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HIV and Hemophilic Children's Growth

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Summary: The acquired immune deficiency syndrome (AIDS) often has profound effects on growth; however, the effects of human immunodeficiency virus (HIV) on asymptomatic children's growth are unknown. Before heat inactivation/HIV donor screening of factor concentrates, many hemophilic children became infected with HIV. We evaluated four hemophilic groups without AIDS, using age-standardized growth parameters: group 1, 41 HIV-seropositive children (median age of 13 years); group 2, 11 HIV-seronegative children (median age of 4 years); group 3, 20 children frequently receiving concentrates, evaluated before 1979 (median age of 9 years); and group 4, 11 children rarely receiving concentrates, evaluated before 1979 (median age of 6 years). Median height for age (HA), weight for age (WA), and weight for height (WH) of groups 1 and 2 exceeded the 50th percentile of referent norms. HA, WA, WH, and weight/height^2 did not vary significantly by group, nor did these decline over periods of 11 to 70 months. However, for those <11 years of age in group 1, HA declined by 25 percentile points over at least a 3 year period. Also, group 1's T helper-to-suppressor cell ratios at 12 ± 3 months following the latest growth evaluation were positively associated with both HA and WA at that last evaluation. Eight children were evaluated before 1979 and again after they seroconverted to HIV. Their measurements as a group did not decline significantly between the two evaluation periods, but the growth percentiles of five of them did decline. We conclude that HIV did not measurably affect the growth of the majority of these asymptomatic infected hemophilic children; however, it may have affected the growth of the younger infected patients and of some individual children evaluated over time. The effects of HIV on growth may precede laboratory immune changes. **Key Words:** HIV—Hemophilia—Factor—Children's growth.

Infants and toddlers with the acquired immune deficiency syndrome (AIDS) often have profoundly deficient growth and development (1,2). Failure to thrive may be the presenting symptom of human immunodeficiency virus (HIV) infection in these children (1,3,4), suggesting that growth effects may in some cases be primary, and not necessarily secondary to the child's overall medical condition. However, this possibility remains uninvestigated. Furthermore, most perinatally infected children some from deprived environments. These environments are associated with increased incidences of prematurity, intrauterine growth retardation, neglect, and abuse, all of which are associated with

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growth failure, independent of HIV effects on growth. Little information exists concerning growth delay in HIV-infected children (a) who have not yet developed AIDS and/or (b) from nondeprived backgrounds. We could find only one report on this topic, which assessed a small number of children with lymphadenopathy, infected through blood products. In that nonrandom, noncontrolled study, 3 of 22 children had medically significant growth failure; 2 of these 3 had evidence of abnormal central nervous system function and growth hormone release (5).

In the years 1980 through 1984, before the widespread use of virus-inactivated/HIV donor-screened factor concentrate products, hemophilic children were at substantial risk of HIV infection; this risk was directly related to age and the amount of factor product used (6). Although the risk of new HIV infection is now minimal, many hemophilic children are already infected with this virus and are at risk of any effects HIV may have upon their growth. We therefore evaluated the effects of HIV to date upon the growth of asymptomatic hemophilic children, taking into consideration their factor product therapy, since the effects of these products on growth have never been studied. We also assessed whether any growth parameters were associated with T helper cell numbers (T_h) or T helper-to-suppressor cell ratios (H/S).

PATIENTS AND METHODS

Growth and development data were obtained retrospectively from the medical records of pediatric patients at two hemophilia treatment centers: one in California and one in Missouri. No patients had AIDS or any underlying chronic disease other than hemophilia when we took growth measurements and extracted data. All patients had medical charts with at least one height and weight measurement for each of at least the previous 3 years (one measurement in each 6 month period for any time period in which the child was <4 years old) and were <16 years old at the time of the first height and weight measurements.

The risk of hemophilia-associated HIV infection is strongly and positively associated with both age and the amount of factor product used (6); thus, it was not possible to find HIV-seronegative and -seropositive patients with comparable ages and factor usage (Table 1). This study's growth measurements were therefore normalized for age (see below). In addition, we separated the effects of HIV infection, amount of blood product used, and age further by studying the following four patient groups, two of which provided temporally current comparison data and two of which provided historic comparison data: group 1, 41 HIV-seropositive children with current growth data obtained; group 2, 11

TABLE 1. *Patient characteristics by study group[a] and type of factor used*

	Group 1	Group 2	Group 3	Group 4
Age (months)[b]				
Median	155	51	111	75
Range	51–271	11–181	44–186	31–139
n	41	11	20	11
Months between first and last evaluation				
Median	29	25	26	20
Range	18–54	11–70	20–46	12–24
n	41	11	20	11
Yearly dose[c]				
factor VIII				
Median	23,000	2,150	16,810	4,700
Range	700–108,000	250–9,020	400–46,800	0–15,000
n	35	8	18	8
Factor IX				
Median	6,275	550	130,000	5,200
Range	600–262,080	—	60,000–200,000	2,400–8,000
n	6	1	2	2

[a] Group 1—41 HIV-seropositive children; group 2—11 HIV-seronegative children; group 3—20 children who received factor concentrates and had growth data from before 1979; and group 4—11 children who rarely received factor concentrates and had growth data from before 1979.

[b] Age at most recent height and weight.

[c] Two patients in group 2 were treated with cryoprecipitate and received no concentrate products.

HIV-seronegative children with current growth data obtained; group 3, 20 children who received factor concentrates at least three to four times a year before 1979, with growth data obtained from prior to 1979 [1979 was the first year of the general AIDS epidemic; the first case of hemophilia-associated AIDS was diagnosed retrospectively as occurring in 1981 (7)]; and group 4, 11 children who received factor concentrates less than three times a year before 1979, with growth data obtained from prior to 1979.

All but eight individuals in group 1 were documented to be seropositive prior to the date of earliest growth data; for these eight individuals, the earliest serotesting was done within 1 year after the earliest growth data. Twelve individuals from group 3 and 6 individuals from group 4 were documented as seronegative in 1979 or thereafter.

Eight children were evaluated before 1979 and again after they were found to be seropositive to HIV. These children were examined separately and also were included in the main analyses. Seven of these are therefore included in both groups 1 and 3 and one in both groups 2 and 4. One of these eight individuals was documented to be seronegative in 1978, one in 1979, five in 1980, and one in 1981.

All HIV serotesting was done using Western blot confirmation procedures recommended by the Centers for Disease Control (CDC). T_h and H/S ratios were quantitated locally, by indirect immunofluorescence on a fluorescence-activated cell sorter with commercial monoclonal antibodies, using Ortho reagents at the California treatment center and Becton-Dickinson reagents at the Missouri treatment center.

All study groups were compared with and on the basis of the National Center for Health Statistics (NCHS)/CDC references (Normalized NCHS/CDC Anthropometric Reference) (8). Z scores (standard deviation units) were determined for the first and last evaluations of the following: weight for age (WA), height for age (HA), and weight for height (WH). Weight/height^2 (W/H^2) was calculated. Children followed beyond 18 years of age were considered age 18 years for WA and HA computations because of reference limits. Also because of reference limits, WH could not be analyzed for those $\geq$11 years of age or for those >145 cm in height. Since the data were not normally distributed, nonparametric statistical methods were used to analyze the data (9). We compared study groups using the Kruskal–Wallis test on those <11 years old, on those $\geq$11 years old, and on the complete group (9). The first and second evaluation periods of children who were their own historic controls were compared using the Wilcoxon signed-rank test. The size of our study groups enables us to detect a true difference of approximately 20 growth percentile points between study group 1 and the other study groups combined, using a two-tailed test, with a significance level of 0.05 and a power of at least 80%. The size also enables us to detect a true difference of approximately 30 growth percentile points between study group 1 and the other study groups combined, using a two-tailed test, with a significance level of 0.05 and power of over 95% (10).

Spearman's rank correlation coefficient (r_s) was used to measure the strengths of association (9) of group 1's latest WA, HA, and W/H^2, change in HA between first and last evaluation, and change in WA between first and last evaluation with immune test results: (a) from the following year (12 ± 3 months), to address whether any HIV-related growth effects might have preceded any immune effects (for H/S and WA, n = 17); (b) in the same year (0 ± 3 months) to address whether any HIV-related growth effects might have occurred concurrently with any immune effects (for H/S and WA, n = 26); and (c) from the previous year (−12 ± 3 months), to address whether any HIV-related growth effects might have occurred secondary to immune and/or clinical effects (for H/S and WA, n = 17).

Three (7%) children in group 1 were black and four (10%) were Hispanic; all those in group 2 were white; one (5%) in group 3 was black and two (10%) were Hispanic; and two (18%) in group 4 were black and three (27%) were Hispanic. The time interval between first and last evaluations ranged between 11 and 70 months (Table 1); this interval did not vary significantly between groups.

RESULTS

Study Group Comparisons

Groups 1 and 2 exceeded the referent 50th percentiles for WA and HA at both the first and last evaluation (Table 2). Groups 3 and 4 had lower median HA percentiles than did groups 1 and 2; these percentiles increased or did not change appreciably between the first evaluation and the last. Median WA did not change between the first evaluation and

TABLE 2. *Median NCHS/CDC percentiles and Quetelet index[a] of all children by evaluation and study group[b]*

	WA %		HA %		WH %,[c]	W/H,[b]
	First	Last	First	Last	Last	Last
Group 1	51.8	50.6	54.6	55.9	64.3	0.0018
Group 2	61.3	53.6	55.5	71.6	31.3	0.0016
Group 3	34.8	35.5	30.1	44.2	45.0	0.0017
Group 4	59.4	59.0	35.2	33.4	60.9	0.0017

[a] Quetelet index = weight/height^2 in kg/cm^2 (W/H^2); weight for age (WA); height for age (HA); weight for height (WH).

[b] Group 1—41 HIV-seropositive children; group 2—11 HIV-seronegative children; group 3—20 children who received factor concentrates and had growth data from before 1979; and group 4—11 children who rarely received factor concentrates and had growth data from before 1979. Five individuals did not have height measurements taken at the last visit.

[c] These data are calculated only for those <11 years old whose height was within the reference limit (group 1: $n = 10$; group 2: $n = 9$; group 3: $n = 12$; group 4: $n = 10$).

last evaluation of these groups. Children <11 years old in groups 1 and 2 were proportionately taller (group 1—68th HA percentile; group 2—78th HA percentile) than they were heavy (59th WA percentile and 57th WA percentile, respectively) at their last evaluation.

The groups did not differ significantly from one another in any of the following: WA, HA, WH (WH measurements and change calculated only for those <11 years old), and W/H^2 at the first evaluation; WA, HA, WH (WH measurements and change calculated only for those <11 years old), and W/H^2 at the last evaluation; and changes in WA, HA, WH (WH measurements and change calculated only for those <11 years old), and W/H^2 between the first and last evaluation. This was also the case when results were compared using the two age subgroups <11 years old and ≥11 years old, except for HA at the first evaluation of those <11 years old and the change in HA between the first and last evaluation for this age group. At the first evaluation, children <11 years old in groups 1 and 2 were taller for age than those in groups 3 and 4 (group 1: 92nd percentile, $n = 14$; group 2: 71st percentile, $n = 10$; group 3: 27th percentile, $n = 12$; and group 4: 42nd percentile, $n = 10$; $p = 0.048$). This difference was no longer significant at this age group's last evaluation, with group 1 having decreased in HA by 25 percentile points, group 2 increased by 7, group 3 increased by 20, and group 4 decreased by 9 (group 1: 67th percentile; group 2: 78th percentile; group 3: 47th percentile; and group 4: 31st percentile). The difference in direction and amount of change in HA by study group for those <11 years old was significant ($p = 0.047$).

Correlation Between Growth Parameters and Immune Test Results of HIV-Infected Children

For group 1, there were no significant associations between any growth parameters at the latest evaluation and T_h numbers in the previous year, same year, or following year. WA, HA, and W/H^2 at the latest evaluation were each positively associated with H/S ratios in the subsequent year (i.e., at 12 ± 3 months after the date of the last growth measurements) (WA: $r_s = 0.53$, $p = 0.03$, $n = 17$; HA: $r_s = 0.67$, $p = 0.02$, $n = 12$; W/H^2: $r_s = 0.60$, $p = 0.03$, $n = 13$). The only other significant association was between the change in HA between the last and first visit and the H/S ratio in the year prior to the last visit ($r_s = -0.85$, $p = 0.0001$, $n = 14$).

Individual Temporal Comparisons

The eight seropositive patients who were evaluated before 1979 and again after known seropositivity to HIV did not change significantly between the two evaluations with regard to WA, HA, WH, or W/H^2 (Table 3). Patients 1, 3, 5, 7, and 8, who showed declines in growth percentiles between their first and last evaluation periods, had none of the following during their second evaluation period: lymphadenopathy at noninguinal sites, thrombocytopenia, neurologic symptoms, systemic opportunistic infections, or cancer. None were on any chronic medication, including steroids; all had their latest transcribed clinical evaluation in 1986. Patient 1 was documented as being HIV seronegative in 1978 and 1980 and HIV seropositive in 1983. He

TABLE 3. *NCHS/CDC percentiles[a] of subjects acting as their own historic controls by study period[b]*

	WA%		HA%	
Patient #	Period 1	Period 2	Period 1	Period 2
1	82.9	43.9	37.7	20.2
2	4.4	58.6	0.4	1.2
3	10.2	4.9	7.2	9.1
4	34.9	53.5	49.7	45.6
5	49.1	17.2	19.7	13.4
6	99.8	98.6	88.7	70.3
7	66.6	47.1	38.3	3.8
8	78.6	28.1	35.5	15.5

[a] Weight for age (WA); height for age (HA); percentile (%).

[b] For individuals #1, 3, 4, 5, and 8, data from the last evaluation during the first time period and the last evaluation during the second time period. For patients #2, 6, and 7, height was not measured at the latest evaluation; therefore, these are data from the last evaluation during the first time period and the next-to-last evaluation during the second time period.

was 8 years old at his first evaluation and was in the 83rd percentile for weight and 38th percentile for height. He was 15 years old at his final evaluation, when he had dropped 39 percentile points for weight and 18 for height, compared to his earlier evaluation. His only notable illness was infectious mononucleosis diagnosed on the basis of a positive monospot in June 1983. He had no clinical or laboratory signs of liver disease or chronic infectious mononucleosis at any time. Patient 3 was HIV seronegative in 1980 and positive in 1983. He had synovectomies in 1983 and 1985. Patient 5 was HIV seronegative in 1980 and positive in 1982. At 8 years of age, he had been in the 49th percentile for weight and had declined to the 17th percentile by 15 years of age. He was treated for oral moniliasis in 1985, and his symptoms resolved after therapy. Patient 7 was seronegative in 1978 and positive in 1983. At 11 years of age, he was in the 67th percentile for weight and 38th percentile for height. By adulthood (22 years of age), he had declined by 20 percentile points for weight and 34 for height. Patient 8 was seronegative in 1980 and seropositive in 1983. His only clinical problem has been folliculitis associated with pigmentary changes, first diagnosed in February 1984. At 11 years of age, he had been in the 79th percentile for weight and 35th for height; he had declined to the 28th and 15th percentiles, respectively, by 17 years of age.

DISCUSSION

Before the use of factor concentrates as therapy for hemophilia became routine, persons with bleeding disorders frequently experienced joint destruction, intracranial bleeding, chronic debilitation, and early death. Factor concentrate therapy, widespread in the United States by the mid-1970s, changed this bleak outlook. In the early 1980s, contamination of these blood components with HIV led to yet another reversal of the U.S. hemophilic population's health outlook. In January 1981, the first case of AIDS was (retrospectively) diagnosed in a person with hemophilia (7). As of November 30, 1988, a total of 813 cases of hemophilia-associated AIDS had been reported to the CDC; 144 of these patients were <18 years old at diagnosis. Although HIV exposure through factor concentrates has been virtually eliminated since 1985 by donor screening for HIV antibody and viral inactivation of concentrate products, approximately 90% of patients who frequently received factor VIII concentrates in 1980–1984 and 50% of those who frequently received factor IX concentrates in 1980–1984 are now infected with HIV (6,11). Preliminary data from several studies suggest that the current incidence of AIDS may be lower in seropositive children compared to adults (J. Goedert, personal communication, 1987; J. Stehr-Green, personal communication, 1987; and our own unpublished findings). Thus, the effects of this virus on the growth of otherwise healthy hemophilic children is of both clinical and scientific importance.

Our study included only two hemophilia treatment centers and the data are limited in that these measurements were done by various persons, using various measuring instruments and scales. We do not feel, however, that variability due to technique or apparatus used can explain either our negative or our positive findings. Some of our findings concerning the study groups 3 and 4 vis à vis NCHS/CDC referent norms and study groups 1 and 2 may reflect the effects of hemophilia complications on growth in the pre-concentrate-therapy era. The findings for groups 1 and 2 suggest that factor concentrate use and hemophilia per se do not directly affect hemophilic children's growth, making potential effects of HIV more readily measurable. More importantly, our findings suggest that HIV may have measurable effects upon the growth of some infected, otherwise asymptomatic hemophilic children. First, children <11 years old in the infected study group 1 declined 25 percentile points in HA between first and last evaluations. Second, five of the eight patients who could be evaluated both before and after HIV exposure declined in their height and/or weight percentiles. Third, H/S ratios in the year following the last evaluation of infected children were positively associated with all three basic growth measures at the last evaluation (WA, HA, and W/H^2), suggesting that growth effects of HIV may precede both clinical and laboratory immune changes. (This last finding, although intriguing and physiologically plausible, must be considered preliminary and interpreted with caution, since our numbers are small, several tests were performed, and our finding concerning an association of H/S ratios with changes in HA is in a direction opposite to the three more physiologically plausible findings noted above.)

This study was designed to be a preliminary one, but is important because the effects of HIV on asymptomatic children's growth have never been assessed, even in an uncontrolled fashion. We as-

sessed the effects of HIV on hemophilic children's growth, using both national standardized growth norms and using comparison groups that permitted us to assess any possibly independent or confounding effects of age or factor usage. At the initiation of this study, several factors made us feel that any growth changes seen in these patients might be meaningful. First, the mean time between infection with HIV and development of AIDS now appears to be more than 5 years, perhaps even more than 10 years (12). Hemophilic patients were infected through blood products they received in 1980–1984; thus, the majority of hemophilic patients are at an earlier point in their HIV infection course than are persons in some other risk groups, e.g., homosexual men (13). Second, the patients we assessed herein had not become infected during early life, a period of relatively rapid growth (although some had been infected during adolescence, a second period of accelerated growth.) Thus, any effects already found in this preliminary study might well eventually progress to a clinically important stage, i.e., any effects found in this study population at this point in time should not be considered subtle. Third, we could not assess the effects of HIV upon these children's sexual development, since these data were not recorded in the medical record.

Our findings suggest that HIV infection has not yet led to clinically significant growth failure in these infected older children. However, some effects of HIV on the younger asymptomatic children in the study population may already be appearing. In light of the preliminary nature of this study and its associated limitations, our positive findings for infected children <11 years old and for some of the children who provided their own temporal comparisons are especially worrisome. These results support the need for a multicenter, prospective, longitudinal study of the effects of HIV on hemophilic children's growth and endocrine function. Our preliminary, controlled study provides an important step toward this prospective study.

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