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Clinical and Immunological Profile of Pediatric HIV Infection in Ibadan, Nigeria

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Abstract

In spite of the increasing number of children living with HIV in Nigeria, published data on their clinical profile are few. We describe the clinical profile at presentation of HIV-infected children at the University College Hospital, Ibadan, in a prospective study. Among 272 children studied (149 [54.8%] males; mean age 4.2 years [range 2 months to 15 years]), infection was acquired through vertical transmission in 252 (92.6%), blood transfusion in 5 (1.80%), and undetermined routes in 15 (5.5%) cases. Clinical features included weight loss (62.5%), prolonged fever (55.4%), generalized lymphadenopathy (48.6%), chronic cough (45.4%), and persistent diarrhea (28.3%). Tuberculosis was present in 45.3%, World Health Organization (WHO) clinical stages 3 and 4 disease in 70.6% and severe immunosuppression in 44.5% of cases. Pediatric HIV in Ibadan is acquired mainly vertically and most cases present with severe disease. Improved access to prevention services and early diagnosis are recommended.

Keywords

pediatric HIV, clinical profile, tuberculosis, co-infection, Nigeria

Introduction

Globally, there were an estimated 33.4 (31.1-35.8) million people living with HIV in the year 2008, including 2.1 million children younger than 15 years.[1] Sub-Saharan Africa remains the region most heavily affected by HIV and accounted for 68% of new HIV infections among adults and 91% of new HIV infections among children in the year 2008.[1] Nigeria is Africa's most populous country, with a population of 140 million in 2006. Although the HIV prevalence rate in Nigeria appears low (4.6% among antenatal clinic attendees in 2008), the country ranks second in terms of actual number of people infected with HIV after South Africa.[2] The number of children living with HIV in Nigeria increased from 150 000 in 2001 to 220 000 in 2007.[3]

Considering the burden of the disease in the country, the clinical profile of infection in children has not been sufficiently described. Published data on the clinical profile of pediatric HIV in the country are few and the number of patients often small.[4-7] In addition, HIV infection in infants was often diagnosed using enzyme-linked immunosorbent assay (ELISA) and Western blots, which are less specific for detection of the infection in this age group because of the transfer of maternal antibodies to babies. In addition, there is conflicting information on the rates of various modes of transmission of the virus in the pediatric population.[4,5,8] With an improving national response to the pandemic, leading to the availability of facilities for proper diagnosis of the infection in children and accrual of larger numbers of patients, it is important to describe more clearly the profile of pediatric HIV infection in Nigeria. The objectives of this study were to describe the clinical and immunological features at presentation as well as modes of transmission of HIV infection in children seen at the University College Hospital (UCH), Ibadan.

Participants and Methods

This was a descriptive study of cases of HIV infection seen at the Pediatric Infectious Disease Clinic of the UCH, Ibadan, between January 2006 and October 2008. The UCH is a tertiary

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hospital situated in Ibadan, south-western geopolitical zone of Nigeria. It serves as a referral center for HIV care in Oyo state, in which it is situated, and neighboring states. The clinic provides care including antiretroviral therapy for HIV-infected children and is sponsored by the Government of Nigeria and Harvard PEPFAR (the United States President's Emergency Plan for AIDS Relief) program. Ethical approval was obtained from the Joint University of Ibadan/UCH Ibadan Institutional Review Committee. With regard to patient enrollment, some patients presented at the clinic with symptoms suggestive of HIV infection, whereas others were diagnosed following case finding among children of patients in the adult HIV care program. Since July 2007, some cases have been diagnosed following Provider Initiated Counseling and Testing offered to all children presenting at the hospital for various complaints.

Initial laboratory diagnosis of HIV infection among children $\geq$18 months was done using a fourth-generation ELISA (Genescreen, Biorad, Paris, France). All ELISA reactive samples were then confirmed by Western immunoblot. However, infection among children <18 months was established using a commercially available HIV DNA polymerase chain reaction kit (Roche amplicor, Roche molecular systems, Inc., Branchburg, NJ, USA). All assays were performed according to the manufacturer's recommendation. CD4 counts were also done for all patients at diagnosis and periodically during follow-up.

Demographic and clinical information were entered onto a case record form. Chronic cough was defined as an unremitting cough that is not improving and has been present for more than 21 days,[9] persistent diarrhea as persistent loose or watery stools 3 or more times daily lasting for 14 days or more, prolonged fever as unexplained persistent fever (intermittent or constant, for longer than 1 month), and generalized lymphadenopathy as enlargement of lymph nodes involving 2 or more noncontiguous sites.[10] Children whose mothers were HIV positive and in whom no other risk factor for HIV infection was identified were classified as having been infected vertically. Children with antecedent history of blood transfusion whose mothers were HIV negative were assumed to have acquired the infection through blood transfusion. Clinical stage at diagnosis was based on the World health Organization (WHO) clinical stages of Pediatric HIV.[10] Immunological status was based on WHO age-appropriate absolute CD4 count thresholds for severe immunosuppression.[10] Diagnosis of tuberculosis (TB) was based on WHO guidelines for national TB programs for children; cases were either smear positive or smear negative with clinical, radiologic features, and, where possible, cytologic features suggestive of TB and response to anti-TB drugs.[9]

Data Management

Data was analyzed using the Statistical Package for Social Science version 15.0. Means, medians, and standard deviations were computed for continuous variables and frequencies for categorical variables. Associations of categorical variables were tested with chi-square and statistical significance set at $P < .05$.

Table 1. Clinical Features at Presentation

Clinical Feature (n = 272)	Frequency	Percentage
Weight loss/failure to thrive	157	62.5
Prolonged fever	139	55.4
Generalized lymphadenopathy	122	48.6
Chronic cough	114	45.4
Persistent diarrhoea	71	28.3
Oral candidiasis	50	19.9
Papular pruritic eruptions	49	19.5
Otitis media	39	15.5
Parotid swelling	18	7.2
Seborrheic dermatitis	11	4.4
HIV encephalopathy	8	2.9

Results

A total of 272 children were enrolled in this study, comprising 149 (54.8%) males and 123 (45.2%) females. Their ages ranged from 2 months to 15 years, with a mean (standard deviation [SD]) of 4.2 (3.50) years and a median of 3 years at presentation. In all, 45 (16.5%) children were aged less than 1 year, 130 (47.8%) were between 1 and less than 5 years, and 97 (35.7%), 5 years and more, at presentation and diagnosis.

Mode of Transmission

The mode of infection was mother-to-child transmission in 252 (92.6%) cases and through blood transfusion in 5 (1.8%) cases. The mode of infection was uncertain in 15 (5.5%) cases including children from orphanages and some orphans whose mothers died of undiagnosed illnesses.

Clinical Features

Common clinical conditions at presentation included weight loss or failure to thrive (62.5%), prolonged fever (55.4%), generalized lymphadenopathy (48.6%), chronic cough (45.4%), persistent diarrhea (29.5%), and oral thrush (19.9%; Table 1).

Tuberculosis Co-Infection

Tuberculosis was present in 123 (45.2%) cases at diagnosis. Among the children with HIV/TB co-infection, pulmonary TB (with or without involvement of extrapulmonary sites) was present in 87% of cases and extrapulmonary TB alone in 13% of cases. The rate of HIV-TB co-infection was highest (55.7%) among children aged 6 to 10 years and lowest (41.9%) among those aged 0 to 5 years (Table 2). Chi-square for linear trend was not statistically significant (χ^2 0.485, $P = .486$).

Clinical and Immunological Classification

Late stage disease (WHO clinical stages 3 and 4) accounted for 70.6% whereas severe immunosuppression was present in 44.5% of cases at diagnosis (Table 3).

Table 2. Age Distribution of Tuberculosis Among HIV-Positive Children

Age Group (years)	No. Enrolled	No. of Tuberculosis Positive	% Tuberculosis Positive
0-5.0	191	80	41.9
>5-10	61	34	55.7
>10-15	20	9	45.0
Total	272	123	45.2

Table 3. World Health Organization Clinical Stages and Immunological Classification of Children at Presentation

Parameter		Frequency	Percentage
Clinical stage	1	53	19.5
	2	27	9.9
	3	102	37.5
	4	90	33.1
	Total	272	100
Immunological classification	Severe immunosupression	121	44.5
	Nonsevere immunosupression	151	55.5
	Total	272	100

Nutritional Status

A total of 173 (63.6%) children were malnourished. Among the malnourished children, 90 (52.0%) had severe immunosuppression compared to 31 (31.3%) of the 99 children with normal weight. Malnutrition was associated with an increased risk of severe immunosuppression ($\chi^2 = 10.936$, $P = .001$).

Among children aged 5 years or less, 1 (0.5%), 46 (24.6%), and 70 (36.6%) had kwashiorkor, marasmus, and were underweight, respectively, whereas only 74 (38.7%) were of normal weight at diagnosis of HIV infection.

Discussion

The age distribution of our patients is similar to the findings by other workers, with the majority of patients being less than 5 years of age.[5,6,11] The proportion of children who presented and were diagnosed before 1 year of age (16.5%) was, however, small and indicates late diagnosis. This may be as a result of lack of facilities for early infant diagnosis in many centers in the country. Another outcome of delayed diagnosis of HIV in Nigerian children is presentation in late stages. In our study, 70.6% of the children presented with features of WHO clinical stages 3 and 4 indicative of advanced and severe disease, respectively, whereas severe immunosuppression was present in 44.5% of cases at diagnosis. Similarly, Ugochukwu in Nnewi, Nigeria, observed that 82% of children were diagnosed at clinical stage 3 and 55.7% had severe immunosuppression.[6]

Recent data support early initiation of antiretroviral therapy (ART) in infants. In the Children with HIV Early Antiretroviral Therapy (CHER) trial, initiation of ART in infants irrespective of clinical stage or CD4 counts was shown to reduce early infant mortality by 76% and HIV progression by 75%, when compared to deferred initiation based on clinical and immunological parameters.[12] More than one third of deaths occurred at home, before caregivers recognized the need for medical attention and in 90% of deaths, there were no antecedent Centers for Disease Control (CDC) stage C or severe stage B events, and the infants died rapidly from the first significant clinical event. Early infant diagnosis and early commencement of treatment should, therefore, be readily accessible to reduce disease progression and mortality in HIV-infected children.

Knowledge of the mode of acquisition of an infection is important for planning prevention and control strategies. Worldwide, the predominant mode of pediatric HIV infection is through vertical transmission, accounting for over 90% of cases.[13] Although most reports from Nigeria have indicated vertical transmission as being the predominant mode of infection, some have indicated a relatively high contribution from blood transfusion. The latter reports include 68% in Enugu, south eastern Nigeria in 1998, 14.3% in south western Nigeria in 2003, and 16.4% in Nnewi South eastern Nigeria in 2006.[4-6] In our study, 92.6% of infections were acquired vertically and 1.8% through blood transfusion, in accordance with the findings from Abuja and Sokoto in Nigeria, with over 90% acquired through vertical transmission and less than 5% through blood transmission.[7,14] A study from Dakar,[15] Senegal, revealed that 99% of pediatric HIV infections were vertically acquired, whereas another study from India[11] reported that 88.66% of infections were vertically acquired and 11.57% acquired through blood transfusion. Although continuing efforts aimed at ensuring blood safety especially in states with a high rate of transfusion-acquired HIV, there is need to improve the access to prevention of mother-to-child transmission services in the country.

The predominant clinical features at presentation in our patients were weight loss or failure to thrive, prolonged fever, persistent generalized lymphadenopathy, and chronic cough, in accordance with the findings by other workers.[4,16] Other important features observed in our study and corroborated by other workers include chronic cough, persistent diarrhea, oral thrush, and skin manifestations.[6,17] These clinical features are important in raising suspicion of HIV infection and therefore screening in centers where provider-initiated HIV counseling and testing is not offered routinely.

HIV is a major factor driving the resurgence of TB; incidence rates of TB in countries with high HIV prevalence have increased appreciably.[18]

Most of the TB cases in children occur in infants and children <5 years of age. The age range of 5 and 14 years has often been called the "favored age" because in this age range children have the lowest rates of TB.[19] Our data show a continuation of a high prevalence of TB beyond 5 years, contrary to the expectation in the normal population. This is probably a resultant effect of HIV since children with HIV infection may be at

increased risk of progressing from TB infection to disease. A previous report on all cases of TB from our center showed that majority of the cases were in the 5- to 10-year age group with 2 peak ages at 5 and 10 years, respectively.[20] Although HIV status of children in the latter study was not known, the author attributed changes observed to be possibly due to the impact of the HIV pandemic.

In various studies in India, 29% to 38% of children with HIV infection had been diagnosed with TB.[11,17] These figures are lower than 45.2% observed in our study. Pol in a study of opportunistic infections in HIV-infected children aged 18 months to 12 years observed a TB co-infection rate of 38%.[17] Considering the high incidence of TB in infancy, exclusion of children younger than 18 months in their study might have contributed to a lower TB co-infection rate than in our study. Other possible causes of wide variability include differences in the TB burdens among adults in each community and difficulties in the definitive diagnosis of TB in children. Prevention and early diagnosis and treatment of TB are essential components of care of HIV-infected patients since the development of TB has been shown to accelerate the course of HIV infection through induction of HIV-1 replication.[21] The WHO recommends TB screening for all HIV-infected children and isoniazid preventive therapy for those infected with TB but asymptomatic.[10]

Malnutrition often accompanies HIV infection and is indicative of advanced and severe disease. The form of severe malnutrition most frequently seen in our patients was marasmus that accounted for 24.6% of children aged 5 years and less, whereas kwashiorkor was rare and represented only 0.5% of the children in the same age group. This is in accordance with previous findings in Burkina Fasso, which indicated that marasmus is the form of severe malnutrition most commonly associated with HIV.[22] The reason for this finding is not clear but may be related to differences in the pathogenesis of the different forms of malnutrition.

Limitation

Although the CD4 percentage is believed to be more valuable than CD4 counts in children under 5 years of age, not all patients had CD4 percentage done at diagnosis. Therefore, CD4 counts were used in this study.

Conclusion

HIV infection is an important problem in Nigeria, and the main route of acquisition in children is by vertical transmission. Presentation is frequently late as most children already have advanced or severe disease at diagnosis and a large proportion are severely immunosuppressed. The predominant clinical features at presentation were weight loss or failure to thrive, prolonged fever, persistent generalized lymphadenopathy, and chronic cough. Tuberculosis co-infection needs to be looked out for in HIV-infected children.

Declaration of Conflicting Interests

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