Risk factors for HIV-related orofacial soft-tissue manifestations in children

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Abstract

A retrospective review of the medical records of 492 children perinatally exposed to the human immunodeficiency virus (HIV) compared the prevalence of orofacial soft-tissue manifestations in HIV-infected and noninfected children, identified risk factors for occurrence of orofacial lesions in HIV-infected children, and investigated specific orofacial lesions as indicators of progression of HIV disease. Application of eligibility criteria and the Centers for Disease Control classification of pediatric HIV infection resulted in selection of a study group of 91 HIV-positive children and a control group of 185 HIV-seronegative children who had seroreverted. Analysis of oral lesions showed that 67% of the study group and 8% of the control group had oropharyngeal candidiasis (OPC), 4% of the study group and 0% of the control group had parotid enlargement, and 3% of the study group and 0% of the control group had herpes simplex; all three differences were significant at $P < 0.04$. No statistically significant association was found between OPC and the risk factors of gender, ethnicity, or mode of delivery (vaginal versus cesarean). However, OPC was associated significantly with all progression markers examined: failure to thrive, use of antiretroviral agents, lower CD4 counts, and development of acquired immunodeficiency syndrome (AIDS). Orofacial manifestations are common in pediatric HIV infection and may serve as markers of infection and predictors of progression of HIV disease to AIDS. (Pediatr Dent 18:121–26, 1996)

By 1992, AIDS had emerged as the seventh leading cause of death among infants and children in the United States, and the effect on certain minority groups has grown increasingly disproportionate.[1] By the end of 1994, for example, more than twice as many black children had died of AIDS-related illnesses as had white children. In the United States, through June 1995, 6611 cases of pediatric AIDS had been reported to the Centers for Disease Control and Prevention (CDC), accounting for approximately 2% of all U.S. cases.[2] It is estimated that in1996 the total number of pediatric cases in the United States exceed 7000.

Most children with perinatal HIV infection appear normal at birth. Clinical problems usually begin within the first year,[3] and for about half of the children oral manifestations are the first sign. Oral manifestations are commonly found in HIV-infected children and pediatric AIDS patients.[4–7] Oral lesions may be the earliest clinical signs of HIV infection and disease progression in the adult population.[8–10] The few studies done in children[5, 7, 11, 12] have shown varying prevalences of oral manifestations of HIV infection in U.S. children. Since the mouth is easily examined, certain oral signs may be used to increase early detection of HIV infection in this vulnerable population, so that early intervention can be provided.

HIV targets primarily CD4 lymphocytes, although significant quantities of HIV probably reside in lymphoid elements throughout infection. In infected adults, CD4 cell counts decline as the disease advances, making them useful markers of the progress of the infection. Children, however, have CD4 cell counts that are normally higher and less consistent than those of adults. As a result, the CD4 count by itself is not as reliable a marker in pediatric cases. However, there is now evidence that, besides being one of the earliest clinical signs of HIV infection, orofacial manifestations are markers of HIV disease progression in both adult [8] and pediatric populations,[7] and they have a prognostic value independent of other commonly used markers such as CD4 counts.

The objectives of this study were: 1) to compare the prevalence of orofacial manifestations in HIV-infected children with that in non-HIV-infected children, 2) to identify risk factors for the occurrence of orofacial lesions in HIV-infected children, and 3) to investigate specific orofacial lesions as indicators of the progression of HIV disease to AIDS.

Subjects and methods

In this retrospective-cohort study we reviewed health evaluations and oral lesion data collected be-

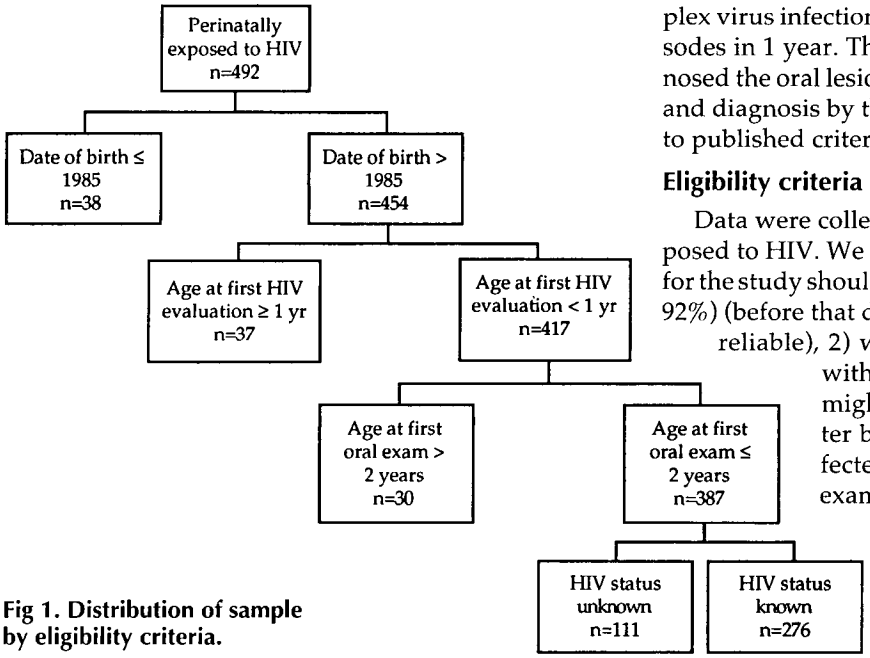

Fig 1. Distribution of sample by eligibility criteria.

TABLE 1. CLASSIFICATION OF STUDY POPULATION (N = 387) BY CDC CRITERIA*

CDC Classification	*N*	*%*
P-0 (indeterminate)	111	28.7
P-1 (HIV-infected, asymptomatic)	4	1.0
P-2 (HIV-infected, symptomatic)	87	22.5
P-3† (Seroreverters/noninfected)	185	47.8

* From: Centers for Disease Control: Classification system for human immunodeficiency virus (HIV) infection in children under 13 years of age. MMWR 36:225, 1987.

† Clinically adapted stage.

tween January 1988 and June 1994 by the Northern California Pediatric HIV Consortium, evaluating a total of 492 perinatally exposed children born to HIV-infected mothers in five health care facilities. These data had been abstracted by public health nurses from hospital medical records onto a standardized CDC form designed for the surveillance of pediatric HIV infection.

To assure that the comparison population was similar in demographic, socioeconomic, and risk factors to the study population, our non-HIV-infected control population consisted of seroreverting children born to HIV-positive mothers in the same study cohort.

The patients' clinical records were reviewed, beginning when a child of an HIV-infected mother was first identified (baseline) and continuing at 6-month intervals thereafter. Demographic, social, medical, and clinical management data were collected. The oral lesions recorded were oropharyngeal candidiasis (OPC) present for 2 months or recurrent despite topical therapy, parotid gland enlargement, and herpes simplex virus infection (HSV) present for two or more episodes in 1 year. The physicians and nurses who diagnosed the oral lesions were trained in their recognition and diagnosis by three of the study authors according to published criteria.[6]

Eligibility criteria

Data were collected on 492 children perinatally exposed to HIV. We determined that candidates eligible for the study should be children: 1) born after 1985 (454; 92%) (before that date, diagnosis and testing were not reliable), 2) who had their first HIV evaluation within 1 year of birth (417; 85%) (children might be followed more consistently after being identified as possibly HIV infected), and 3) who had their first oral exam within 2 years of birth (387; 79%) (to ensure follow-up begins at an early age). The HIV serostatus of 111 of the 387 eligible children was indeterminate, but was known for 276 children (Fig 1).

CDC stage classification

An overview of the CDC's 1987 classification of HIV infection in children younger than 13 years of age is shown in Table 1.[13] This classification reflects the broad range of pediatric HIV infection from the indeterminate stage to the symptomatic. Table 1 shows the proportions of the 387 children in our study group in each class. For purposes of the study, those in classes P-1 and P-2 are grouped as the HIV-infected group (N = 91) and those in class P-3 as the noninfected group or control group (N = 185). Children in class P-0 were excluded from the study because of the indeterminate nature of their infection.

Statistical analysis

The demographic distributions of the HIV-infected and noninfected children and the occurrence of oral manifestations are described by group using percentages. CD4 count and mode of delivery were analyzed at baseline rather than at the last chart review in order to restrict the data to events occurring before age 2 years.

Response variables, the oral manifestations of HIV infection, were dichotomous (ever/never since birth). Consequently, odds ratios describe the associations of the oral manifestations with risk factors and with measures of disease progression. When calculating odds ratios, a correction of 0.5 was added to every cell in tables that contained a zero. The significance of these associations is presented via 95% confidence intervals on the odds ratios and via two-sided Fisher's exact tests. Confidence intervals were calculated using an asymptotic variance estimate.[14] A Mantel-Haenszel summary odds ratio adjusted for age was computed for the associations of OPC with HIV status and with CD4 counts.[15] Because the

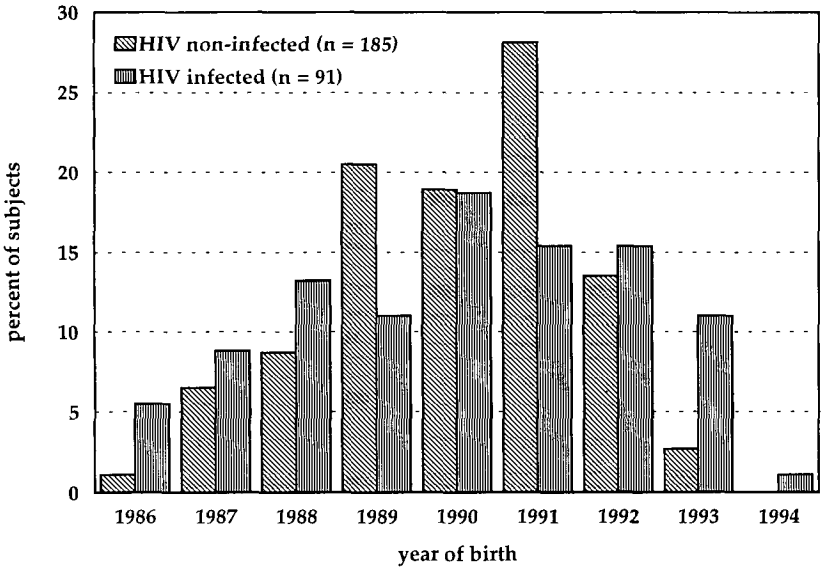

Fig 2. Distribution of subjects by HIV status and year of birth.

number of subjects in age-specific categories might be small, for graphic presentation we smoothed the data across ages via a running average smoother.

Finally, the Wilcoxon rank-sum test was used to assess the association between age and infection status, and also to estimate the association between numerical variables and occurrence of oral manifestations.

Results

Demographics

Demographic data on the study cohort are shown in Table 2. Both within and between the HIV-infected and noninfected groups, the proportions of males and females were similar. The data on ethnicity indicate that the sample was predominantly children of minority groups. African-American children especially and, to a lesser extent, Hispanic children were over-represented in the sample relative to their representation in the general population of Northern California. Thirty percent of HIV-infected and 16% of noninfected subjects were white.

Frequency distributions of the year of birth of study subjects by HIV status are shown in Fig 2. As with gender, year of birth distributions of the HIV-infected and noninfected groups were similar. At the first chart review the median ages were 5 and 4 months for HIV-infected and noninfected children, respectively, suggesting that follow-up of the noninfected children began slightly earlier, on average (Wilcoxon $P = 0.01$).

Age at last contact

The age at last contact for the 91 HIV-infected children was as follows: 24% were younger than 1 year old; 35% were between 1 and 2 years; 11% were between 2 and 3 years; and 30% were between 3 and 7 years.

Of the 185 noninfected children, 7% were younger than 1 year of age at last contact; 64% of children were between 1 and 2 years, comprising the majority of this group; 20% were between 2 and 3 years, and 9% were 3 years or older.

At the final chart review the median age was 20 months for both groups; the age ranges were 1 month to 7 years for HIV-infected children and 2 months to 5.5 years for noninfected children. The ages at last chart review of the two groups were not significantly different (Wilcoxon $P = 0.55$).

Oral lesion rates

Table 3 shows the rates of oral lesions present in the HIV-infected and noninfected groups during the study period. Among the HIV-infected children, 67% had OPC, 4% had parotid enlargement, and 3% had HSV. Eight percent of the noninfected children were diagnosed with OPC, but none with parotid enlargement or HSV. Odds ratios estimate that the HIV-infected children were 15 to 25 times more likely to have an orofacial manifestation than the noninfected children, which was statistically significant at $P < 0.04$ by Fisher's exact test. By far, the most

TABLE 2. DEMOGRAPHIC CHARACTERISTICS OF THE STUDY COHORT

Characteristic	*Noninfected* (N = 185) N	%	*HIV-infected* (N = 91) N	%
Gender				
Male	101	55	46	51
Female	84	45	45	49
Ethnicity				
African-American	125	68	44	48
White	29	16	27	30
Hispanic	23	12	17	19
Asian	4	2	2	2
Unknown	4	2	1	1

TABLE 3. ORAL LESION RATES IN NONINFECTED AND HIV-INFECTED CHILDREN

Oral Lesion	*Noninfected Rate* (N = 185)	*HIV-Infected Rate* (N = 91)	*OR (95% CI)*
OPC	8%	67%	25 (12–50)
PE	0%	4%	19 (1–358)
HSV	0%	3%	15 (1–287)

OPC = oropharyngeal candidiasis; PE = parotid enlargement; HSV = herpes simplex virus infection; OR = odd ratio; CI = confidence interval.

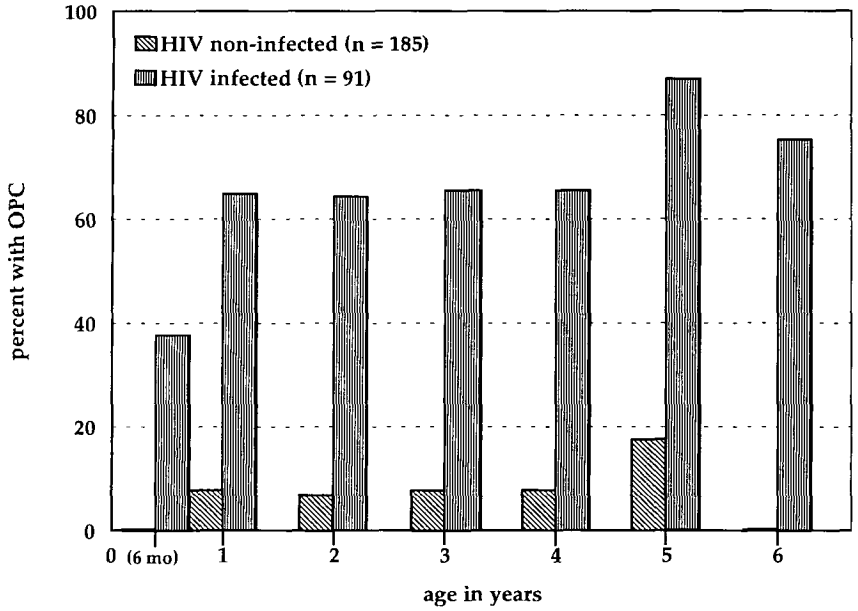

Fig 3. Percent of subjects ever having oropharyngeal candidiasis by age and HIV status at last record review (smoothed).

common orofacial manifestation was OPC, and it was selected for further analysis.

Risk factors associated with oropharyngeal candidiasis in HIV-infected children

We hypothesized that among HIV-infected children there would be no association with gender, but that minority race/ethnicity and vaginal delivery might be risk factors for developing OPC. We anticipated that differential access to health care by race/ethnicity might be associated with rates of OPC. We hypothesized also that the presence of vaginal candidiasis at delivery might be associated with the early development of OPC due to transmission of *Candida* to the baby during passage through the birth canal. We also wanted to know whether HIV-infected infants tended to develop OPC at a particular age, since *Candida* is common in non-HIV-infected newborn infants.

The associations between these factors and OPC are shown in Table 4. No statistically significant association between a child's risk of developing OPC and the risk factors of gender and ethnicity was found. Children born vaginally were slightly more likely than children delivered by cesarean section to develop OPC; however, this association was not statistically significant.

The rate of development of OPC increased in the first year of life and then stabilized thereafter (Figure 3). Thus, the development of OPC seems to peak by 1 year of age. The age-adjusted odds ratio for the association of OPC with HIV infection was 33 (95% CI 16–67).

Association of OPC with progression of HIV disease

It was of interest to determine whether OPC development in children was associated with indicators of the progression of HIV disease, such as failure to thrive, use of antiretroviral drugs, declining CD4 cell counts, and an AIDS diagnosis.

Progression of HIV disease as defined by failure to thrive showed a statistically significant association with the development of OPC (Fisher's $P < 0.001$; Table 5). Children with OPC were 7 times more likely to experience failure to thrive than were children without OPC. This may have been due to a more rapid progression of HIV disease in these children.

The presence of OPC was also highly associated with antiretroviral use (Fisher's $P = 0.006$; Table 5). Children receiving antiretroviral therapy (ART) were 4.4 times more likely to have OPC. OPC may have occurred as a result of antiretroviral drug use or because these children were more ill than those not receiving ART. The use of these drugs also may reflect an AIDS diagnosis: 85% of children with AIDS had histories of ART compared with 70% of children without AIDS. OPC rates were 15% in children with no ART and no AIDS, 57% among those with ART but no AIDS, and 88% among those with ART and AIDS. Thus, use of antiretrovirals indicates an earlier stage of disease progression than AIDS itself.

OPC rates in the HIV-infected children varied inversely with their CD4 counts (Wilcoxon $P = 0.04$; Fig 4). The median CD4 count nadir among children younger than 2 years of age with and without OPC was 995 and 1700 cells per μL, respectively. Nine of 10 children with missing CD4 counts entered the study before data on this variable were collected (born 1986–1988); however, before age 2, six had OPC and an AIDS diagnosis, two had neither OPC nor AIDS, and one had OPC but no AIDS diagnosis. The tenth child with missing CD4 data also had OPC but no AIDS. As with antiretroviral therapy, low CD4 counts may be an earlier indicator of HIV disease progression than AIDS.

TABLE 4. RISK FACTORS ASSOCIATED WITH OPC

Risk Factor	N	*OPC rate*	*OR (95% CI)*
Gender			
Male	46	76%	1.0
Female	45	58%	0.43 (0.2–1.1)
Ethnicity			
White	27	70%	1.0
Black	44	66%	0.81 (0.3–2.3)
Hispanic	17	65%	0.77 (0.2–2.8)
Mode of delivery			
Cesarean	17	41%	1.0
Vaginal	42	50%	1.43 (0.5–4.5)
Unknown	32	53%	—

OPC was significantly associated both with low CD4 counts and with an AIDS diagnosis. Odds ratios indicate that children with OPC were 4 times more likely to have low CD4 counts and almost 9 times more likely to have AIDS than children without OPC (Table 5). After adjusting for age, the odds ratio associating CD4 < 1000 with OPC was 4.9 (95% CI 1.9–12.9).

Discussion

Studies[4, 7-9, 12] have established that orofacial manifestations are highly prevalent in immunocompromised children. Very little evidence, however, exists as to specific risk factors for orofacial manifestations, timetables for their onset, or their association with the presence and progression of HIV disease. In this study, the most common oral manifestation was OPC, which was found in 67% of the HIV-infected children. One of the advantages of this study was the similarity between the HIV-infected study cohort and the noninfected comparison group, which was drawn from the same population of children perinatally exposed to HIV. This comparison group had an OPC prevalence of 8%. This striking increase in risk of OPC in HIV-infected children demonstrates the utility of this diagnosis as a marker of HIV infection in children. Specifically, studies[16] show that in the noninfected general population of children, *Candida* is present in approximately 4% of newborn infants during the first few weeks of life and is very unlikely to appear in the older infant.

One of the limitations of our study is that these data were collected by chart review and represent the child's history through the time of the review. For example, among subjects who were 3 years old at the last record review, OPC may have been diagnosed at a much younger age. Age-adjusted comparison of OPC rates in HIV-infected and noninfected subjects were included to control for potentially different numbers of visits. Although sick children usually visit health care clinics more frequently than healthy children, the disparity in the rates of oral manifestations by HIV status are too large to be explained by different numbers of clinic visits.

The early appearance of OPC in the HIV-infected children during the first year of life suggests that it may distinguish those children who were perinatally exposed to HIV and will ultimately prove to be infected from those who will serorevert. Parotid enlargement and HSV were also found in the infected group, although their prevalence was not as high as that of OPC. Nevertheless, because these conditions are so rare in the general pediatric population, the presence of these manifestations in children is strongly suggestive of HIV-related immunodeficiency. Since the mouth is relatively easy to examine, the presence of oral signs will help dental and medical professionals to detect pediatric HIV infection early and begin interventions that might delay progression of the disease to AIDS. Early recognition and management of oral lesions may help to reduce morbidity in this vulnerable population.

Risk factors for OPC development showed slight variations in the association of gender and ethnicity. Access to health care, which has been shown to vary with ethnicity, can play a major role in disease development.[17, 18] These variations in HIV disease within underserved ethnic groups require further investigation. Similarly, mode of delivery could be associated with OPC development in perinatally exposed children, and should be investigated further. The rate of

TABLE 5. ASSOCIATION OF OPC WITH MARKERS OF PROGRESSION TO HIV DISEASE

Markers of Progression	N	*OPC rate*	*OR (95% CI)*
Failure to thrive			
No	39	44%	1.0
Yes	51	84%	7.0 (3–19)
Antiretroviral use			
No	20	40%	1.0
Yes	71	75%	4.4 (2–12)
CD4 counts			
> 1000	54	35%	1.0
< 1000	27	70%	4.4 (2–12)
Unknown	10	80%	—
AIDS diagnosis			
No	43	44%	1.0
Yes	48	88%	8.8 (3–25)

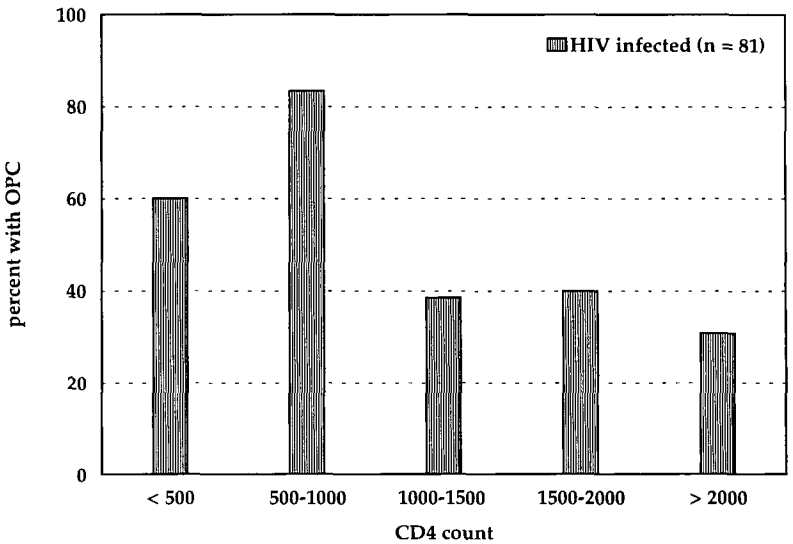

Fig 4. Percent of subjects ever having oropharyngeal candidiasis by CD4 counts at baseline record review (age ≤ 2 years).

development of OPC increased in the first year of life and stabilized thereafter; therefore, young infants should be monitored most closely for oral manifestations. Since most healthy infants will not develop OPC in the second semester of life, the presence of OPC in children of this age who are not subject to other risk factors, such as antibiotic use or illness, should be considered a possible manifestation of immunodeficiency.

OPC development was strongly associated with all four markers of the progression of HIV disease examined—failure to thrive, use of antiretroviral agents, declining CD4 counts, and progression to AIDS. Thus, OPC should be considered a marker of the progression of HIV disease in infants and children, and the frequency of episodes may be an indicator of the stage of HIV disease. Monitoring of the CD4 counts in association with OPC will provide additional clinical signs of disease progression.

In conclusion, this study found that HIV-infected children are 15 to 25 times more likely than noninfected children to develop orofacial manifestations. The presence of oral manifestations in HIV-seropositive children younger than 1 year of age, when combined with other indicators such as CD4 counts, is a significant indicator of a child's prognosis and a crucial factor in planning interventions and treatments. Primary care of these patients should include a careful oral examination at regular intervals, with an emphasis on oral health promotion/prevention and early intervention.

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