	0.413
Soft tissue wasting	4 (13.3)	8 (6.7)	1.449	0.229

Table 5: Comparison of radiographic findings at different CD4 counts

Lesion	CD4 %		Chi-square	*P* value
	<15 N=30	≥15 N=33		
Abnormal chest X-ray	22 (73.3)	29 (87.9)	2.156	0.142
Reticulonodular nodular	6 (20.7)	29 (6.1)	0.010	0.922
Homogenous	3 (10)	6 (18.2)	3.508	0.061
Lymphadenopathy	15 (50.0)	7 (21.2)	0.014	0.905
Pleural effusion	1 (3.3)	0 (0.0)	1.118	0.290
Cavitatory changes	3 (10)	0 (0.0)	2.272	0.132
Miliary TB	2 (6.7)	1 (3.0)	0.458	0.498
Soft tissue wasting	2 (6.7)	3 (9.1)	0.126	0.722

Bugaje and Aikhionbare[14] in which there were more males than females (2.1:1). This difference might be attributed to varying cultural practices in which more attention may be given to the survival of a male child than a girl child, hence male children may be given better medical attention by their parents.

With regards to chest radiographic features, 76.7% of the patients in this study had abnormal chest findings which is in keeping with studies carried out in Spain and Uganda,[22,23] and this has been attributed to the fact that the lung is frequently the site for secondary infections in children with HIV wherein greater than 70% suffer from at least one episode of respiratory infection during the course of illness. However, this is different from the findings in an adult population from the same environment where only 35.5% of the patients presented with abnormal chest radiographic findings,[24] further corroborating the fact that children with HIV tend to present more often with pulmonary infection than adults with HIV.

The present study further highlighted the differences in age with regards to presence of abnormal chest radiographic findings in the children. The highest number was recorded in children below 5 year. This reiterates the importance of giving early treatment and care to prevent mortality in this age group, this is similar to reports from other countries with heavy HIV burden where one-third of deaths among children with HIV was below 5 years.[2] In below 5-year group, it is surprising that the least number of abnormal radiographic features was found among the infants compared with the older age groups. This could be due to the fact that younger children have a more aggressive disease and shorter survival than older children with HIV infection. Generally, pulmonary lesions were found more commonly on the right, lymphadenopathy being the commonest presentation, followed by reticulonodular, focal consolidation, and diffuse opacities [Table 2]. This finding is similar to the common findings in children with HIV from other studies.[7,25-26] It has been suggested that this disparity in the chest radiographic presentation between adults and children with HIV is probably due to ineffective cell-mediated autoimmune response as a result of immature cells in children.[27]

As was the routine practice in the program, the patients were screened for TB out of which 30 patients were confirmed to have TB. Out of the 126 patients who underwent mantoux test, 4 (3.1%) were found to be positive which was much lower than the findings by Brahmbhatt *et al.*[28] This finding is not unexpected, as the diagnosis of TB in children with HIV infection has posed challenges to researchers.[29,30] TB is the most common opportunistic infection in HIV-positive patients as childern acquire the disease through contact with infected adults.[30] This study as in other studies showed that the different non-radiological methods of establishing PTB in children is laden with many flaws and surrounded by considerable uncertainty. It is difficult to obtain sputum from children therefore gastric aspirate is used as an alternative to sputum for identification of AFB. The yield of mycobacterium TB from sputum or gastric washing is poor. Although an elevated ESR may be expected in children with TB, a recent study found that one-third of children with TB had a normal ESR at the time of diagnosis suggesting little value in using ESR as a diagnostic test for childhood TB.[31]

In a study by Temiye, *et al.* in Lagos that involved 124 HIV-positive children less than 15 years of age, co-infection with TB was the most common associated illness and more than a quarter of all the cases were affected. In addition none of the patients tested were positive to Mantoux test, and only 2 out of the 32 cases managed for TB had positive gastric washings for TB.[32] Computerized tomography (CT) has higher pick up rate of pulmonary disease than chest X-rays.[7,33] Although it is often difficult to diagnose the TB based on abnormal chest radiograph alone, the high incidence of TB in patients with HIV has been well documented, HIV-positive children are at risk of acquiring the disease from their adult contacts.[31] The radiological presentation of pulmonary TB has been reported to be similar to that of HIV non-infected children, but the response to treatment is poorer, just as the tuberculin test yields poor results.[4,30] Cavitation has been implicated as the most important radiologic finding in post-primary disease. Cavitation implies a high bacillary burden, high infectivity, and is associated with numerous complications including endobronchial spread, tuberculous empyema, and hematogenous dissemination.[10] This significant finding in this study may be due to resurgence of TB in these patients when they became immunocompromised.

There was no significant statistical difference in the chest radiographic pattern between children with different levels of immunosupppression. This aspect of the data should however be interpreted with caution as CD4 percent results were obtained in less than half of the patients. CD4 lymphocytes are the primary cellular target for HIV infection. Pneumocystis jiroveci pnuemonia and other opprotunistic infections involving the lungs are more prevalent at lower CD4 counts whereas the radiological appearance of bacterial pneumonias is unaffected by the immune status.[29] It has been shown that the risk of TB as co-infection in children with HIV is four times higher when the CD4 cell percentage is less than 15% than in children with CD4 cell percent of greater than 15%.[34]

This study being retrospective has some limitations including incomplete data of some of the patients, and also that lateral chest radiograph could not be conducted for those patients with lymphadenopathy so as to complement the AP radiographs, thereby increasing pick up rate. CT which is the gold standard examination for investigating chest diseases especially when radiographic findings are equivocal could not be performed mainly due to the high cost. Further studies are needed to prospectively document the various

radiographic patterns and prevalence of lymphadenopathy in HIV-positive children.

Conclusion

Abnormal chest radiographs were recorded in a large percentage of the HIV-positive children. The commonest features were lymphadenopathy, reticulonodular opacities, and diffuse opacities, whereas cavities were significantly higher in patients who were confirmed to have TB. In a resource poor setting, routine chest radiographic screening at presentation is useful for the early detection and treatment of pulmonary disease which is the main cause of mortality in HIV-positive children.

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