ARTICLE

HIV-related oral candidiasis in Nigerian children: A marker of HIV disease progression

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Background. Opportunistic infections such as oral candidiasis (OC) in HIV-infected children are generally seen with severe depression of the CD4+ count.

Objectives. To evaluate usefulness of OC as a marker of disease progression in HIV-infected Nigerian children.

Method. Newly diagnosed HIV-infected children, antiretroviral therapy (ART)-naïve with oral lesions, attending a paediatric infectious diseases unit in Nigeria from July 2006 to June 2007 were enrolled. Clinical OC was registered if the attending physicians observed a pseudomembranous oral lesion. The Dynal beads technique (Dynal Biotech, Oslo, Norway) was used for CD4 counting. CD4 counts were categorised using the Centers for Disease Control and Prevention classification.

Results. The study population comprised 78 HIV-infected children aged 4 - 90 months (mean 20.54±7.23 months) with a male/female ratio of 1.05:1. The prevalence of OC was 20.5% (16 cases) in the study population. The median CD4 count of children with HIV-associated OC is within the severe immunosuppression level for age group, while all children without OC had median CD4 counts above the severe immunosuppression level for age group (p=0.000). Reliability of OC as a surrogate marker of severe immunosuppression yielded a modest sensitivity, high specificity and positive predictive value (44.44%, 92.15% and 75%, respectively).

Conclusion. The high prevalence of OC in HIV-positive children was confirmed. The significant relationship of OC with severe immunosuppression suggests that in settings in which CD4 counts are not available, OC may be considered as a clinical surrogate for severe CD4 depletion. However, the absence of OC does not necessarily exclude severe immunosuppression.

Paediatric HIV infection has been increasing in Nigeria over the years, with 74 520 new cases estimated for 2006.[1-2] Disease usually progresses faster and the outcome is more serious than in adults, resulting in a high mortality rate due to serious opportunistic infections (OIs).[2,3] For this reason, early prophylactic measures and specific antiretroviral therapy (ART) are mandatory. The absolute CD4+ lymphocyte count and percentage and more recently the plasma viral load have been considered the most reliable markers of disease progression in HIV-infected patients[3-4] and have been the basis for indicating ART as well as prophylaxis against OIs. However, these tests require resources and technical expertise, neither of which is routinely available in resource-poor settings such as Nigeria. The oral cavity is an important source of diagnostic and prognostic information in HIV-infected patients.[5] The importance of certain oral lesions, particularly candidiasis, as clinical indicators of HIV infection and markers of clinical progression to AIDS due to their association with CD4 cell count is well documented[5-6] and they may be valuable markers of disease progress in resource-poor settings. OC can be an early sign of illness or disease progression in HIV/AIDS and other immuno-compromised states.[5-7] Evidence from a carefully designed prospective longitudinal study on a Mexican cohort of HIV/AIDS patients not receiving ART revealed that the onset of OC and oral hairy leukoplakia was heralded by a sustained reduction in the CD4 cell count, with an associated sharp increase in viral load.[7] The prevalence of OC has been observed to increase with severity of HIV infection. In a study by Korting, 'the microbiological recoveries of OC from 62 HIV-infected adults were 57.5% for CDC stage I patients, 76.5% for stage II patients and 87.5% for stage III patients'.[8] OC in children has been less well studied, with only limited numbers of individuals examined. However, between 20% and 70% of children with HIV infection or AIDS have been reported to show clinical signs of OC.[9] This study aimed to evaluate OC as a marker of disease progression in HIV-infected Nigerian children.

Subjects and methods

Seventy-eight newly diagnosed HIV-infected children, antiretroviral-naïve with oral lesions, attending the paediatric infectious diseases unit at the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Nigeria, from July 2006 to June 2007 were enrolled. Ethical approval was obtained from the ethical committee of UMTH. Written consent for participation in the study was obtained from children's parents/caregivers. Their HIV status was confirmed by a Western blot test after an initial reactive enzyme-linked immunosorbent assay (ELISA) (Orgenic, Israel). The polymerase chain reaction (PCR) for HIV-1 DNA was used to confirm HIV status in children aged less than 18 months. On enrolment, a fill-in protocol detailing biodata, clinical history and physical examination was conducted for each of the patients with special emphasis on clinical features

of HIV. Clinical OC was registered if the attending physicians observed a pseudomembranous oral lesion. The Dynal beads technique (Dynal Biotech, Oslo, Norway) was used for CD4 counting. This technique uses paramagnetic polymer beads coated with anti-CD4 monoclonal antibodies to capture and isolate the CD4 from the blood. Other investigations done were directed by the clinical condition of the patients. Information obtained was entered onto a data sheet and analysed for correlation of CD4 count with presence or absence of OC. The degree of immunosuppression was based on the CD4 counts obtained from each child's medical report in accordance with the Centers for Disease Control and Prevention (CDC) immunological classification of paediatric AIDS: severe, moderate or absent.[10] Data were analysed using SPSS statistical software version 11. Means (± standard deviation (SD)), medians and percentages were used to express data and the chi-square test (x^2) was used for comparison. Tables were used for illustration where appropriate. A p-value of <0.05 was considered significant for all statistical comparisons.

Results

The study population comprised 78 HIV-infected children aged 4 - 90 months (mean 20.54±7.23 months). Of the 78 children, 40 (51.3%) were male and 38 (48.7%) female, with a male/female ratio of 1.05:1. The prevalence of OC was 20.5% (16 cases) among the study population. The relationship between OC and median CD4 count for the various age groups is shown in Table I. The median CD4 count of children with HIV-associated OC was within the severe immunosuppression level for age group, while all children with HIV infection without OC had median CD4 counts above the severe immunosuppression level for age group (x^2=23.130, DF=2, p<0.0001), classified

according to their degree of immunosuppression; 11 (68.75%) had severe and 5 (31.25%) moderate immunosuppression. No child had OC without immunosuppression. Reliability of OC as a surrogate marker of severe immunosuppression is shown in Table II. The sensitivity, specificity and positive predictive values were 44.44%, 92.15% and 75%, respectively.

Discussion

The prevalence of oral lesions in HIV-infected individuals is still high in developing countries and OC is the predominant oral lesion seen, with a prevalence ranging from 20% to 70%.[4-6,9] The 20.5% prevalence of OC in the present study supports these findings. Furthermore, the presence or absence of candidiasis in infected children may be directly related to the use of antiretroviral agents and the time of AIDS diagnosis.[11] All patients in this study were antiretroviral-naïve.

OIs in HIV-infected children are generally seen in patients with severe depression of the CD4 count.[5,6,9] It is therefore reasonable to assume that OIs reflect a severe drop in CD4 count, thereby making them a possible surrogate for CD4 cell count. An inverse relationship between CD4 counts and the prevalence of OC has been reported whether patients are on ART or not.[12] Korting[8] and Fong *et al*.[13] found that the microbiological recovery of OC in HIV-infected patients increases with advancing CDC stages. Similarly, the median CD4 count of patients with HIV-related candida ranged between 107 and 189 cells/µl in different studies.[14] The median CD4 counts within the severe immunosuppression ranges for age in our study verified these studies. Greenspan and Greenspan[15] also confirmed that the frequency of candidiasis increases as the CD4 count decreases, showing a relationship with the advance of HIV disease.

TABLE I. RELATIONSHIP BETWEEN CD4 COUNT (CELLS/µL) IN PATIENTS WITH AND WITHOUT ORAL CANDIDIASIS FOR VARIOUS AGE GROUPS

Age (years)	\multicolumn{2}{c}{Oral thrush present}		\multicolumn{2}{c}{Oral thrush absent}	
	N	CD4 count (median (range))		N	CD4 count (median (range))
<1	8	502* (201 - 780)		18	810 (404 - 10 960)
1 - 5	5	354* (244 - 660)		21	724 (377 - 890)
>5	3	184* (162 - 301)		23	481 (174 - 732)

*Severe immunosuppression (CDC).[10]

p<0.0001 (significant difference between the median CD4 cell counts of the children with and without oral thrush).

N = number of children.

TABLE II. RELIABILITY OF ORAL CANDIDIASIS AS A SURROGATE MARKER OF SEVERE IMMUNOSUPPRESSION

OC	\multicolumn{2}{c}{Severe immunosuppression*}	Total
	Present	Absent	
Positive	12	4	16
Negative	15	47	62
Total	27	51	78

*CDC classification.[10]

Sensitivity = 44.44%, specificity = 92.15%, positive predictive value = 75%, negative predictive value = 75.8%.

p<0.0001 (significant difference between the median CD4 cell counts of the children with and without oral thrush).

An inverse relationship between CD4 counts and the prevalence of OC has been reported, whether patients are on ART or not.

OC can be used as a clinical adjunct to the CD4 count in deciding when to initiate ART and prophylaxis against OI, especially in children, in whom the CD4 count alone is not a reliable marker of disease status because children tend to have higher and less consistent CD4 levels than adults, and a low CD4 count is often a late finding.[16-17] There are also profound alterations in T-cell assays, so susceptibility to infections cannot always be correlated with immunological markers. A modest sensitivity of 44.4%, a high specificity of 92.15% and a positive predictive value of 75% for OC as surrogate for severe immunosuppression in this study is in agreement with studies by Ghate *et al.*[18] and Patton,[19] which suggests that it can be used as a clinical marker of disease progression and in initiating therapy.

In conclusion, this study has confirmed a high prevalence of OC in HIV-infected children. The significant relationship of OC with severe immunosuppression suggests that when OC is present it may be used as a clinical surrogate for severe CD4 depletion. The World Health Organization (WHO) recently recommended that all children less than 12 months of age receive ART irrespective of the clinical severity of disease or the degree of immunosuppression. In HIV-infected children over 12 months of age who attend clinics where CD4 monitoring is not possible, the presence of OC suggests severe immunosuppression and that it is time to initiate ART. However, absence of OC does not imply that a child does not have severe immunosuppression. It is hoped this approach will help in scaling up provision of ART to over 660 000 HIV-infected children who currently need care, particularly in rural settings where laboratory monitoring is often unavailable.

Further studies using larger samples and better control groups may address some of the weaknesses of the present study.

References

1. Federal Ministry of Health Nigeria. *2005 National HIV/syphilis Seroprevalence Sentinel Survey among Pregnant Women Attending Antenatal Clinics: Technical Report.* April. Abuja: Federal Ministry of Health, 2006.

2. National Seroprevalence Sentinel Surveys: current population estimates using the AIDS impact model. *HIV/AIDS Emergency Action Plan, Federal Republic of Nigeria* 1991; 1994; 1996; 1999.

3. Chattopadhya D, Baveja UK, Bose M, Kumar A. Disease progression markers during asymptomatic phase of HIV-1 infected children with unimpaired CD4 cell values: evaluation of repeat CD4 cell evaluation vs other immunological parameters. *J Trop Pediatr* 2002; 48: 340-347.

4. Mellors JW, Munoz A, Giorgi JV, *et al.* Plasma viral load and CD4 lymphocyte as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; 126: 946-954.

5. Aggarwal A. Paediatric HIV infection. In: Gupte S, ed. *Recent Advances in Paediatrics.* New Delhi: Jaypee Brothers, 2004: 364-359.

6. Vajpayee M, Kanawal S, Seth P, Wig N. Spectrum of opportunistic infection and profile of CD4 counts among AIDS patients in North India. *Infection* 2003; 31: 93-97.

7. Blignaut E, Patton LL, Nittayananta W, Ramirez-Amador V, Ranganathan K, Chattopadhyay A. HIV phenotypes, oral lesions, and management of HIV-related disease. *Adv Dent Res* 2006; 19: 122-129.

8. Korting HC. Clinical spectrum of oral candidiasis and its role in HIV-infected patients. *Mycoses* 1989; 32: Suppl. 2, 23-29.

9. Kline M. Oral manifestations of pediatric human immunodeficiency virus infection: a review of the literature. *Pediatrics* 1996; 97(3): 380-387.

10. Centers for Disease Control and Prevention (CDC). 1994 revised classification system for HIV infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994; 43(No RR-12): 4.

11. Ramos-Gomez FJ, Hilton JF, Canchola AJ, Greenspan D, Greenspan JS, Maldonato YA. Risk factors for HIV-related soft-tissue manifestations in children. *Pediatr Dent* 1996; 18: 143-146.

12. Vargas KG, Jolly S. Carriage frequency, intensity of carriage and strain of oral yeast species vary in progression to oral candidiasis in human immunodeficiency virus positive individuals. *J Clin Microbiol* 2002; 40: 341-350.

13. Fong IW, Laurel M, Burford-Mason A. Asymptomatic oral carriage of *Candida albicans* in patients with HIV infection. *Clin Invest Med* 1997; 20: 85-93.

14. Kumarasamy N, Vallabhaneni S, Timothy P, *et al.* Clinical profile of HIV in India. *Indian J Med Res* 2005; 121: 377-394.

15. Greenspan JS, Greenspan D. Oral manifestations of HIV infection and AIDS. In: Broder S, Merigan TC, Bolognesi D, eds. *A Textbook of AIDS Medicine.* Baltimore: Williams & Wilkins, 1994: 525-539.

16. Leggott PJ. Oral manifestations of HIV infection in children. *Oral Surg Oral Med Oral Pathol* 1992; 73: 187-192.

17. Pizzo PA, Wilfert CM. Markers and determinants of disease progression in children with HIV infection. The Pediatric AIDS Sena Workshop II. *J Acquir Immunodefic Syndr Hum Retrovirol* 1995; 8: 30-44.

18. Ghate MV, Mehendala SM, Mahajan BA, *et al.* Relationship between clinical conditions and CD4 count in HIV-infected persons in Pune, India. *Natl Med J India* 2000; 13 (14): 183-187.

19. Patton L. Sensitivity, specificity, and positive predictive value of oral opportunistic infections in adults with HIV/AIDS as markers of immune suppression and viral burden. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology & Endodontics* 2004; 90(2): 182 - 188.