Oral Lesions and their Association with CD4 Count and Viral Load in HIV Positive Nigerian Children

Oladokun Regina E[1], Okoje Victoria N[2], Osinusi Kikelomo[1], Obimakinde Obitade S[3]

[1]Department of Paediatrics, College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria. [2]Department of Oral and Maxillofacial Surgery, College of Medicine, University Of Ibadan and University College Hospital, Ibadan, Nigeria. [3]Department of Oral and Maxillofacial Surgery, Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria.

Abstract

Background: Oral lesions may indicate the presence of HIV infection and may differ in children and adults in different regions.
Aim: To determine the prevalence, types of oral lesions in HIV positive children and their association with the clinical stage, CD4 count and viral load.
Methods: A cross-sectional study involving consecutive HIV positive children whose sero-positive status was confirmed with ELISA screening and Western immunoblot. Oral lesions were diagnosed clinically by a trained dental surgeon using previously established classification. Data obtained was analyzed with SPSS 15.0
Results: There were 127 children with age range of 3 to 204 months (median: 60 months) and male preponderance of 58.3% (n=74). 55.9% (n=71) of the subjects had oral lesions and pseudomembranous candidiasis (55.9%) was the commonest followed by caries (12.7%), xerostomia (7.8%) and gingivitis (6.9%). Correlation between prevalence of oral lesions and clinical stage of the disease did not reveal any statistically significant association (p=0.354). Also there is no statistically significant difference in prevalence of oral lesions between children on Antiretroviral Therapy (ART) and those who are not on ART (p=0.875). Incidence of oral lesions was however associated with lower mean baseline CD4 count (p= 0.004) but not with mean log10 viral load (p=0.256).
Conclusion: This study has shown that HIV associated oral lesions are prevalent in our environment and antiretroviral therapy does not have significant correlation with occurrence of these lesions in HIV infected children. CD4 count is a better indicator of disease progression than viral load.

Key Words: Oral Lesions, HIV, Children, ART, CD4 Count, Viral Load

Introduction

The Human Immunodeficiency Virus infection is one of the most devastating epidemics known to man [1-3]. At the end of 2009, about 33.3 million persons were estimated to be infected with HIV and 22.5 million (68%) of this cohort were in Sub-Saharan Africa [1]. In the same year 260,000 children less than 15yrs died from HIV/AIDS [1] and 91% of all new infections among children was said to occur in sub-Saharan Africa [1,2]. Ten percent of paediatric AIDS is attributable to Nigeria and annual child deaths due to AIDS in Nigeria was projected to increase from around 37,000 in the year 2000 to about 56,000 in 2010 [4,5].

Certain oral lesions including hairy leukoplakia, oral and pharyngeal candidiasis have been reported to provide strong indication of the presence of HIV infection and featured in the clinical classifications of the disease [6-11]. Oral lesions in HIV infection are also known to be predictors of disease progression and have been reported to contribute substantially to deterioration in quality of life of HIV infected patients [9-14]. Children are said to be more vulnerable and they tend to deteriorate clinically at a faster rate than adult because of their developmental stage and immaturity of their immune system [12-19]. Oral lesions in Paediatric HIV infection has been reported to vary considerably compared to adults and few authors have attempted to characterize these lesions in paediatric populations [18-21].

The literature is rich with studies on oral manifestation of HIV infection in adult population globally. However, there is lack of data on correlation between paediatric HIV associated oral lesions and other prognostic variables like CD4 count and viral load of infected subjects in West African sub region. This formed the basis for the present study which aimed to determine the prevalence of oral lesions and their correlations with CD4 count and viral load in HIV positive Nigerian children.

Materials and Methods

This was a cross-sectional study involving consecutive patients with confirmed HIV infection accessing care in the Paediatric infectious diseases clinic of the University College Hospital (UCH), Ibadan, Nigeria. Informed consent was obtained from the caregivers and the study was approved by our institutions ethical review board. HIV testing was by rapid antibody tests and confirmation for those less than 18 months was by DNA Polymerase Chain Reaction

(PCR) and for those ≥18 months Western blot was used to confirm HIV infection. The revised version of World Health Organization (WHO) Clinical Staging and Disease Classification System for clinical diagnosis of paediatric HIV infection in resource constrained setting was adopted for the study The diagnosis of the WHO Clinical Stage was mainly presumptive and included laboratory tests when necessary. World Health Organization 2007 case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Available at: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf.)

Corresponding author: Okoje V N, College of Medicine, University of Ibadan and University College Hospital, Ibadan, Nigeria, Tel: +2348037496174; e-mail: vnokoje@gmail.com

As per the unit protocol, patients eligible for ART were placed on first line regimen consisting of Zidovudine, Lamivudine and Nevirapine while those failing on first line regimen were switched to second line therapy consisting of Abacavir, Lamivudine and Lopinavir/ritonavir. CD4 count and viral load were carried out at baseline and were repeated at 3 monthly intervals.

For the study, the lips, buccal mucosa, floor of the mouth, tongue, soft and hard palate, gingival, salivary glands and the oropharynx were examined. Lesions were diagnosed based on their clinical appearance and histological diagnosis where applicable. Classification of orofacial lesions was then made using previously established classification criteria for children as described by Ramos-Gomez et al. [16].

The oral examination was conducted by a calibrated consultant Oral and Maxillofacial surgeon who has been pre trained on diagnosis of oral lesions in HIV and histologic diagnosis was done where applicable. Other information recorded in a proforma included the socio-demographic characteristics of the children, clinical stage of the disease, CD4 count and viral load at the time of examination. Data obtained was analyzed with the SPSS package version 15.0. Descriptive statistic of patients' demography was done. Correlation between oral lesions, ART and clinical stages of the disease was done with pierson's chi [2] while mean CD4 count and viral load at baseline on the prevalence of oral lesions were separately compared using student t test. A level of significance of p= 0.05 was used in all the statistical tests.

Results

A total of 127 children participated in this study. Males accounted for 74 (58.3%) while 53 (41.7%) were females giving a M: F of 1.4:1. The age of the subjects ranged from 3 to 204 months with a median of 60 months. More than half (51.2%) of the children in the study population were aged 60 months and above while those less than 24 months of age accounted for 11.8% . *Table 1* showed the demographic characteristics of the patients, WHO clinical stage of the disease at diagnosis, CD4 count and viral load.

The prevalence of oral lesions in this study was 71 (55.9%) out of which single type lesion was observed in 33.1% while the remaining patients had multiple lesions. Thus, 102 oral lesions were seen in 71 patients. The most common lesion was pseudomembranous candidiasis (55.9%); all the lesions seen in our subjects are shown in *Table 2*.

Although a higher percentage of patients who were not on ART (ART naïve) had oral lesions (86.7%) when compared with those patients on ART (51.8%), this difference was however not statistically significant (p = 0.875). Also, correlation between oral lesions and clinical stages of the disease was not statistically significant (p=0.354). *Table 3* showed that the comparison of mean CD4 count for patients with oral lesions and those without at presentation was statistically significant (p= 0.004). Similarly, analysis of the 2 groups after 3 months was still statistically significant (p=0.003). However, the picture for viral load is different as there was no statistically significant difference in the baseline mean $\log_{10}$ viral load of patients with oral lesions and those without oral lesions at presentation and after 3 months (p=0.256 and 0.846 respectively).

Out of 112 children on ARV, 58 (51.8%) had oral lesions (with multiple response and a total of 90 oral lesions) (*Table 4*) compared with 86.7% among those not on ARV (p=0.008). There was no significant difference in the type of ARV

Table 1. *Characteristics of study population.*

Characteristic	Number of respondents
Age (Months)	
<24	15(11.8)
24-59	47(37.0)
≥ 60	65(51.2)
Sex	
Male	74(58.3)
Female	53(41.7)
Religion	
Christianity	76(59.8)
Islam	51(40.2)
WHO Clinical Stage of HIV at diagnosis	
I	24(19.0)
II	32(25.4)
III	45(35.7)
IV	25(19.8)
CD4 Count (Cells/µl)	
<350	36(28.3)
350 - <750	50(39.4)
≥ 750	41(32.3)
Viral (Copies/ml)	
<10,000	52(40.9)
10,000 -<100,000	29(22.8)
≥ 100,000	46(36.2)

Table 2. *Percentage distribution of types of oral lesions seen among HIV positive children.*

Types of Oral lesion (n=127)	Frequency	Percentage
Pseudomembraneous candidiasis	57	55.9
Angular cheilitis	4	3.9
Parotid gland enlargement	6	5.8
Herpetic stomatitis	3	3.0
HIV gingivitis	7	6.9
Caries	13	12.7
Xerostomia	8	7.8
Mucosal pigmentation	2	2.0
Kaposi Sarcoma	2	2.0

Table 3. *Association between Oral lesion, CD4 count and viral load.*

Variable	Oral lesion	Mean(SD)	t-value	P-value
CD4 count at diagnosis	No	871.38(631.91)	2.917	0.004
	Yes	564.75(551.48)		
	Total	699.95(605.49)		
CD4 count at 3months	No	1005.63(814.38)	3.064	0.003
	Yes	624.54(586.16)		
	Total	792.57(718.66)		
***Viral load at diagnosis**	No	4.68(1.36)	1.142	0.256
	Yes	4.40(1.23)		
	Total	4.53(1.29)		
***Viral load at 3month**	No	3.64(1.27)	0.194	0.846
	Yes	3.59(1.31)		
	Total	3.61(1.29)		

*Mean values reported in logarithms

Table 4. *Orofacial lesions in patients on ARV.*

Oral Lesion	Total Frequency %	1st Line ARV	2nd Line ARV
Pseudomembranous Candidiasis	45(77.6%)	39(67.2%)	6(10.3%)
Angular Chelitis	4(6.9%)	3(5.2%)	1(1.7%)
Salivary gland Enlargement	4(6.9%)	4(6.9%)	0
Herpes simplex	1(1.7%)	1(1.7%)	0
Linear gingival Erythemia	2(3.4%)	2(3.4%)	0
Recurrent Herpetic Ulcer	1(1.4%)		
Recurrent Apthous Ulcer	1(1.4%)	0	2(3.4%)
Caries	12(20.7%)	10(17.2%)	2(3.5%)
Xerostomia	5(8.6%)	4(6.9%)	1(1.7%)
Melanotic Hyper pigmentation	1(1.7%)	1(1.7%)	0
Delayed tooth eruption	12(20.7%)	10(17.2%)	2(3.4%)
Kaposi Sarcoma	2(3.4%)	1(1.7%)	1(1.7%)
Total	**90(100%)**	**75(87.9%)**	**15(12.1%)**

regimen as 51.5% of children on first line regimen had oral lesions compared with 53.8% among those on second line regimen (p = 0.875).

Discussion

The prevalence of orofacial lesions of 55.9% seen in this study is high compared to a previous study from north central part of Nigeria but slightly lower than 61.9% reported by Adebola et al. [14] in north western Nigeria. Our finding is also higher than 41.2% reported in Tanzania [19] and 46% from Chennai, South India [18]. A previous review of oral lesions in HIV infected children revealed prevalence rates of 33 to 50% which is lower than finding from the present study [10].The disparity in various findings may have some racial and geographic implications. Moreover, the clinical and immunological status of the subjects at the point of evaluation may offer additional explanation for the disparity [14,17].

In agreement with some studies cited, we did not find a statistically significant difference in the prevalence of oral lesions in the ART naïve population compared with those on ART [14,19,22]. This is surprising since the goal of ART is to reduce viral load with a resultant restoration of immune function and reduced incidence of opportunistic infections. On the contrary, some authors affirmed that the occurrence of HIV related oral lesions in children receiving ART is significantly lower than those who were not on ART [7,12,21,23]. Other studies have indicated that incidence of some specific oral lesion such as candidiasis was found to be significantly reduced in subjects on ART [14,24-26]. We also found that the clinical stage of the disease at presentation did not correlate significantly with oral lesion meaning that the presence or absence of oral lesions is not an indicator of clinical progression of HIV infection.

The most prevalent orofacial lesion found in this study was pseudomembranous oral candidiasis (55.9%) which has also been described by many clinicians as the commonest orofacial manifestation of paediatric HIV infection [6,9,11-16]. The study by Adebola et al. [14] in northern Nigeria however reported angular cheilitis variant as the predominant lesion. Studies from Tanzania [19] and Mozambique [23] revealed that Parotid gland enlargement was the most prevalent paediatric orofacial lesion in their environments. On the contrary, we observed a relatively lower incidence of parotid gland enlargement of 5.8% which is comparable to previous reports from Nigeria [6,14] and Uganda [25]. Interestingly, only 6.9% of patients with orofacial lesions in the present study had gingivitis while none had HIV associated periodontitis. This is contrary to studies from northern Nigeria where gingival/ periodontal lesions were the second most common oral manifestations in both adult and children populations [8,14,22]. The difference may probably be an indication of sociocultural and geographic diversity between different regions of the country.

Dental caries which was seen in 12.7% of our subjects has also been reported by other authors as one of the oral lesions that is frequently associated with HIV/ AIDS [21,23,27-30]. Hicks and co- workers in a longitudinal study found that dental caries, particularly in the primary dentition occur out of proportion in HIV infected children when compared with uninfected subjects [27]. This is in agreement with other reports that justifies a high caries incidence particularly in the primary dentition in HIV infected children [23,28-30]. Other lesions which were observed with low prevalence like kaposi sarcoma, herpetic stomatitis and recurrent aphthous ulceration are comparable to previous reports [15,20]. Lesions like kaposi sarcoma, Non- Hodgkins lymphoma and hairy leukoplakia have been reported to have low prevalence in paediatric HIV infection [7,13,14,17,19,21]. This is however a sharp demarcation from studies involving adult populations where these lesions are of higher prevalence [9,16,22,24].

In agreement with other authors, CD4 counts of children with oral lesions were significantly lower than those without oral manifestations [19,21,31]. Previous studies have shown a correlation between certain oral lesions and CD4 cell counts and these lesions have been proposed as prognostic markers for the progression of HIV-infection to AIDS [14,23,25,26,31]. A Lower CD4 count is expected to predispose individuals to increased susceptibility to oral lesions. However, a study conducted by Nabbania et al. [30] among a group of Ugandan children found no significant correlation between CD4 count and oral lesions. Concerning the association between oral lesions and viral load, it was surprising that the overall mean log 10 viral load in our study did not show any significantly difference in the presence or absence of oral lesions. This finding suggests that CD4 cell count rather than viral load is

a better indicator of disease progression. However, Patton et al. [32] reported that hairy leukoplakia and oral candidiasis correlated with higher viral load, independent of CD4 cell count.

Conclusion

This study has shown that HIV associated oral lesions are prevalent in our environment and antiretroviral therapy does not have significant correlation with occurrence of these lesions in HIV infected children. We also concluded that CD4 count is a better indicator of disease progression than viral load.

Acknowledgement

The authors acknowledge the resident doctors and other medical staff for their cooperation and support during the course of this study.

References

1. UNAIDS Report on the global AIDS epidemic 2010.

2. WHO, UNAIDS, UNICEF. Toward universal access: Scaling up priority HIV/AIDS interventions in the health sector: Progress report 2010.

3. Ogunbosi BO, Oladokun RE, Brown BJ, Osinusi KI. Prevalence and clinical pattern of paediatric HIV infection at the University College Hospital Ibadan, Nigeria: a prospective cross sectional study. *Italian Journal of Pediatrics*. 2011; **37**: 29.

4. Federal Ministry of Health, Nigeria. National Guidelines for Paediatric HIV and AIDS Treatment and Care. 2010.

5. National Action Committee on AIDS (NACA). HIV/AIDS Emergency Action Plan: A 3-year strategy to deal with HIV/AIDS in Nigeria.

6. Ashir GM, Gofama MM, Rabasa AI, Bashir F, Halima IU. HIV-related oral candidiasis in Nigerian children: a marker of HIV disease progression. *Journal of Child Health*. 2008; **2**: 152-54.

7. Olaniyi TO, Sunday P. Oral manifestation of HIV infection in 36 Nigerian children. *Journal of Clinical Pediatric Dentistry*. 2005; **30**: 89-92.

8. Greenspan JS, Barr CE, Sciubba JJ, Winkler JR. Oral manifestations of HIV infection: Definitions, diagnostic criteria and principles of therapy. *Oral Surgery, Oral Medicine , Oral Pathology, Oral Radiology*. 1992; **73**: 142-144.

9. Ranganathan K, Hemalatha R. Oral Lesions in HIV Infection in Developing Countries: an Overview. *Advances in Dental Research*. 2006; **19**: 63-68.

10. Samaranayake LP. Oral mycoses in HIV infection. *Oral Surgery, Oral Medicine*, *Oral Pathology*. 1992; **73**: 171-180.

11. Tirwomwe JF, Rwenyonyi CM, Muwazi LM, Besigye B, Mboli F. Oral manifestations of HIV/AIDS in clients attending TASO clinics in Uganda. *Clinical Oral Investigations*. 2007; **11**: 289-292.

12. Bendick C, Scheifele C, Reichart PA. Oral manifestations in 101 Cambodian patients with HIV infection and AIDS. *Journal of Oral Pathology & Medicine*. 2002; **31**: 1-4.

13. Bosco VL, Birman EG. Oral manifestations in children with AIDS and in controls. *Pesqui Odontol Bras* 2002; **16**: 7-11.

14. Adebola AR, Adeleke SI, Mukhtar M, Osunde OD, Akhiwu BI, Ladeinde A. Oral manifestation of HIV/AIDS infection in paediatric Nigerian patients. *Nigerian Medical Journal*. 2012; 53: 150-154.

15. Ramos-Gomez F. Dental considerations for the paediatric AIDS/HIV patient. *Oral Diseases*. 2002; **8**: 49-54.

16. Ramos-Gomez FJ, Flaitz C, Catapano P, Murray P, Milnes AR, Dorenbaum A. Classification, diagnostic criteria, and treatment recommendations for orofacial manifestations in HIV-infected pediatric patients. J*ournal of Clinical Pediatric Dentistry*. 1999; **23**: 85-95.

17. Fine DH, Tofsky N, Nelson EM, Schoen D, Barasch A. Clinical implications of the oral manifestations of HIV infection in children. *Dental Clinics of North America*. 2003; **47**: 159-174.

18. Ranganathan K, Geethalakshmi E, Krishna Mohan Rao U, Vidya KM, Kumarasamy N, Solomon S. Orofacial and systemic manifestations in 212 Paediatric HIV patients from Chennai, South India. International Journal of *Paediatric Dentistry*. 2010; **20**: 276–282.

19. Hamza OJ, Matee MI, Simon EN, Kikwilu E, Moshi MJ, Mugusi F, Mikx FH, Verweij PE, van der Ven AJ. (2006) Oral manifestations of HIV infection in children and adults receiving highly active anti-retroviral therapy(HAART) in Dar es Salaam, Tanzania. *BMC Oral Health*. 2006; **6**: 12.

20. Katz MH, Mastrucci MT, Leggott PJ, Westenhouse J, Greenspan JS, Scott GB. Prognostic significance of oral lesions in children with perinatally acquired human immunodeficiency virus infection. *American Journal of Diseases of Children*. 1993; **147**: 45-48.

21. Ponnam SR, Srivastava G, Theruru K. Oral manifestations of human immunodeficiency virus in children: An institutional study at highly active antiretroviral therapy centre in India. *Journal of Oral and Maxillofacial Pathology*. 2012; **16**: 195-202.

22. Arotiba JT, Adebola RA, Iliyasu, Babashani M, Shokunbi WA, Ladipo, et al. Oral manifestations of HIV/AIDS infection in Nigerian patients. *Nigerian Journal of Surgical Research*. 2005; **7**: 176-181.

23. Sales-Peres SH, Mapengo MA, de Moura-Grec PG, Marsicano JA, Sales-Peres Ade C, Sales-Peres A. Oral manifestations in HIV+ children in Mozambique. *Ciência & Saúde Coletiva*. 2012; **17**: 56-60.

24. Taiwo OO, Hassan Z. The impact of Highly Active Antiretroviral Therapy (HAART) on the clinical features of HIV- related oral lesions in Nigeria. *AIDS Research and Therapy*. 2010; **7**: 19.

25. Rwenyonyi CM, Kutesa A, Muwazi L, Okullo I, Kasangaki A, Kekitinwa A. Oral manifestations in HIV/AIDS infected children. *European Journal of Dentistry*. 2011; **5**: 291-298.

26. Glick M, Muzyka BC, Lurie D, Salkin LM. Oral manifestations associated with HIV-related disease as

markers for immune suppression and AIDS. *Oral Surgery, Oral Medicine, Oral Pathology*. 1994; **77**: 344-349.

27. Hicks MJ, Flaitz CM, Carter AB, Cron SG, Rossmann SN, Simon CL, Demmler GJ, Kline MW. Dental caries in HIV-infected children: a longitudinal study. *Paediatric Dentistry*. 2000; **22**: 359-364.

28. Madigan A. Murray PA, Houpt M, Catalanotto F, Feuerman M. Caries experience and cariogenic markers in HIV positive children and their siblings. *Paediatric Dentistry*. 1996; **18**: 129-136.

29. Howell RB, Jandinski J, Palumo P, Shey Z, Houpt M. Dental caries in HIV-infected children. *Paediatric Dentistry*. 1992; **14**: 370-371.

30. Nabbania J, Gitta S, Peterson S, Rwenyonyi CM. Orofacial manifestations in HIV positive children attending Mildmay Clinic in Uganda. *Odontology*. 2013; **101**: 116-120.

31. Bodhade AS, Ganvir SM, Hazarey VK. Oral manifestations of HIV infection and their correlation with CD4 count. *Journal of Oral Science*. 2011; **53**: 203-211.

32. Patton LL, McKaig RG, Eron JJ, Lawrence HP, Straussn RP. Oral hairy leukoplakia and oral candidiasis as predictors of HIV viral load. AIDS. 1999; **13**: 2174-2175.