Parotid Gland Enlargement in Pediatric HIV Population

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Objectives: *To establish the significance of parotid enlargement, state frequency, cytological features and effect of antiretroviral therapy (ART) on parotid enlargement among a pediatric HIV population.* ***Study design:*** *A 6 month cross sectional survey that utilised clinical features, serial immunological indices and fine needle aspiration cytology.* ***Results:*** *287 HIV positive children were seen at special paediatric clinic of the University College Hospital, Ibadan, Nigeria, 114 (39.7%) had oral features and among these 24 (8.4%) had parotid involvement comprising of 10 males and 14 females. The overall mean age was 43.4 + 39.7 months compared with 59.6 + 36.5 months in the parotid enlargement group (p = 0.03). Mean ages of parotid enlargement and non enlargement group was significantly different (p = 0.03). The mode of transmission was vertical in (91.7%), 87.5% was bilateral (87.5%) and (75%) presented as a syndrome state with generalised lymphadenopathy. The predominant cytology was lymphoid hyperplasia (62.5%). ART resulted in marked clinical reduction in all the cases and statistically significant improvement in serum indices of CD4 count, CD4% and viral load (p = 0.001, 0.000 & 0.009 respectively).* ***Conclusion:*** *HIV positive children often present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of lymphoid hyperplasia predominated. ART resulted in satisfactory reduction of the swellings in most of the cases with no need for further intervention.*

Keywords: *Parotid gland enlargement, Syndrome, HIV,children.*

INTRODUCTION

The incidence of parotid enlargement has increased dramatically with the emergence of HIV epidemic and in the developed nations, it is estimated that among the HIV population, 3 to 6% of adult and 1 to 10% of children present with parotid enlargement,[1,2] while in developing Asia and sub-Saharan Africa, there are sporadic reports of even higher prevalence.[3,4,5]

Until the mid 1980's, several authors reported cystic parotid swelling as being rare and without mention of HIV infection in any of the patients,[6,7,8] but in a 1988 report of nine cases of parotid enlargement by Shugar *et al* ,[9] the first association of parotid enlargement with HIV infection was made and since then, numerous articles have been devoted to the findings and management of parotid gland swelling in HIV-positive adults.[1,10,11,12]

Apart from the fact that the previously very rare occurrence of parotid cystic enlargement is now on the increase with the advent of HIV infection, parotitis also demonstrated the highest positive predictive value (67%) for the diagnosis of HIV infection compared with 53% for oral candidiasis and 47% for chronic diarrhea.[13] As a result of this, the authors of the study recommended that any child having chronic or recurrent parotitis should be investigated for HIV and that more studies from developing countries with diverse geocultural and medical practices should be carried out.

In a study among an adult HIV population, a syndrome state consisting of bilateral cystic parotid swelling, generalised lymphadenopathy involving the cervical lymph nodes with persistent circulating CD8 lymphocytosis and diffuse general CD8 lymphocytic infiltration called diffuse infiltrative CD8 lymphocytosis syndrome (DILS) was initially documented.[14] However, later studies on HIV positive children have led to the suggestion that DILS is associated with slower disease progression and that there is longer patient survival than in patients without the syndrome.[11,15,16,17] In another limited study of paediatric HIV population involving four cases, an attempt was made at classifying parotid enlargement into three major groups based on the clinical and pathological findings; the groups included 1. Persistent generalised lymphadenopathy (PGL), 2. Benign lymphoepithelial lesion (BLEL) and 3. Benign lymphoepithelial cyst (BLEC).[18]

The aims of the present study were; to establish the significance of parotid enlargement in HIV disease progression, to determine the frequency of DILS among a paediatric HIV population and also to document the cytological features of parotid enlargement through fine needle aspiration biopsy.

MATERIALS AND METHOD

A cross sectional survey was carried out among children aged less than 15 years presenting at the Paediatric HIV specialist clinic of the University College Hospital (UCH) Ibadan over a six month period.

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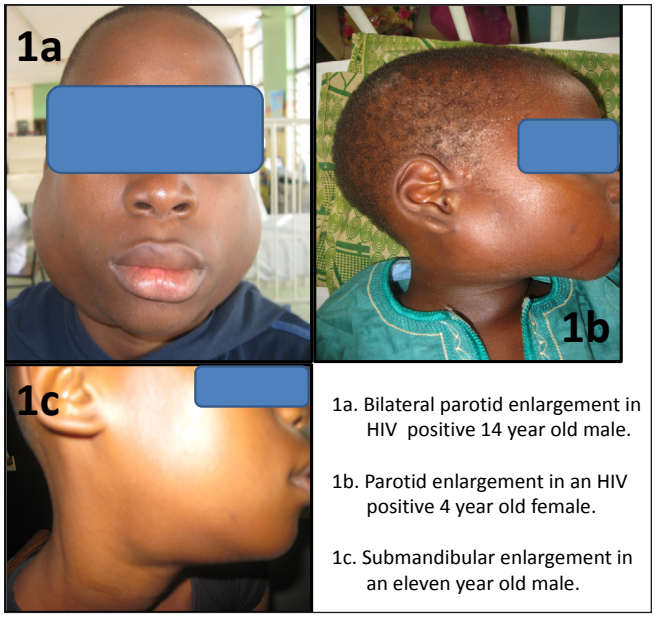


1a. Bilateral parotid enlargement in HIV positive 14 year old male.

1b. Parotid enlargement in an HIV positive 4 year old female.

1c. Submandibular enlargement in an eleven year old male.

The HIV programme is jointly supported by the Federal Government of Nigeria and the USA President's Emergency Plan for AIDS Relief (PEPFAR). Prior to enrolment in the program, the children were tested for HIV by rapid antibody tests and confirmation for those less than 18months was by DNA Polymerase Chain Reaction (PCR) and for those ≥ 18months Western blot was used to confirm HIV infection.

The information obtained for this study included: The children's biodata including the age, sex, medical and immunisation history, family history, HIV status of parents, clinical stage and co-morbidities were recorded. The 2007 revised version of World Health Organization (WHO) Clinical Staging and Disease Classification System for presumptive clinical diagnosis of paediatric HIV lesion in resource constrained setting was adopted for the present study.[19] Laboratory indices of CD4, CD4% and viral load were also obtained.

The diagnosis of parotid swelling was based on clinical and fine needle aspiration cytology findings as recommended by Dave *et al*.[18] Informed consent was obtained from the caregivers prior to enrolment.

The data were managed with version 16 software of statistical package for social sciences (SPSS), initial data entry and cleaning was made on the spread sheet and followed by statistical analysis: continuous variables of age, CD4 count, CD4 percent and viral load were summarised into mean and standard deviation and further compared using Student's t- test, while proportions were expressed as percentages and compared using Chi square statistics.

RESULTS

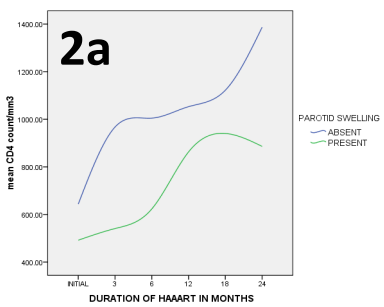
Over the study period, a total of 287 children were seen at the paediatric HIV specialist clinic, out of which, 114 (39.7%) presented with oral manifestations while 173 (60.3%) had no oral features.

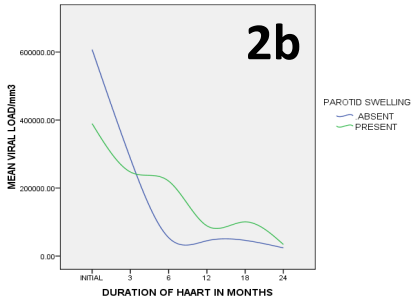
Among those with oral manifestations, there were 24 HIV positive children (8.4%) with parotid enlargement comprising 10 males and 14 females; the overall mean age was 59.6 ± 36.5 months while the mean ages of males and females were 44.9 ± 27.4 and 70.1 ± 39.4 months respectively. There was no significant difference in mean ages between the males and females (p = 0.09), there was however a significant difference in the mean age of those with parotid swelling when compared with those without parotid swelling (p = 0.03) with the mean age of the parotid swelling group being 16 months higher than the mean age of 43.4 ± 39.7 months in the children without parotid swelling.

Majority (87.5%) of the parotid enlargement cases were bilateral although one side was often bigger than the other (figure 1a, 1b). Only two cases presented as unilateral parotid enlargement and there was a case of unilateral submandibular gland involvement (figure 1c).

Table 1. Clinical stage, immunological and virological parameters at first presentation

Parameters	Parotid swelling present (N = 24)	Parotid swelling absent (N = 263)	Total (N = 287)	Chi squared value (X^2)	P value
	n (%)	n (%)			
Clinical stage					
I	0 (0)	39 (14.8)	39		
II	13 (54.2)	43 (16.4)	56	21.74	0.00
III	6 (25.0)	117 (44.4)	123		
IV	5 (20.8)	64 (24.4)	69		
CD4 count (Cells/µl)					
< 750	20 (83.3)	158 (60.1)	178	4.11	0.04
> 750	4 (16.7)	105 (39.9)	109		
CD4 percent					
<25	19 (79.2)	219 (83.3)	238	0.05	0.58
>25	5 (20.8)	44 (16.7)	49		
Viral load (Copies/ml)					
<10,000	6 (25)	44 (16.7)	50		
10,000 - < 100,000	6 (25)	79 (30.0)	85	0.44	0.35
≥ 100,000	12 (50)	140 (53.3)	152		





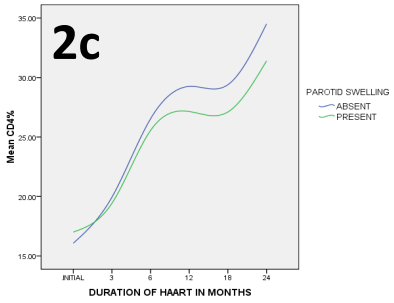


Figure 2: Chronic effect of HAART on serum indices With and without parotid swelling:

Figure 2a: Effect of HAART on CD4 count.

Figure 2b: Effect of HAART on mean viral load.

Figure 2c: Effect of HAART on mean CD4%.

The mode of transmission of HIV was vertical (mother-to-child) in all but one case; 23 (95.8%). The exception was an eleven year old female whose mode of transmission was probably via blood transfusion as she had received transfusion five years earlier and both parents were HIV negative The time duration between the diagnosis of HIV and present study ranged from 3 to 85 months with mean of 33.5 $\pm$18.8 months. Fourteen children (58.3%) with parotid enlargement were diagnosed and confirmed to be HIV positive at the UCH Paediatric HIV clinic while the remaining ten children (41.7%) had a preliminary HIV screening elsewhere but were referred for confirmation of HIV and further management at the UCH.

Eighteen of the parotid enlargement cases (75%) presented with generalised lymph node involvement. Two groups of lymph nodes were involved in four cases (16.7%) and one node type was involved in two cases (8.3%). Cervical lymph node was always involved in all cases either as single, double, or generalised nodal involvement.

Table 1 shows that at first presentation, more children with parotid swelling presented at earlier stages of the infection when compared with those without parotid swelling ($X^2 = 21.74$; P = 0.009). However, more children with parotid swelling had lower baseline CD4 count (<750 cells/µl than those without parotid swelling.

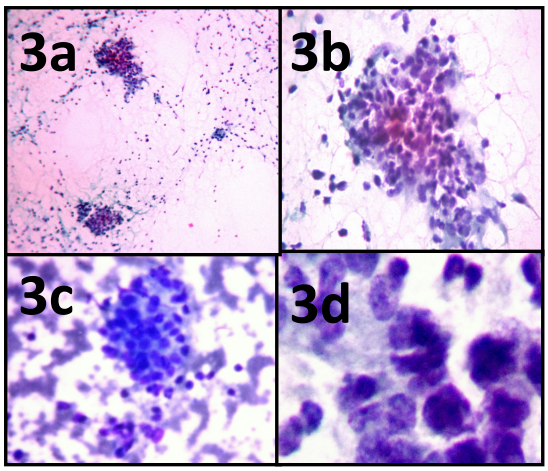
The mean values of the CD4 count, CD4% and Viral load were 490.9 cells/µl, 16.9 % and 389,535.1 copies/ml respectively. Following antiretroviral therapy, the most recent indices of mean CD4 count, CD4 % and viral load were 886.1 cells/µl, 31.4% and 34,233.8 copies/ml respectively with the improvement in the immunological and virological indices being statistically significant (p = 0.001; 0.000 & 0.009 respectively) in the parotid enlargement group.

Figure 2a shows a significantly lower mean CD4 count among children with parotid swelling when compared with those without swelling throughout the period of antiretroviral therapy (t = 3.952; p = 0.000). Figure 2b however shows a higher but insignificant difference in initial mean CD4% among the parotid enlargement cases but during the course of ART there was more rapid improvement in the mean CD4% of those without parotid swelling compared with those with parotid swelling. Figure 2c shows a higher viral load among those without parotid swelling at presentation but during the course of therapy, more rapid reduction in the mean viral load was noted among the group without swelling compared with those with parotid swelling.

Fine needle aspiration cytology (FNAC) revealed background generalised, marked lymphocytosis and occasional macrophages in all the cases examined, however, only 5 cases (20.8%) of the aspirates had cellular aggregates suggestive of epithelial components (figure 3a -d). Among these 5 cases, only 2 out of 14 children that were under the age of 5 years presented epithelial components of parotid enlargement while 3 out of the 10 children that were above 5 years presented epithelial components of enlargement (the difference between the two groups was not statistically significant X^2 = 0.19; p = 0.67 fishers exact).

Twenty-two out of the 24 patients were already on antiretroviral therapy (ART) with duration of therapy ranging from 5 to 60 months and mean of 27.5 $\pm$ 15.8 months. All the patients on ART were initiated on three drug regimen that always comprised of Zidovudine (AZT) and Lamivudine (3TC); the third combination was varied to include Nevirapine (NVP) and efavirenz (EFV) in 9 and 12 patients respectively while the last patient's therapy included Abacavir (ABC). At the time of the study, 19 patients were still on 1st line regimen while three had been switched to 2nd line regimen which included a protease inhibitor.

Out of the 22 patients on ART, there was total resolution of the swelling in 15 (68.2%). Though there was more than 50% size reduction of the swelling in the remaining 7 cases, the swelling having persisted after ART.



Photomicrograph of parotid gland FNAC:
Figure 3a & 3b: Giemsa stain shows aggregates of epithelial cells amidst numerous chronic inflammatory cells (a) x 100; (b) x 400.
Figure 3c & 3d: Papanicolaou smear of parotid lymphoepithelial cyst (c & d) showing clumps of mature epithelial cells with occasional anucleate epithelial squames derived from cystic wall (c) x 100; (d) x 400.

DISCUSSION

The study showed that 8.4% of a cohort of HIV positive children presented with parolid swelling. Generally, the causes of swellings in and around the parotid region in paediatric age group include infective conditions such as mumps (epidermic parotitis), tuberculosis and chronic sialadenitis; autoimmune disorders such as Sjogren's and sicca syndrome; benign neoplasms such as lipoma & mixed salivary gland tumour and malignancies such as lymphoma and Kaposi's sarcoma.[20,21,22,23,24,25]

Mumps present acute constitutional symptoms alongside bilateral tenderness and it is often self limiting with resolution within a few weeks, while sialadenitis is associated with debilitation, acute tenderness especially in the region of duct orifice and pain at meal times. Fine needle aspiration of sialadenitis reveals scanty inflammatory cells.[26,27]

While Sjogren's syndrome is associated with xeropthalmia and keratoconjuctivitis, these features may be absent in HIV parotitis[28] The histological distinction between AIDS-related parotid lymphoepithelial cysts and the cystic benign lymphoepithelial lesions of Sjorgren's syndrome is that in AIDS, the cysts occur in the parotid lymph nodes, whereas in Sjogren's syndrome, cysts occur in the parotid gland parenchyma. Furthermore, in contrast to Sjogren's syndrome, in which infiltrates are composed of T lymphocytes in the normal CD4/CD8 proportion of half to one, in DILS infiltrates are composed predominantly of CD8 T cells.[29,30,31] Non-Hodgkin's lymphomas in AIDS patients are usually high-grade large cell lymphomas and on FNAC, they are characterised by a monotonous population of large, atypical lymphoid cells with non cleaved nuclei, multiple nucleoli, and scanty basophilic cytoplasm.[32]

The mean age of presentation of parotid swelling in this study which was 59.6 $\pm$ 36.5 months is comparable with the previously documented mean range for HIV associated parotid enlargement of 50 months to 62 months among the paediatric population,[17,18] also the older age of presentation compared with those without parotid enlargement within the paediatric age group is in line with other studies suggesting that HIV parotid enlargement in children is associated with slower disease progression that allow enough time for immunoproliferative reaction.[11,15,16,17] Furthermore, in support of the slow progression of disease among the parotid enlargement cases, fewer proportion (45%) presented advanced stages (stage III and IV) of HIV in this group despite the older age of presentation, while among those without parotid swelling majority (65%) presented with advanced stages of disease.

In this study, the prevalence of parotid enlargement, the predominance of vertical route of transmission and the overwhelming bilateral cases as compared with unilateral cases are all within the usually documented pattern of presentation of HIV associated parotid enlargement in paediatric HIV population.

The high frequency of bilateral presentation is a finding that supports systemic process rather than local pathomechanism of parotid enlargement among HIV population. The pathomechanism of parotid enlargement in HIV patients has been related to lymphoproliferative activity of intraparotid lymph nodes, florid response of normal intraglandular lymphocytes and/or extraglandular lymphocytic infiltration into salivary gland tissue.[1,22,23] The lymph nodes in the parotid glands occasionally contain salivary gland acini and ducts from where intra nodal epithelial proliferation results in cyst formation.[1,30] Submandibular gland enlargement in HIV patients is considered to be very rare compared with that of parotid gland due to the extra salivary capsule location of submandibular lymph node during embryogenesis as against the intra capsular location of the parotid lymph node.[29,33] Since HIV infection involves lymph nodes primarily, nodal involvement of parotid region results in early parotid gland enlargement, while in the submandibular region; lymphadenitis without submandibular glandular enlargement is often the result. However in exceptionally large cyst formation of submandibular node involvement, there is prominent enlargement of the whole submandibular region; a case of such submandibular region involvement with cytological features of lymphoepithelial cyst was observed in this study.

The diagnostic criteria developed by Itescu and Winchester[8,14] for DILS require that the subject be HIV-seropositive, have bilateral salivary gland enlargement or xerostomia for more than six months, and have histological confirmation of salivary or lacrimal gland lymphocytic infiltration in the absence of granulomatous or neoplastic involvement. In majority of cases seen in the present study, the high occurrence of bilateral parotid swelling and generalised lymphadenopathy involving the cervical lymph node and the relatively slow clinical progression are suggestive of DILS in HIV infection.

The mean CD4 count was significantly lower among the parotid swelling group despite the florid lymphocytosis on aspiration cytology which further suggested that the lymphocytic infiltrates were predominantly CD8; however a direct measurement of CD8 and HLA-DR5 was not done in this study except in only one child and was found to be elevated. While raised CD8 count is usually associated with DILS, some authors have observed reciprocal reduction of CD4 count as a unique feature of DILS in keeping with present study.[2,12,18] Contrary to the lowered CD4 count in DILS, the parotid enlargement that occurs without HIV infection in Sjogren's syndrome and lymphoepithelial cyst is associated with normal CD4 count and normal CD4 to CD8 ratio.[34,35] Rarely, lowered CD4 count may occur in Sjogren's syndrome in the absence of HIV infection

in association with a condition called Idiopathic CD4 lymphocytopenia but patients with this condition are seronegative for HIV infection.[36,37]

An earlier study of parotid enlargement among paediatric HIV population indicated more frequent occurrence of lymphoid hyperplasia in the younger age group while lymphoepithelial cyst was commoner in the older age group, the authors therefore considered lymphoid hyperplasia as the precursor of lymphoepithelial lesion and lymphoepithelial cyst formation.[17,18]

On cytology, the present study also revealed more cases of lymphoid hyperplasia among the parotid enlargement cases, a previous study considered lymphoid hyperplasia as a stage of reversible inflammation which responded favourably to antiretroviral therapy while cyst resolution along the course of antiretroviral therapy was considered to reflect a return of normal salivary duct activity following reduction of viral load, improved CD4 count and reduced HIV cytokines in salivary gland.[1]

However, concerning the appropriate therapy for HIV associated parotid enlargement, other authors opined that ART and FNAC will only reduce the enlargement of HIV associated parotid cyst without total resolution.[10,18] Furthermore, radiotherapy was considered to predispose patients to xerostomia, mucositis, and malignant transformation.

The role of bleomycine and deoxycycline sclerotherapy in management of lymphoepithelial cyst among children was considered in an attempt to avoid surgery but sclerotherapy was unsuitable due to persistent residual swelling following the therapy and scarring that makes future surgery difficult in adults;[38] these limitations led to the suggestion by Steehler that the only definitive treatment of parotid lymphoepithelial cyst with or without HIV infection is surgical excision.[10] However another school of thought considered surgical intervention as high risk procedure in view of possibility of damage to facial nerve and possible morbidity in already immunocompromised patients.[18]

In majority of the cases in the present study, marked reduction in parotid enlargement and significant improvement in CD4 count, CD4 % and Viral load was observed following the commencement of HAART, the marked parotid reduction following combination antiretroviral therapy was also observed by Tripathi *et al* [12] who associated the combination of AZT and protease inhibitor with the most successful outcome. In the present study however, there was clinical persistence of the swelling in seven children despite marked size reduction. The overall recurrence rate of parotid enlargement could not be documented due to the short duration of follow up.

CONCLUSION

HIV positive children often present with bilateral parotid enlargement. A presumptive diagnosis of DILS was made in this cohort based on the classical clinical and cytological features. Following the commencement of antiretroviral therapy, further treatment was not needed due to satisfactory appreciable reduction of the parotid swellings. In view of the high positive predictive value of bilateral parotid swelling for HIV infection, all patients with such swelling should be screened for HIV infection and the unresolved cases on therapy should be monitored for possible malignant transformation.

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