Human Immunodeficiency Virus Infection in Hemophilic Children

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ABSTRACT. The following groups were compared: (1) children <18 years old who have hemophilia-associated acquired immunodeficiency syndrome (AIDS) with other children with AIDS and with adults who have hemophilia-associated AIDS and (2) asymptomatic HIV-infected hemophilic children with asymptomatic HIV-infected hemophilic adults. Children with hemophilia-associated AIDS were older than other children with AIDS (medians 13 and 1 years, respectively) and less frequently had lymphocytic interstitial pneumonitis (5% *v* 48%) but had similar incidences of *Pneumocystis carinii* pneumonia (51% *v* 53%) and similar case to fatality ratios (59% *v* 61%). Children with hemophilia-associated AIDS had *P carinii* pneumonia significantly less often than did adults with hemophilia-associated AIDS, but both had similar case to fatality ratios (adults 72% with *P carinii* pneumonia, 68% dead). Significantly more hemophilic children than adults with AIDS were nonwhite (30% *v* 14%) and resided in the tristate area of New York/New Jersey/Pennsylvania (43% *v* 25%). The immune effects of human immunodeficiency virus (HIV) to date on asymptomatic pediatric and adult hemophiliacs are similar but may be more severe in adults. It is concluded that, although some of the clinical manifestations of AIDS (eg, lymphocytic interstitial pneumonitis) occurring or not occurring in older children infected through blood factor products differ from those of other children with AIDS, disease outcome to date is equally poor. The reasons for the differences between hemophilic children and hemophilic adults with and without AIDS warrant further investigation. *Pediatrics* 1988;82:565–570; *human immunodeficiency virus, acquired immunodeficiency syndrome, hemophilia.*

ABBREVIATIONS. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; CDC, Centers for Disease Control; T_H, $T_{helper\ lymphocyte}$; T_s, $T_{suppressor}$ lymphocyte; H/S, T_H to T_s ratio.

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Human immunodeficiency virus (HIV) is increasingly recognized as a pediatric problem. In this study, we defined the effects of HIV in children infected after infancy through blood components by describing the immune and clinical status of infected hemophilic children and comparing them with other infected children and with infected adults. We addressed the following questions: (1) What are the epidemiologic characteristics of hemophilic children with AIDS and do hemophilic children with AIDS differ from other children with AIDS? (2) Do hemophilic children with AIDS differ from hemophilic adults with AIDS? (3) What are some of the effects of HIV infection on the immune systems of hemophilic children without AIDS and how do these effects differ from those seen in infected hemophilic adults?

MATERIALS AND METHODS

Patients

For both the hemophilic and nonhemophilic groups, we defined "pediatric" as individuals <18 years of age at the time of the AIDS diagnosis or first immunologic evaluation. Data concerning patients with hemophilia-associated AIDS were obtained through the surveillance system maintained by the Division of Host Factors, Center for Infectious Diseases, Centers for Disease Control (CDC); approximately 97% of hemophilia-associated AIDS cases are recorded in this system.[1] Data concerning other patients with AIDS were obtained from the AIDS surveillance system maintained by the AIDS Program, Center for Infectious Diseases, CDC. These two systems are interactive and complementary. Remaining data concern a cohort of 217 hemophilic individuals from hemophilia treatment centers throughout the United States who were using factor concentrate products and did not have HIV symptoms at the time of enrollment between February and June 1984.[2] From March through August 1985, 173 (80%) of these persons returned for further evaluation, and in May 1986, all participating hemophilia treatment centers were contacted to determine whether any members of the initial cohort had AIDS. The informed consent of each participant, and of their guardians, when applicable, was obtained at each stage of the cohort study.

Previous analyses and data suggested that the seroconversion curve to HIV may differ for factor VIII- and factor IX-recipient populations.[3,4] Because of this potential bias, for immune test analyses, cohort participants were divided on the basis of their HIV serologic results, as follows: study group 1, factor VIII recipients who were seropositive at the 1984 evaluation; study group 2, factor IX recipients who were seropositive at the 1984 evaluation, study group 3, factor VIII and factor IX recipients who were seronegative at 1984 evaluation and seropositive in 1985; and study group 4, factor VIII and factor IX recipients who were seronegative at both the 1984 and 1985 evaluations.

Laboratory Methods

Serum specimens from cohort participants were tested for HIV antibody by Western blot analysis, as previously described,[4] at a dilution of 1:100, and banding patterns were compared with those of a known positive control serum. Serologic reactions with any combination of the 18-, 25-, and 41-kd proteins of HIV were scored as positive. We used a fluorescence-activated cell sorter (FACS IV, Becton-Dickinson, Sunnyvale, CA) to quantitate lymphocyte subpopulations by indirect immunofluorescence with commercial monoclonal antibodies (OKT3 for T cells, OKT4 for T_{helper} lymphocytes [T_H], and OKT8 for $T_{suppressor}$ lymphocytes [T_S] [Ortho Diagnostics, Raritan, NJ]) and fluorescein-conjugated anti-mouse immunoglobulin (CDC).[5,6] Immunoglobulins G, A, and M were quantitated using a DuPont (aca) discrete clinical analyzer (DuPont Company, Wilmington, DE).

Statistical Analysis

We compared dichotomous or categorical variables using the Fisher exact test (two-tailed). A weighted linear regression, using the number of patients with hemophilia-associated AIDS for each time period in which AIDS was diagnosed, was performed to describe the relationship of age of patients with hemophilia-associated AIDS to time (quarterly and yearly).[7] A test for a linear trend in proportions was used to assess the relationship of racial distribution to time (quarterly).[7] The Wilcoxon rank sum test was used to test for differences in immunologic results between selected study groups.[8] The Wilcoxon signed rank test was used to compare the initial and follow-up immune test results within study groups.[8] Spearman's rank correlation coefficient (r_s) was used to measure the strength of the association between the results of selected immune tests and age within each of the cohort study groups.[8] Significance levels were set at .05.

RESULTS

AIDS Surveillance

Hemophilic v Nonhemophilic Children. As of Sept 15, 1986, 37 (10%) of 383 patients <18 years old with AIDS had received blood components for a clotting defect. Nonhemophilic and hemophilic

children with AIDS differed in that the age and race distributions of the former group (median 1 year of age, range 1 to 17 years of age) were consistent with predominantly intrauterine or perinatal infections; in the latter group, age (median 13 years, range 3 to 17 years and race distributions were consistent with postnatal transmission (Table 1). The proportions with a diagnosis of *Pneumocystis carinii* pneumonia did not differ for hemophilic (51%) and nonhemophilic (53%) children; two (5%) hemophilic and 166 (48%) nonhemophilic children were reported to have lymphocytic interstitial pneumonitis ($P < .0001$). Case to fatality ratios did not differ for hemophilic and nonhemophilic children.

Hemophilia-Associated AIDS. As of Sept 15, 1986, 37 (15%) of 238 patients with hemophilia-associated AIDS were <18 years of age at the time of their AIDS diagnosis (Table 1). The median age of patients with hemophilia-associated AIDS has not changed significantly since the first case was diagnosed (retrospectively) in January 1981. The proportion of patients surviving as of February 1987 did not differ significantly by age group (pediatric [40%] and adult (median 36 years of age, range 18 to 81 years of age) hemophilic cases [32%]). Proportionately fewer pediatric patients with hemophilia-associated AIDS had *P carinii* pneumonia than did adult patients (51% *v* 72%, $P = .020$). More had diagnoses of *Mycobacterium avium* (three [8%] *v* 13 [6%]), cryptosporidiosis (five [13%] *v* eight [4%]), herpes virus infection (four [11%] *v* seven [3%]), or Burkitt lymphoma (one [3%] *v* one [0]), but these differences were not statistically significant.

Coagulation defects were similar for pediatric and adult patients with hemophilia-associated AIDS (89% and 88%, respectively, with hemophilia A; 11% and 6%, respectively, with hemophilia B; 0% and 6%, respectively, with von Willebrand disease or other defects). The blood product usage and inhibitor status of these patients were also similar (differences were not significant). Significantly more pediatric than adult patients with hemophilia-associated AIDS were black or Hispanic ($P = .027$); black and white children did not differ in their use of locally produced blood products (including cellular products, cryoprecipitate, and plasma) or other risk factors for AIDS. No hemophilic children or their parents were reported to be either homosexual or illicit users of IV drugs. The racial distribution did not vary significantly throughout time in either the pediatric or adult groups. Only one black or hispanic child was <10 years old; that black child was 3 years of age.

Significantly more pediatric than adult patients with hemophilia-associated AIDS resided in the tristate area of New York/New Jersey/Pennsylvania (43% *v* 25%, $P = .045$) (Hemophilic patients living in one of these three states frequently received their care in a hemophilia treatment center in another of these three states.) One white and three Hispanic children lived in California; three white and three black children lived in New Jersey; four white, two black, and one Hispanic children lived in New York: and three white children lived in Pennsylvania.

Hemophilia Cohort

Pediatric v Adult Participants: Overview. Pediatric cohort participants (median age 13 years at time of enrollment, range 3 to 17 years of age) did not differ significantly from adult participants (median age 27 years at enrollment, range 18 to 66 years of age) in either racial distribution (89% white/7% Hispanic/4% other *v* 92% white/5% black/1% Hispanic/2% other or unspecified) or factor usage in the year before being evaluated in 1985 (median 57,074 units, range 8,280 to 1,544,946 *v* 70,625 units,

TABLE 1. Characteristics of Persons With AIDS, by Age Group and Risk Category: Centers for Disease Control, Sept 15, 1986

Characteristics	Pediatric*		No. (%) of Adult Hemophilic Patients (n = 201)
	No. (%) of Hemophilic Patients (n = 37)	No. (%) of Nonhemophilic Patients† (n = 346)	
Sex			
Male	37 (100)	182 (53)	194 (97)
Female	0 (0)	164 (47)	7 (3)
Race			
White	26 (70)	57 (16)	173 (86)
Black	7 (19)	205 (59)	13 (6)
Hispanic	4 (11)	81 (23)	15 (7)
Other/unknown	0 (0)	3 (1)	0 (0)
Known deaths	22 (59)	212 (61)	136 (68)

* Defined as <18 years of age at time of AIDS diagnosis.
† Includes 277 children of a parent with or at risk of having AIDS, 49 receiving blood components for nonclotting disorders, and 20 from other transmission categories.

range 4,050 to 383,782, respectively). For factor VIII recipients, 75% of pediatric and 88% of adult participants were HIV seropositive in 1984 (not significant); 88% and 94% were HIV seropositive in 1985 (not significant). HIV seropositivity was not correlated with age in either year. For factor IX recipients, 53% of pediatric and 36% of adult participants were seropositive in 1984 (not significant); 65% and 43% were seropositive in 1985 (not significant). By May 1986, AIDS had developed in five of 147 initially enrolled adults (3%) and 0% of all 70 initially enrolled pediatric participants (not significant); one 8-year-old boy who died of causes other than CDC-defined AIDS was found at autopsy to have HIV infection of the CNS. In addition, three adults and four children had AIDS-related symptoms at the time of their 1985 evaluation (not significant). (AIDS-related symptoms consisted of affirmative self-report of the following; swollen glands for more than 1 month or any combination of the following: diarrhea for more than 1 week, unintentional weight loss in the past 3 months, fever, and/or thrush.)

Pediatric v Adult Participants: Intrastudy Group Differences. Within each seropositive study group, pediatric participants tended to have higher T_H numbers and T_H to T_S (H/S) ratios than did adults (Table 2). The differences were not significant in any study group; however, the correlation of T_H numbers with age was significant for study groups 1 and 3. Similarly, changes in these values between 1984 and 1985 did not differ significantly between pediatric and adult participants within each seropositive study group. All seropositive study groups had significant declines in T_H numbers and/or H/S ratios between the 1984 and 1985 evaluations (data not shown). Lymphocyte and platelet counts did not differ significantly for pediatric and adult members of each study group (data not shown). Serum IgG, IgA, and IgM levels were less for pediatric participants within study groups 1, 3, and 4 (data not shown).

Interstudy Group Differences for Pediatric Participants. In 1985, pediatric members of all seropositive study groups had lower T_H numbers than did the pediatric members of study group 4; however, this difference was significant only for study group 1 ($P < .001$). Similarly, in 1985, H/S ratios were lower for pediatric members of study groups 1 to 3 than for members of study group 4 (study group 1, $P < .0001$; study group 2, $P = .004$; study group 3, $P = .020$). In 1985, pediatric members of study groups 1 and 2 had significantly higher serum IgG levels than pediatric members of study group 4 ($P = .0004$ and $P = .015$, respectively); pediatric study group 2 had higher IgA levels than pediatric study group 4 ($P = .015$). Serum IgM levels did not vary significantly between pediatric study groups.

TABLE 2. Median Lymphocyte Populations and Ratios of T_{Helper} to $T_{Suppressor}$ Lymphocytes of Participants, by Study and Age Group, Hemophilia Cohort, 1985*

Study Group	T_H	T_S	H/S
1			
Pediatric	532	681	0.8
Adult	433	686	0.6
2			
Pediatric	794	758	0.9
Adult	588	878	0.7
3			
Pediatric	681	660	1.2
Adult	590	594	0.9
4			
Pediatric	885	605	1.7
Adult	880	609	1.4

* Study group 1, factor VIII recipients who were seropositive in 1984; study group 2, factor IX recipients who were seropositive in 1984; study group 3, all participants who were seronegative in 1984 and seropositive in 1985; study group 4, all participants who were seronegative in both 1984 and 1985. "Pediatric" is defined as <18 years of age at the time of the 1984 evaluation. T_{helper} (T_H) values are given as lymphocytes per microliter: laboratory normal adult range, 408 to 1,583/μL. $T_{suppressor}$ (T_S) values are given as cytotoxic lymphocytes per microliter. Laboratory normal adult range, 190 to 820/μL. T_{helper} to $T_{suppressor}$ lymphocyte ratio (H/S): laboratory normal adult range 1.0 to 3.9. Correlations between adult and pediatric study groups, using Spearman's test were as follows: group 1, $r = .218$, $P = .039$ for T_H, not significant for T_S or H/S; group 2, not significant; group 3, $r = .563$, $P = .029$ for T_H, not significant for T_S or H/S; group 4, not significant for T_H or T_S, $r = .337$, $P = .042$ for H/S.

DISCUSSION

To date, the literature concerning pediatric HIV infection has been limited to perinatally acquired AIDS.[9–12] We have expanded this topic by evaluating HIV infection in symptomatic and asymptomatic hemophilic children. Consistent with two previous reports of pediatric AIDS, we found that the immune effects of HIV in children were similar to those in adults,[10,13] ie, prolonged infection with HIV was associated with a decrease in T_H numbers and H/S ratios. Our findings differ from those in the other pediatric AIDS literature in three respects. First, only two hemophilic children with AIDS (aged 4 and 7 years) had lymphocytic interstitial pneumonitis. Lymphocytic interstitial pneumonitis may be related to disease acquisition in infancy; 48% of this study's nonhemophilic children with AIDS, most of whom became infected perinatally, had lymphocytic interstitial pneumonitis. Second, we did not find children with HIV infection to be significantly less lymphopenic or more hyper-γ-globulinemic than adults[9,10,12,14]; at least this was

true when both groups consisted of hemophilic patients. There was, however, a suggestion of higher T_H numbers in our pediatric cohort members compared with the adult group. Third, we did not find case to fatality ratios to be worse for children with AIDS who were predominantly infected perinatally with HIV than for those with AIDS who were infected at a later age through factor infusion.[15]

We found some striking differences between pediatric and adult patients with hemophilia-associated AIDS that cannot be fully explained. First, a significantly higher proportion of pediatric patients were nonwhite; this was neither related to other risk factors nor related to areas of residence, suggesting neither unreported risk factors nor receipt of cellular blood products from donors who were at risk. Furthermore, the racial preponderance cannot be explained on the basis of an ethnic predilection for hemophilia. No ethnic group is believed to have a predilection for hemophilia A or B; the racial distribution of the hemophilia cohort discussed in this paper supports this tenet in regard to those using factor concentrates. The racial difference is particularly interesting because nonwhites are also disproportionately represented in other AIDS risk groups.[16] Thus, in having a lower proportion of nonwhites than other AIDS groups, patients with adult hemophilia-associated AIDS are the anomaly. This could be due to improvements in recognizing and treating hemophilic patients from ethnic minorities associated with the institution of government-funded hemophilia treatment centers in the 1970s (ie, many minority hemophilic patients might not have lived to adulthood), although the racial distribution of the hemophilic cohort suggests that this is not the case. Age- and race-specific hemophilic population figures would help greatly in interpreting this finding, but these data do not exist. (It is estimated that 40% of hemophilic patients do not receive their care at hemophilia treatment centers; age- and race-specific data are unobtainable for these individuals. In addition, many hemophilia treatment centers do not have sufficient personnel to provide these data for their patient population.) We recently completed a study of patients with hemophilia-associated AIDS reported by the CDC suggesting that hematologic care of black patients with AIDS may have differed from that of white patients in that blacks less frequently received care at a hemophilia treatment center.[17] Disparity in medical care may be a factor in the age-related racial differences seen here. Significantly more pediatric patients with hemophilia-associated AIDS than adults resided in New York/Pennsylvania/New Jersey. The data are unclear as to whether this could represent, in part, transmission from local blood products, unreported risk factors in the adolescents (eg, drug abuse or homosexuality), an atypical age distribution for the hemophilic population in these three states, or better recognition of AIDS by pediatricians in those states. Pediatric patients with hemophilia-associated AIDS differed clinically from adults in having a lower incidence of *P carinii* pneumonia. This difference might be due to (1) better or earlier diagnosis of AIDS-related diseases in pediatric patients, (2) differences in viral inoculum and/or in host factors related to disease outcome, and/or (3) unwillingness to seek early medical care, possibly related to denial, on the part of the adults.

IMPLICATIONS

Results of this study suggest that age and route of acquisition may be important factors in HIV disease manifestations and warrant further study. In addition, new avenues of research are needed for further interpretation of some of the differences between pediatric and adult hemophilic patients with AIDS.

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ANNOUNCEMENT OF 1989 NEONATAL-PERINATAL MEDICINE EXAMINATION

The Sub-Board of Neonatal-Perinatal Medicine of the American Board of Pediatrics will administer its next certifying examination on **Friday, Nov 3, 1989.**

The following criteria must be met to be eligible to sit for the examination:

1. Certification by the American Board of Pediatrics.
2. Physicians who enter neonatal-perinatal medicine training prior to Jan 1, 1989, may apply for admission to the examination on the basis of their completion of 2 years of full-time subspecialty residency training in neonatal-perinatal medicine. Three years of full-time subspecialty residency training in neonatal-perinatal medicine is required of those physicians entering training on or after Jan 1, 1989.

Physicians who entered neonatal-perinatal medicine training on or after Jan 1, 1986, will be required to complete the required training in a program accredited for training in neonatal-perinatal medicine by the Residency Review Committee (RRC) for Pediatrics.

3. Verification of training and recommendation by Program Director.

Each application will be considered individually and must be acceptable to the Sub-Board of Neonatal-Perinatal Medicine.

Registration for this examination will extend from **Dec 1, 1988, to March 31, 1989.** Requests for applications received prior to the opening of registration will be held on file until that date, at which time application materials will be sent to those who have requested them.

The application fee for the examination is $800 ($275 processing and evaluating free plus $525 examination fee). Candidates not approved to take the examination will be refunded the $525 examination fee. The processing and evaluating fee will be retained.

Please direct inquiries to: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1651. Telephone: (919) 929-0461.

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