Age and Human Immunodeficiency Virus Infection in Persons with Hemophilia in California

ROBERT C. HOLMAN, MS, EDWARD D. GOMPERTS, MD, JANINE M. JASON, MD, CHARLES F. ABILDGAARD, MD, MICHAEL T. ZELASKY, BS, AND BRUCE L. EVATT, MD

Abstract: Thirteen hemophilia centers provide comprehensive care to approximately 90 percent of persons with hemophilia in California. For 1987, these centers reported patient human immunodeficiency virus (HIV) antibody status, age group, level of clotting factor deficiency, and hemophilia type on 1,438 persons with hemophilia A and B; HIV serologic status was known for 860 persons (59.8 percent) of whom 537 (62.4 percent) were HIV-antibody-positive. The HIV positivity rate increased with age after taking into account hemophilia type, clotting factor level and treatment center type. The three-year cumulative incidence of reported AIDS (acquired immunodeficiency syndrome) cases based on the number of HIV positive patients, was 11.6 percent. The cumulative incidence rate was 14.6 percent (54 of 370) for those patients over 20 years of age and 4.8 percent (8 of 167) for those under 21 years of age. Although a comparable distribution of the date of diagnoses of AIDS was seen by age group, there appeared to be a bimodal distribution in the rate of AIDS among the age groups, with the 6–12-year-olds and the 21 and older age groups showing higher incidence rates. (*Am J Public Health* 1990; 80:967–969.)

Introduction

Acquired immunodeficiency syndrome (AIDS) was first documented in persons with hemophilia early in the course of the AIDS epidemic in the United States.[1] Studies of stored serum specimens showed that a high percentage of hemophilic persons became infected with human immunodeficiency virus (HIV) over a relatively short time. Most patients became infected between 1981 and 1984; the peak incidence of infection occurred in 1982 and 1983.[2,3] The reasons for the quick spread of infection in this population were the widespread use of commercial clotting factor concentrates prepared from pools of sera collected from between 2,000 to 20,000 donors[4] and the widening prevalence of this infection in the United States, and therefore in the donor population, before HIV blood screening practices were in effect.

The Centers for Disease Control (CDC) collects data characterizing AIDS in the United States hemophilic population through state health departments.[5,6] This reporting mechanism has been exceptionally efficient, with at least 97 percent of the cases reported.[5]

The duration of HIV infection before the onset of AIDS varies from as short as a few months to an as yet indeterminate number of years, with a median of nearly 10 years.[7] However, the duration or latency period to AIDS in persons with hemophilia may differ from that of other AIDS risk groups.[8–10] The most important factor in disease progression is time from primary infection, but factors as diverse as geographic location[11] and HLA (human lymphocyte antigen) type[12] may play a role. In this study, the HIV seroprevalence and incidence of AIDS in hemophilic persons in California were estimated to assess associations with age, hemophilia type, and clotting factor level.

Methods

Five federally funded California hemophilia centers (FFC) provide comprehensive care to approximately 65 percent of the persons with hemophilia A and B in California[13] and report activities annually to the federally funded agency. An additional 25 percent of the patients receive care through eight other centers (SSC) and report voluntarily. It is estimated that the remaining 10 percent of the patients receive care through health maintenance programs, the military, or private practitioners. As part of their 1987 annual report, both groups of centers were asked to include additional information for all hemophilia patients on HIV antibody test result (positive, negative, or not tested); age group of patient (<5 years, 6 to 12 years, 13 to 16 years, 17 to 20 years, or above 20 years); level of clotting factor deficiency (<5 percent or 5 percent–40 percent); and type of hemophilia (Factor VIII or Factor IX deficiency). The HIV antibody testing of hemophilia persons is voluntary, with encouragement to all patients. Mild hemophilia persons were usually followed less actively at the centers, and centers were less aggressive about testing younger children since they were much less likely to be infected because viral-activated products had usually been used.

For this study, AIDS cases were those reported to CDC as of 9/2/88 by any center, physician, and local department of health within California, that were diagnosed between 1/1/85 and 12/31/87, and were verified by the reporting official to have received their care from one of the 13 reporting centers. The inclusive time period of 1985–87 was used because use of viral inactivated products was instituted in 1984, and seroconversion had virtually ceased by 1985.[14] Thus the number of seropositive persons was stable for this period and the cumulative incidence of AIDS is the number of reported AIDS cases divided by the number of known HIV seropositive patients during the inclusive three-year period of 1985–87. The age group of AIDS cases is based on age as of 1987, the year of the annual report. Similar analyses were repeated when California hemophilia-associated AIDS cases included those not reported by FFCs or SSCs.

Logistic regression analysis was used for both the univariate and multivariate analyses to calculate odds ratios (OR) and 95 percent confidence intervals (CI).[15,16] Univariate analyses were performed on each of the four categorical variables (age group, hemophilia type, clotting factor level, and treatment center type). Next, for HIV-tested patients, a multivariate analysis was used to analyze the four variables in a full model to adjust for the effects of potential confound-

Address reprint requests to Robert C. Holman, MS, Division of Immunologic, Oncologic, and Hematologic Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA 30333. Dr. Jason, Mr. Zelasky, and Dr. Evatt are also at that Division at CDC; Dr. Gomperts is with the Division of Hematology-Oncology, Children's Hospital of Los Angeles; Dr. Abildgaard is with the Department of Pediatrics, School of Medicine, University of California at Davis. This paper, submitted to the Journal July 31, 1989, was revised and accepted for publication January 18, 1990.

ing variables. Logistic regression analysis was also used to compare between the HIV-positive patients in relation to outcome of AIDS. For this analysis, the three categorical variables were age group (≤20 and ≥21 years of age), hemophilia type, and clotting factor level.

Results

Most patients (72.0 percent) were reported from the five major centers which also tested proportionally more patients (Table 1). Clotting factor levels <5 percent and age were also associated with testing, but factor deficiency was not associated.

Of the 860 tested patients, 537 (62.4 percent) were HIV-antibody-positive and 323 (37.6 percent) were antibody-negative. The odds ratio of HIV seropositivity increased with age group (Table 2). The odds of HIV seropositivity may have stabilized beginning with the 13–16-year age group: ORs of the 13–16 and 17–20 year-old age groups did not differ from those 21 years of age or older (OR = 1.3, CI = [0.7–2.4]; OR = 1.5, CI = [0.9–2.7], respectively). Factor VIII deficient patients were more likely to be HIV positive than factor IX deficient patients, and patients with clotting factor levels <5 percent were more likely to be HIV positive than patients with clotting factor levels ≥5 percent. Using a full logistic model, there were no differences in HIV positive rates in patients from the two groups of centers; the differences in HIV positive rates by age, hemophilia type, and clotting level remained.

TABLE 1—HIV Testing Status of Hemophilia Patients by Patient Characteristics

Characteristics	Number of Patients	Percent Tested	OR	(95% CI*)
Age Group (year)				
≤5	155	45.8	1.0**	
6–12	222	57.2	1.6	(1.0, 2.4)
13–16	98	57.1	1.6	(0.9, 2.6)
17–20	127	62.2	1.9	(1.2, 3.1)
≥21	836	63.0	2.0	(1.4, 2.9)
Factor Deficiency				
IX	306	55.2	1.0**	
VIII	1132	61.0	1.3	(1.0, 1.6)
Clotting Factor Level				
≥5%	404	44.8	1.0**	
<5%	1034	65.7	2.4	(1.9, 3.0)
Treatment Center Type				
SSC	402	49.8	1.0**	
FFC	1036	63.7	1.8	(1.4, 2.2)

*95% confidence interval.
**Reference group.

Sixty-two patients from the hemophilia reporting centers were reported with an AIDS diagnosis made in 1985–87 in California. This represented 11.6 percent of known seropositive patients in the centers. Age was the only factor associated with AIDS diagnosis (Table 3). Eight of 167 of those less than 21 years old developed AIDS, six persons 6–12 and 2 persons 17–20. Distribution of the date of diagnosis for the eight persons <21 years of age was similar to that of the older population. However, a difference in the rate of AIDS was seen between age groups. This distribution was bimodal with the 6–12-year-old group showing higher rate (10.0 percent) than those in the 13–16 and 17–20 age groups (0.0 percent and 3.2 percent, respectively), although not as high as the ≥21 age group. Results similar to those described above were also seen in the analysis of all 72 patients who were reported by the centers as developing AIDS through 1987.

Discussion

Most persons with hemophilia became infected with HIV in 1981 to 1984.[2,3] After 1984, viral-attenuated clotting factor concentrates became widely used resulting in only rare seroconversions in uninfected persons.[17] Therefore, a low seroprevalence in hemophilic children under 6 years of age and an increasingly higher prevalence in older persons with hemophilia was to be expected.[18] In addition, we found this association to remain when taking into account the hemophilia type, clotting factor level, and treatment center type. We also found that older persons with hemophilia were at a higher risk of AIDS, as was shown in a recent study.[19] Although patients between 6 and 12 years had a higher rate than those of other age groups <21 years, there was a small number of cases in each of those age groups.

Why patients followed by one set of centers were more likely to be tested than patients from the other set is not

TABLE 2—HIV Serologic Status of Patients by Patient Characteristics

Characteristics	No.	Percent HIV+	Univariate OR	Univariate (95% CI*)	Multivariate OR	Multivariate (95% CI*)
Age Group (year)						
≤ 5	71	4.2	1.0**		1.0**	
6–12	127	47.2	20.3	(6.1, 67.9)	22.2	(6.6, 75.0)
13–16	56	75.0	68.0	(18.4, 250.7)	91.2	(23.9, 347.6)
17–20	79	78.5	82.7	(23.1, 295.8)	152.0	(40.8, 566.2)
≥21	527	70.2	53.4	(16.6, 172.3)	103.9	(31.6, 340.9)
Factor Deficiency						
IX	169	52.1	1.0**		1.0**	
VIII	691	65.0	1.7	(1.2, 2.4)	2.0	(1.3, 3.0)
Clotting Factor Level						
≥5%	181	30.4	1.0**		1.0**	
<5%	679	71.0	5.6	(3.9, 8.0)	9.7	(6.5, 14.6)
Treatment Center Type						
FFC	660	60.3	1.0**		1.0**	
SSC	200	69.5	1.5	(1.1, 2.1)	1.1	(0.7, 1.7)

*95% confidence interval.
**Reference group.

TABLE 3—AIDS Status of Hemophilia Patients by Patient Characteristics

Characteristics	Number HIV +	Percent AIDS	OR	(95% CI*)
Age Group (year)				
≤20	167	4.8	1.0**	
≥21	370	14.6	3.4	(1.6, 7.3)
Factor Deficiency				
IX	88	9.1	1.0**	
VIII	449	12.0	0.7	(0.3, 1.6)
Clotting Factor Level				
≥5%	55	10.9	1.0**	
<5%	482	11.6	0.9	(0.4, 2.3)

*95% confidence interval.
**Reference group.

known. The eight hemophilia programs with a lower testing rate were usually staffed by health care workers providing care to patients with a variety of hematologic and oncologic diseases, whereas the five centers with a higher testing rate were more hemophilia focused.[13]

In this retrospective study, the denominator of HIV seropositive persons shifted over part of this period, with the prevalence of infection increasing during 1981 through 1984. Although this might affect our results, the substantial differences observed suggest that these estimates, which cannot be better specified, are not likely to account for the observed differences. Also, as expected, the tested group consisted of patients that were older and/or with severe hemophilia, both of these factors would tend to bias the associations with HIV seropositivity toward nonsignificance. That is, the patients not tested were younger and probably at a lower risk of infection; therefore, if tested, the seropositivity rate of younger patients would be lower and the observed difference detected in age may be even greater than noted by our estimates. The analysis of the rate of AIDS was performed using AIDS cases from the defined centers as the numerator and patients with a positive HIV antibody status determined from those tested as the denominator. Thus, the age bias in HIV testing would only tend to underestimate the denominator for younger persons. The observed age difference of the rate of AIDS may thus be more dramatic than estimated herein.

The reason for the discrepancy in AIDS prevalence between age groups may be that younger hemophilic patients received less clotting factor than older hemophilic patients, that is, they were exposed to the HIV virus later than their older counterparts and have an "earlier" phase of the infection. Although it cannot be proved or disproved by this study, because specific dates of seroconversion are not available on these patients, this hypothesis is unlikely. The critical variable in hemophilia treatment may be the frequency of infusions and extent of exposure to different clotting factor concentrate lots, not age. Persons bleeding more frequently will be exposed to more lots of commercially prepared clotting factor concentrates and therefore be more likely to receive concentrates from a contaminated lot. Young, active hemophilic boys ages 3 or 4 years through adolescence are the most physically active and consequently have frequent hemorrhages requiring infusion therapy.[20] However, the rate of AIDS would be expected to be high through adolescence, not just for the 6- to 12-year olds age group. While exceptions certainly occur, the size of the currently reported population would result in a relatively homogeneous group. Further, the epidemiologic curves of AIDS diagnosis over time for those <21 and ≥21 years are similar. Consequently, reasons for the differences in the biological response to HIV infection between the two broad age groups should be sought among physiologic mechanisms. In addition, if age differences were representative of the true differences in the population, and age is an important cofactor in the development of AIDS, the important scientific and public health implications merit further investigation.

ACKNOWLEDGMENTS

The authors thank Jeanette Stehr-Green, MD, Terence Chorba, MD, and Allen Hightower, MS, for reviewing the manuscript, Tom Gyurik and Judy Thomas, RN, for assistance in obtaining patient information, Carey Numoto for assistance in manuscript preparation, and the following individuals and Hemophilia Centers of California for their contributions: *Alta Bates Hospital,* B. Lewis, MD; *Children's Hospital of Northern California,* J. Addiego, MD; *Children's Hospital of Stanford,* B. Glader, MD; *Children's Hospital of San Diego,* G. Hartman, MD; *Loma Linda Hospital,* A. Bedros, MD; *University of California at Irvine,* J. Katz, MD; *University of California at San Francisco,* M. Koerper, MD; *University of California at San Diego,* H. Anderson, MD; *Orthopedic Hospital of Los Angeles,* S. Dietrich, MD; *USC/County Hospital,* T. Sun, PA.

REFERENCES

1. Centers for Disease Control: *Pneumocystis carinii* pneumonia among persons with hemophilia A. MMWR 1982; 31:365–367.
2. Eyster ME, Goedert JJ, Sarngadharan MG, Weiss SH, *et al:* Development and early natural history of HTLV-III antibodies in persons with hemophilia. JAMA 1985; 253:2219–2223.
3. Evatt BL, Gomperts ED, McDougal JS, Ramsey RB: Coincidental appearance of LAV/HTLV-III antibodies in hemophiliacs and the onset of the AIDS epidemic. N Engl J Med 1985; 312:483–486.
4. Centers for Disease Control: Update: Acquired immunodeficiency syndrome (AIDS) among patients with hemophilia—United States. MMWR 1983; 32:613–615.
5. Centers for Disease Control: Surveillance of hemophilia-associated acquired immunodeficiency syndrome. MMWR 1986; 35:669–671.
6. Stehr-Green JK, Holman RC, Jason JM, Evatt BL: Hemophilia-associated AIDS in the United States, 1981 to September 1987. Am J Public Health 1988; 78:439–442.
7. Centers for Disease Control: AIDS and human immunodeficiency virus infection in the United States: 1988 Update. MMWR 1989; 38:1.
8. Goedert JJ, Biggar RJ, Weiss SH, *et al:* Three-year incidence of AIDS in five cohorts of HTLV-III-infected risk group members. Science 1986; 231:992–995.
9. Ekert H: AIDS incubation period. Nature 1987; 329:494.
10. Turner MJ, White JO, Soutter WP: AIDS incubation period in male haemophiliacs. Nature 1987; 330:702.
11. Pennsylvania AIDS Surveillance Study Group: Geographic differences in hemophilia-associated AIDS incidence in Pennsylvania. Blood 1987; 70:1208–1210.
12. Steele CM, Ludlam CA, Beatson D, Peutherer JF, *et al:* HLA haplotype A1 B8 DR3 as a risk factor for HIV-related disease. Lancet 1988; 1:1185–1188.
13. Bureau of Health Care Delivery and Assistance. Region IX Comprehensive Hemophilia Care Program Regional Activities: Progress report. Los Angeles, California, 1988.
14. Centers for Disease Control: Update: Acquired Immunodeficiency Syndrome (AIDS) in persons with hemophilia. MMWR 1984; 33:589–592.
15. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York: John Wiley & Sons, 1989.
16. SAS Institute: SUGI Supplemental Library User's Guide, 1983 Edition. Cary, NC: SAS Institute, 1983.
17. Centers for Disease Control: Safety of therapeutic products for hemophilia patients. MMWR 1988; 37:441–444, 449–450.
18. Eyster ME, Gail MH, Ballerd JO, Al-Monhiry H, Goedert JJ: Natural history of human immunodeficiency virus infections in hemophiliacs: Effects of T-cell subsets, platelet counts, and age. Ann Intern Med 1987; 107(1):1–6.
19. Goedert JJ, Kessler CM, Aledort LM, *et al:* A prospective study of human immunodeficiency virus type 1 infection and the development of AIDS in subjects with hemophilia. N Engl J Med 1989; 321:1141–1148.
20. Lusher JM: Diseases of coagulation: The fluid phase. *In:* Nathan DG, Oski FA (eds): Hematology of infancy and childhood. Philadelphia: WB Saunders, 1987; 1305–1315.