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TEMPORAL TRENDS IN MUCOCUTANEOUS FINDINGS AMONG HUMAN IMMUNODEFICIENCY VIRUS-1 INFECTED CHILDREN IN A POPULATION-BASED COHORT

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Abstract

Objective—To provide data regarding prevalence of pediatric Human Immunodeficiency Virus-1 (HIV-1) mucocutaneous manifestations in the era of highly active antiretroviral therapy (HAART).

Methods—We conducted population-based, prospective, multi-center pediatric HIV-1 surveillance among 276 children with perinatally acquired HIV-1 from 1988– 2009. All CDC category A, B, and C mucocutaneous conditions were evaluated.

Results—CDC defined HIV-1 related mucocutaneous conditions among the 276 children were: 152, category A; 60, category B; 1, category C. Nearly half (43.4%, [66/152], 35.0% [21/60]) of category A and B diagnoses, respectively occurred in the first year of life, with 59.2% (90/152) and 61.7% (37/60), respectively occurring in the first 2 years of life. The most frequent infectious diagnosis was oropharyngeal thrush (42.4%, [117/276]); the most common inflammatory diagnosis was diaper dermatitis (25.7% [71/276]). There was a temporal decline in prevalence of A and B mucocutaneous diagnoses which was significant for category A: 123, pre-HAART cohort; 29, post-HAART cohort ($p < 0.01$), and category B: 55, pre-HAART; 5, post-HAART ($p < 0.01$).

Conclusions—In children with perinatal HIV-1, there was a significant decline in CDC category A and B mucocutaneous diagnoses by temporal cohort, consistent with the introduction of antiretrovirals and HAART. Clinical category A and B mucocutaneous diagnoses were most

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Author Contributions: Drs Sturt, Maldonado, and Berk are responsible for the study concept and design. Dr. Maldonado was involved in data acquisition. Drs Sturt, Anglemyer, Berk, and Maldonado were involved in analysis and interpretation of the data. Dr. Anglemyer was responsible for statistical analysis and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Sturt and Maldonado were responsible for drafting of the manuscript and Drs Sturt, Maldonado, Berk, and Anglemyer were responsible for critical revision of the manuscript for important intellectual content. Dr. Maldonado obtained funding and provided study supervision.

Conflicts of Interest: Dr. Maldonado is on vaccine advisory boards for Merck and Novartis. Dr. Sturt received funding from Pfizer to attend a conference in 2010. Drs. Anglemyer and Berk have nothing to disclose.

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common in the first 2 years of life, emphasizing the importance of early HIV-1 testing and HAART initiation.

Keywords

Perinatal human immunodeficiency virus (HIV-1); acquired immunodeficiency syndrome (AIDS); highly active antiretroviral therapy (HAART); Mucocutaneous; dermatology; skin

Introduction

The increasing availability of antiretroviral agents has improved the treatment of human immunodeficiency virus-1 (HIV-1) infection and decreased perinatal transmission. Mucocutaneous conditions are common among HIV-1 infected children, at presentation and throughout disease progression, and are part of the Center for Disease Control (CDC) Revised Classification System for children less than 13 years of age with HIV-1(1). Clinical categories within this staging system were designed to provide prognostic indicators: category N, not symptomatic; category A, mild symptoms; category B, moderate symptoms; category C, severe symptoms or Acquired Immunodeficiency Syndrome (please see: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm>). Clinical categories are mutually exclusive and must be associated with HIV-1 infection. Mucocutaneous manifestations of pediatric HIV-1 can be broadly categorized as infectious, inflammatory, neoplastic, or other(2). They may be multiple, atypical in their presentation, specific for HIV-1 infection, or more severe, frequent, or treatment-resistant in HIV-1-infected children relative to uninfected children(2, 3).

We have conducted a surveillance project of perinatal HIV-1 in Northern California through the Pediatric Spectrum of Disease (PSD) project. This population-based cohort has allowed us to describe clinical and epidemiologic aspects of perinatal HIV-1(4). In this study, we extended analysis of this cohort to children born through 2008 and characterize the spectrum of mucocutaneous conditions and identify temporal trends in a population-based cohort of perinatally HIV-1 infected children.

Material and Methods

Study Design

The study population was identified through Stanford University's PSD project, as previously described(4). PSD was a longitudinal, multi-center pediatric HIV-1 surveillance study which concluded at the end of 2009, involving the major referral hospitals in Northern California with pediatric HIV-1 clinics. It followed all children born to known HIV positive mothers and all children later identified as HIV-1 infected. The surveillance area comprises 12 counties in Northern California, with a total population of approximately 10 million. A single study nurse visited each study site in six month intervals to collect, from medical records, initial and updated information on newly and previously identified children, respectively. Race/ethnicity was defined by the participants.

To maintain confidentiality and prevent duplication of records, each patient was assigned an anonymous unique identifier and entered into a standardized database. The study was approved yearly at Stanford University and the Institutional Review Board at each surveillance hospital. Given the study design, the requirement for informed consent was waived.

Subjects and Definitions

Children were included in the current study if they had perinatal HIV-1 infection, were born during 1988–2008, and followed at a surveillance hospital. Mucocutaneous diagnoses were extracted from chart notes written in the medical record by the patient's primary provider. Because the CDC 1994 Revised Classification System does not provide a definition for dermatitis, we identified diagnoses of dermatitis from the provider's medical record and classified them as infectious or inflammatory(5). Since the 1994 Classification System (1) states that inflammatory/drug-related causes should not be used for classification, only conditions commonly attributed to tissue involvement with micro-organisms were classified as infectious, and were evaluated as category A/B/C(5).

We grouped patients, according to their date of birth, into two cohorts reflecting the introduction of HAART and other major temporal changes in the guidelines for the management of pediatric HIV-1. The main outcome measure was the prevalence of pediatric mucocutaneous conditions over two cohorts: pre-HAART 1988–1995; post-HAART: 1996–2008. The pre-HAART cohort represents a period characterized by: the 1990 FDA's approval of zidovudine(6), delayed HIV-1 diagnoses, and lack of combination antiretroviral therapy, improved HIV-1 identification and treatment, the 1992 guidelines recommending prophylaxis for *Pneumocystis jiroveci* pneumonia (7), the advent of the PACTG 076 trial (8). The post-HAART cohort represents the effects of the 1995 recommendations for prenatal HIV-1 testing, the introduction of the protease inhibitor in 1996, and the advent of HAART (9, 10).

Use of Antiretrovirals

All FDA approved antiretroviral agents prescribed by the treating physician were considered. HAART was defined as at least 3 antiretrovirals of two classes(11). Regimens with 3–4 NRTIs were considered dual therapy. Ritonavir, when used in combination with other PIs for pharmacologic boosting, was not considered as an individual agent. Throughout the study, three categories of antiretroviral regimens (ARVs) were considered: none, mono or dual (M/D) and HAART. One month was chosen to allow sufficient time for therapeutic onset, as previously described(4).

Statistical Analysis

The main outcomes were CDC clinical category A, B, or C mucocutaneous diagnoses(1). Simple logistic regression analyses were performed to estimate the association between baseline demographics (age at HIV-1 diagnosis, race, sex), mucocutaneous diagnoses, and temporal birth cohorts, as defined above. The analysis was performed using R (Zuerich, Switzerland). P-value<0.05 was considered statistically significant. CD4 counts/percents, within 180 days of each cutaneous diagnosis, were identified for each patient. The child's immune status at the time of diagnosis was then estimated using the CDC's Revised Classification System(1)

Results

There were 276 perinatally HIV-1 infected included in the analysis; 55.4% were female and 44.6% were male. The median age at first HIV-1 evaluation was 82 days (IQR 0–422 days). The median age of children with a category A and B mucocutaneous diagnosis were both 1.4 years with IQRs 0.5–3.6 years and 0.77–2.76 years, respectively. Approximately 24.0% (66/276) of children died during follow-up. Of the 276 children in the study, 93.4% (62/66) died of HIV-1 related causes.

Of the 276 children, there were no notable differences in Category A or B skin diagnoses between sexes. Race, sex, and age at first diagnosis were not statistically different within categories of illness. During follow-up children had at least one illness (cutaneous or otherwise) in the following categories: 82.6%, Category A; 71.7%, Category B; 46.4%, Category C. Of 276 children, the following had CDC classified mucocutaneous diagnoses at any time during follow-up: 152, category A; 60, category B, 1, category C. Of children who were diagnosed with a Category A mucocutaneous condition, 43.4% (66/152) were diagnosed in the first year of life, 59.2% (90/152) in the first 2 years of life; of children who were diagnosed with a Category B dermatologic condition, 35.0% (21/60) were diagnosed in the first year of life, 61.7% (37/60) diagnosed in the first 2 years of life. The most frequent infectious mucocutaneous diagnoses were oropharyngeal thrush (42.4%, [117/276]), and varicella-zoster virus infection (19.2% [53/276]). The most common inflammatory conditions were diaper dermatitis (25.7% [71/276]) and drug rash (10.1%, 28/276). The age-adjusted immune status for each condition is shown in Table 1. The prevalence of combined varicella zoster disease decreased significantly across cohorts: 25.1%, pre-HAART; 4.9%, post-HAART ($p<0.05$). The prevalence of diaper dermatitis decreased significantly across cohorts: 32.8%, pre-HAART; 8.6% post-HAART ($p<0.05$). The prevalence of drug rash decreased significantly: 12.8%, pre-HAART; 3.7%, post-HAART ($p<0.001$). There was not a significant decline in diagnoses of eczema or atopic dermatitis by cohorts.

The proportions of children receiving antiretrovirals at the time of their first Category A skin diagnosis were: non-HAART ARV 25.0% (38/152); HAART 9.2% (14/152); and no therapy 65.7% (100/152). The proportions of children receiving antiretrovirals at the time of their first Category B cutaneous diagnosis were: non-HAART ARV 41.6% (25/60); HAART ARV 5.0% (3/60); and no therapy 53.3% (32/60). The only category B mucocutaneous diagnosis which occurred while children were on HAART was oropharyngeal thrush. The child diagnosed with Kaposi's Sarcoma was not on HAART at the time of diagnosis.

Comparing the pre and post-HAART eras, there was a decline in the odds of first category A and B mucocutaneous diagnosis (Table 2). The decline was significant for category A diagnoses: 123, pre-HAART; 29, post-HAART ($p<0.01$), and for category B diagnoses: 55, pre-HAART; 5, post-HAART ($p<0.001$) (Table 2). The decline in category A and B diagnoses remained significant when varicella-related diagnoses were removed.

Discussion

HAART initiation in the perinatally HIV-1 infected population decreases morbidity and mortality (4, 12, 13). Studies following HIV-1 infected children longitudinally in the HAART era have also shown decreasing proportions of infectious complications (14–16) and mucocutaneous manifestations (17). However, few data exist regarding the prevalence of mucocutaneous manifestations in children with perinatal HIV-1 over multiple birth cohorts. Our 22 year, longitudinal, population-based study demonstrates a statistically significant decline in clinical category A and B mucocutaneous diagnoses between the pre and post-HAART cohorts. Our use of cohorts is a surrogate marker for major temporal changes in the guidelines for the management of pediatric HIV-1.

The decline in morbidity attributed to mucocutaneous manifestations of perinatal HIV-1 seen over multiple cohorts can most likely be attributed to the use of antiretroviral medications, including the eventual introduction of HAART in 1996. Another factor that may contribute to the reduction of cutaneous manifestations is the licensure of the varicella vaccine in 1995, with a subsequent decline in varicella disease in areas with adequate vaccine coverage (18). This vaccine was first recommended for use in HIV-1 infected children in 1999, and required asymptomatic/mildly symptomatic clinical status and CD4 %

>25 cells/mm³ (19). The recommendations changed in 2007 to include similarly asymptomatic/mildly symptomatic HIV-1 infected children with a CD4 % of >15 cells/mm³ (18). Given the retrospective study design, we cannot distinguish the effect of HAART versus varicella vaccination in the changing prevalence of varicella disease (20). However, when varicella related mucocutaneous conditions were removed from the analysis, the results were unchanged, suggesting that the introduction of HAART drove the reported decline in category B conditions. Also, since there were no reports of varicella vaccination in our study subjects and previous studies have shown post-vaccine seroconversion rates, as well as vaccine receipt, to be low in the perinatal HIV-1 population (20), it is most likely that HAART use drove the reported decline in prevalence of varicella disease.

Clinical category B conditions did not decline significantly with the use of mono/dual therapy. Early clinical trials showed that only small percentages of children receiving dual therapy were able to achieve an undetectable viral load (21). Since viral load testing was not routinely recommended in clinical practice until the late 1990's, viral loads were not routinely available until cohort 3 (22). Thus, it was not possible to compare viral loads across cohorts. A significant decline in category B diagnoses in our cohort occurred once HAART was introduced, mirroring the reported trend in decline in overall opportunistic infections in the HAART era (14). It is interesting to note that although the uptake of HAART increased across birth cohorts, the prevalence of drug rash decreased significantly. The explanation for this trend is unclear. However, a recent randomized, controlled trial of extended infant nevirapine use to prevent breastfeeding transmission of HIV-1 showed that <1% of infants who received extended nevirapine had a Grade 2B or worse rash (23). This suggests that rashes in children exposed to antiretrovirals are less likely to be associated with antiretrovirals, and may be related to factors and comorbidities associated with untreated HIV infection. Unfortunately, there is a paucity of literature attempting to characterize causes, types, and trends in drug rashes in HIV-infected individuals, particularly in children. In HIV-infected adults, antibiotics are often implicated in drug rashes (24) and lower CD4 counts have been associated with increased incidence of drug rashes (25). In our study, perhaps later birth cohorts and patients taking HAART developed fewer rashes because of enhanced immunologic status or because they received fewer drug exposures, particularly to antibiotics.

One unique finding in our cohort was that the majority of clinical category A and B mucocutaneous manifestations occurred in the first two years of life. Our findings further emphasize the importance of early HIV-1 testing and HAART initiation. In our cohort, most mucocutaneous manifestations were infectious (26). The overall prevalence of mucocutaneous conditions we report is consistent with other publications in children with perinatal HIV-1 (17, 27).

Another high prevalence cutaneous manifestation in our cohort was "dermatitis". The use of "dermatitis" in the 1994 CDC Classification System (1) likely influenced the preferential use of this term during documentation in medical charts by the HIV-1 specialists in our study. As a result of the language in the CDC Classification System (1), more specific mucocutaneous conditions may not have been documented, since "dermatitis" was a Category A diagnosis. The inclusion of this less-specific term is a weakness of the CDC Classification System (1) and more research about the prognostic significance of more specific mucocutaneous conditions is required.

Although longitudinal, our study was not randomized and data collection was limited to information documented by providers at the participating facilities. As such, the majority of the mucocutaneous diagnoses were made by the patient's HIV-1 specialist. The diagnoses reported in this publication are common in HIV-1 and Primary Care and the minority are

formally referred to Dermatology (28). Thus, our manuscript reflects the spectrum of conditions in a “real world” setting. Incomplete capture of perinatally infected children may also have biased outcomes. However, we previously demonstrated the high capture rate in our population-based study, thus reducing recruitment bias (29). To standardize data collection, one individual extracted data from patient records during the entire study period in all the participating facilities.

Conclusion

Over 22 years of longitudinal follow-up, there was a significant decline in mucocutaneous diagnoses by clinical cohort, consistent with the introduction of antiretrovirals and eventually HAART. Clinical category A and B mucocutaneous diagnoses were most common in the first 2 years of life, emphasizing the importance of early HIV-1 testing and HAART initiation.

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Infectious and Inflammatory Mucocutaneous Manifestations of 276 Children with Perinatal HIV-1 by Age-Adjusted Immune Status

Table 1

Infectious*	N (%)	Category A (%)	Category B (%)	Category C (%)	Missing	Inflammatory	N (%)	Category A (%)	Category B (%)	Category C (%)	Missing (%)
Combined Oropharyngeal Thrush**	117					Diaper Dermatitis	71	30/71 (42.3)	16/71 (22.5)	17/71 (24.0)	8/71 (11.3)
Oral Thrush (<2m)	91	33/91 (36.3)	12/91 (13.2)	30/91 (33.0)	16/91 (17.6)	Drug Rash	28	8/28 (28.6)	5/28 (17.6)	11/28 (39.3)	4/28 (14.3)
Oropharyngeal Candidiasis (>2m)	48	15/48 (31.3)	10/48 (20.8)	21/48 (43.8)	2/48 (4.2)	Atopic Dermatitis	24	13/24 (54.2)	4/24 (16.7)	2/24 (8.3)	5/24 (20.8)
Combined Varicella Zoster Virus (VZV)	53					Insect Bite	23	11/23 (47.8)	6/23 (26.1)	3/23 (13.0)	3/23 (13.0)
Primary Varicella	36	16/36 (44.4)	6/36 (16.7)	2/36 (5.6)	12/36 (33.3)	Eczema	21	11/21 (52.4)	2/21 (9.5)	5/21 (23.8)	3/21 (14.3)
Disseminated VZV	12	4/12 (33.3)	3/12 (25.0)	2/12 (16.7)	3/12 (25.0)	Seborrheic Dermatitis	7	2/7 (28.6)	2/7 (28.6)	1/7 (14.3)	2/7 (28.6)
One Dermatomal Herpes Zoster	21	9/21 (42.9)	n/a	5/21 (23.8)	7/21 (33.3)	Leiomyosarcoma	3	n/a	n/a	n/a	3/3 (100.0)
Herpes Zoster‡	2	n/a	n/a	1/2 (50.0)	1/2 (50.0)	Contact Dermatitis	2	1/2 (50.0)	n/a	n/a	1/2 (50.0)
Tinea	29	11/29 (37.9)	5/29 (17.2)	6/29 (20.7)	7/29 (24.1)	SJS/EM	2	n/a	1/2 (50.0)	1/2 (50.0)	0/2 (0.0)
Impetigo	29	11/29 (37.9)	9/29 (31.0)	5/29 (17.2)	4/29 (13.8)	Urticaria	2	n/a	n/a	n/a	2/2 (100.0)
Cellulitis	28	16/28 (57.1)	3/28 (10.7)	7/28 (25.0)	2/28 (7.1)	Kaposi's Sarcoma	1	n/a	n/a	1/1 (100.0)	0/1 (0.0)
Combined Herpes Simplex Virus (HSV)	20					Acanthosis	1	n/a	n/a	n/a	1/1 (100.0)
HSV	19	7/19 (36.8)	4/19 (21.1)	4/19 (21.1)	4/19 (21.1)	Heat Rash	1	1/1 (100.0)	n/a	n/a	0/1 (0.0)
Recurrent HSV Stomatitis‡	2	n/a	1/2 (50.0)	1/2 (50.0)	0/2 (0.0)						
Subcutaneous Abscess	16	5/16 (31.3)	3/16 (18.8)	3/16 (18.8)	5/16 (31.3)						
Molluscum	15	4/15 (26.7)	5/15 (33.3)	1/15 (6.7)	5/15 (33.3)						
Viral Exanthem/Measles	6	n/a	n/a	2/6 (33.3)	4/6 (66.7)						
Cutaneous Candidiasis	9	3/9 (33.3)	2/9 (22.2)	3/9 (33.3)	1/9 (11.1)						
Scabies	3	n/a	2/3 (66.7)	n/a	1/3 (33.3)						
Furuncle	2	1/2 (50.0)	n/a	1/2 (50.0)	0/2 (0.0)						

* Combined outcomes are not mutually exclusive, children had multiple conditions

** Includes all children regardless of age at diagnosis/length of condition

‡ Herpes Zoster, two distinct episodes/more than one dermatome

§ Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes in one year)

Table 2
Mucocutaneous Manifestations of 276 Children with Perinatal HIV-1 Grouped by Cohort^{1,2}

Birth Cohort	Category A (N=152)		Category B (N=60)		Category C (N=1)		Mean Duration of Follow-up [Years (SD)]
	OR	N (%)	OR	N (%)	OR	N (%)	
Pre-HAART: 1988–1995 (n=195)	Ref	123 (63.1)	Ref	55 (28.2)	Ref	1 (<1)	12.0 (6.7)
Post-HAART: 1996–2009 (n=81)	0.33**	29 (35.8)	0.17**	5 (8.3)	--	0 (0)	7.3 (3.9)

¹ Row percentages

² Columns are not mutually exclusive, children could have had multiple category A, B, and C diagnoses

** p value < 0.01