CONCISE REPORT

HTLV-III/LAV Antibody Status of Spouses and Household Contacts Assisting in Home Infusion of Hemophilia Patients

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Thirty-four adult and pediatric hemophilia A and B patients and 50 nonhemophilic members belonging to 28 families were enrolled in August 1984 in a study of human T cell lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) antibody status and T cell subpopulation numbers. All 50 household contacts, including three spouses of LAV antibody-positive adult hemophiliacs, were immunologically normal and serologically negative with respect to HTLV-III/LAV. Based on Western blot serologic testing of blood samples collected intermittently between July 1981 and August 1984 from 33 representative St Louis hemophiliacs studied during the period from 1981 to 1984, the average time since seroconversion was estimated as 20 months. One spouse of a seropositive hemophiliac and 23 parents of 27 seropositive pediatric hemophiliacs assisted regularly with home infusions. These infusion assistants have collectively experienced 44 person-years of concentrate infusion "exposure" without seroconversion. These results suggest that the likelihood for transmission of HTLV-III/LAV from hemophiliacs to persons assisting in their therapy is extremely low.

THE POSSIBILITY of contracting acquired immunodeficiency syndrome (AIDS) through the use of clotting factor concentrates and other blood components has raised considerable concern among patients with hemophilia and related disorders, their families, and the medical and public health community. In addition to the possible risks of infection to sexual partners of hemophiliacs, other family members often engage in nonsexual forms of intimacy, which may include contact with oral secretions. Furthermore, many family members assist directly in administering factor concentrate to hemophiliacs on home therapy programs. The potential risk of accidental infection through contact with the factor or infusion equipment is especially troubling, given the recent report of seroconversion to human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) antibody positivity in a nurse who sustained a needle stick exposure to blood of an AIDS patient.[1]

In this study we assess the prevalence of both HTLV-III/LAV seropositivity and AIDS-related immunologic abnormalities in a group of hemophiliacs, their household contacts, and, specifically, those family members of HTLV-III/LAV–seropositive hemophiliacs who assist in home infusions. Based on the seroconversion curve for this population of hemophiliacs, we attempt to estimate the number of person-years of at-risk contact between nonhemophilic household members and their associated seropositive hemophiliac(s).

MATERIALS AND METHODS

Clinical and epidemiologic data. In August 1984, adult and pediatric patients closely followed at the Missouri-Illinois Regional Hemophilia Center in St Louis and their household contacts were asked to participate in a voluntary study of their immunologic and HTLV-III/LAV serologic status. Twenty-eight families were enrolled. Each family was composed of one or more hemophilia A or B patients receiving commercially produced factor concentrates and one or more nonhemophilic household contacts. The participants included 34 hemophiliacs and their associated 50 household contacts, consisting of 20 mothers, 8 fathers, 1 grandmother, 11 siblings, 6 spouses (ie, steady sexual partners of six months or more), and four children.

Participants were asked about factor usage, the receipt of other blood products during the preceding five years, sexual practices, any AIDS-associated illnesses or symptoms, and possible practices unrelated to hemophilia therapy that would place the participants at risk for AIDS. Family members were also asked whether and to what extent they assisted in the hemophiliac's factor infusions.

Informed consent for these studies was obtained from the human subjects according to the guidelines of the Committee on the Protection of the Rights of Human Subjects from each of the institutions involved in this study.

Laboratory data. Peripheral blood samples were collected for enumeration of the T cell subpopulations with the fluorescence-activated cell sorter (FACS IV*) (Becton Dickinson, Sunnyvale, Calif); commercial monoclonal antibodies (Ortho Pharmaceutical Corp, Raritan, NJ) detecting pan-T (OKT3), T helper/inducer (OKT4), and T suppressor/cytotoxic cells (OKT8); and fluorescein-conjugated goat anti-mouse immunoglobulin (Coulter* Immunology, Hialeah, Fla).[2]

Serum samples were tested by Western blot analysis at the Centers for Disease Control (CDC) by methods described elsewhere.[3] In brief, banding patterns formed by the reactivity of a 1:100 dilution of each subject's serum with culture supernatant-derived HTLV-III/LAV antigen were compared with those of a known positive control serum. Serologic reactions with any combination of the 18-kilodalton (kd), 25-kd, and 41-kd proteins of HTLV-III/LAV were scored as positive.

Basis of risk calculation. Serum samples were available from blood collections between 1981 and 1984 for 16 of the hemophilic

*Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the US Department of Health and Human Services.

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participants in the August 1984 study and for an additional 17 hemophiliacs studied only during the preceding interval. The latter group did not differ statistically in any way, including the average quantity of factor used, from those being studied for the first time in August 1984. Therefore, the estimated average date of seroconversion, derived from the observations of the 33 patients who had been studied earlier, was considered to be applicable to all of the August study participants.

The three serum samples from late 1981 and the two from early 1982 were uniformly seronegative. However, the seropositivity rate for samples collected during the last six months of 1982 rose to 86% (6/7). This change in seroprevalence from uniformly seronegative (0/5) to overwhelmingly seropositive was statistically significant ($P = .008$; Fisher's exact test [FET], one-tailed). For each six-month interval thereafter, the seropositivity rate for newly tested hemophiliacs ranged from 58% to 88%, with an average of 77%. The seroprevalence rate for samples collected prior to mid-1982 (0/5) was also significantly lower than that for all patients whose first sample was collected after mid-1982 ($P = .0015$; FET, one-tailed).

Based on the data above, we chose late December 1982 as the average date of seroconversion for these seropositive hemophiliacs, since the seroconversion curve was then already at its maximal plateau. Therefore, for family contacts of the seropositive individuals studied in August 1984, there had been an estimated average of 20 months of exposure to one or more seropositive hemophiliacs in the household (December 1982 to August 1984). With respect to any household members assisting in factor infusions of a seropositive hemophiliac, approximately 20 "at-risk" months of factor infusion contact would have elapsed by the time of August 1984 assessment.

RESULTS

Spouses and other household contacts. No family member in the 28 households studied indicated any activities associated with other risks for AIDS, such as homosexuality or intravenous drug abuse. Twenty-three households included one or more of the 29 seropositive hemophiliacs. These households contained 42 nonhemophilic members, including 19 mothers, 6 fathers, 1 grandmother, 9 siblings, 3 spouses, and 4 children. None of the spouses or children of adult hemophiliacs nor the parents, siblings, or grandparents of pediatric hemophiliacs had an absolute number of T4 cells, T8 cells, or T4/T8 ratio which was outside the normal ranges for our laboratory. None were HTLV-III/LAV antibody seropositive. The distributions of each T cell subpopulation, as well as the T4/T8 ratio, were not significantly different from normal healthy adult controls. No family member had any signs or symptoms of the AIDS-related complex.

Risk associated with infusion assistance. Twenty-five parents had assisted their 26 hemophilic children with factor VIII or IX infusions during the previous five years. Of the parents, 23 had been assisting one or more of the 24 children who were HTLV-III/LAV antibody positive. Parents assisting more than one child were considered to have had additive exposure opportunities, with each seropositive child representing another 20 months of presumed "exposure." One spouse had regularly assisted with infusion of her seropositive husband during the previous five years. Therefore, the household members assisting in factor infusions had experienced approximately 44 person-years of home therapy exposure without apparent infection.

DISCUSSION

Two instances of AIDS transmission to household contacts of hemophilic patients have now been reported.[4,5] The first instance involved a relatively sexually inactive elderly couple. The second instance involved the development of AIDS by the child of a subsequent AIDS case, whose wife is also seropositive. The seronegativity of all family members in our study supports the impression of the relative infrequency of acquisition of AIDS through casual nonsexual exposures. However, additional surveys of more families of hemophiliacs are necessary to develop an improved estimate of the presumably low, but apparently definite, prevalence of seropositivity and incipient immunologic abnormalities in close contacts. The recent report that HTLV-III/LAV can be found in seminal fluid[6,7] increases the urgency to make this assessment among spouses, while the identification of the same virus in salivary samples from asymptomatic HTLV-III/LAV–infected persons is of concern to all household contacts.[8]

Recent studies in several populations of US and European hemophiliacs have shown that seroprevalence to HTLV-III/LAV has been rising over the last several years[9] and support the general time frame for seroconversion that we observed.[10,11] Although it is possible that some of our seronegative family contacts are incipient seroconverters, the 20-month average interval of exposure of household contacts to the seropositive hemophiliacs in our study seems to be well above the latency interval of up to eight weeks between HTLV-III/LAV inoculation and seroconversion which has been observed in experimental studies in primates.[12,13] It may be, however, that the latency interval is dependent upon the size of the inoculum and that accidental exposures of household contacts and medical personnel through needle sticks will be associated with even longer intervals before seroconversion. Our derived estimate of a low risk—44 person-years without seroconversion—must be reassessed when other longitudinal studies can better quantitate the true risk, the true person-years, and the associated error of estimation.

During the training sessions for family members who will assist in home infusion therapy programs, considerable attention is devoted to advice on prevention of accidental injury and to the proper procedures for handling infusion supplies and equipment. No estimate of the efficacy of these efforts to prevent the accidental infection with AIDS has been available. A recent report documented that none of 33 accidental exposures of hospital employees to HTLV-III/LAV–infected persons' blood (via needle sticks, splattering of the eye with blood, and blood spills on an open cut) had been followed by seroconversion.[14] A similar finding of uniform seronegativity was based on HTLV-III/LAV antibody testing of sera from 40 health care workers with documented exposure to potentially infectious inocula from AIDS patients.[15] It seems reasonable to postulate that risk can be minimized through adherence to published guidelines for handling blood products and equipment.[16]

The convenience of home therapy programs has undoubtedly contributed to the overall improvement in the quality of life and greater survival of the average hemophiliac.[17] In the

context of the AIDS epidemic, it is helpful to have observed that nonhemophiliacs repeatedly assisting in the infusion of factor concentrates seem to have a relatively low degree of attendant risk of seroconversion to HTLV-III/LAV.

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REFERENCES

1. Anonymous: Needlestick transmission of HTLV-III from a patient infected in Africa. Lancet 2:1376, 1984 (editorial)

2. Hoffman RA, Kung PC, Hansen WP, Goldstein G: Simple and rapid measurement of human T lymphocytes and their subclasses in peripheral blood. Proc Natl Acad Sci USA 77:4914, 1980

3. Tsang VCW, Peralta JM, Simons AR: Enzyme-linked immunoelectrotransfer blot techniques (EITB) for studying the specificities of antigens and antibodies separated by gel electrophoresis. Methods Enzymol 92:377, 1983

4. Pitchenik AE, Shafron RD, Glasser RM, Spira TJ: The acquired immunodeficiency syndrome in the wife of a hemophiliac. Ann Intern Med 100:62, 1984

5. Ragni MV, Urbach AH, Kiernan S, Stanbouli J, Cohen B, Rabin BS, Winkelstein A, Gartner JC, Zitelli, BZ, Malatack JJ, Bontempo FA, Spero JA, Lewis JH: The acquired immunodeficiency syndrome in the child of a haemophiliac. Lancet 1:133, 1985

6. Ho DD, Schooley RT, Rota TR, Kaplan JC, Flynn T: HTLV-III in the semen and blood of a healthy homosexual man. Science 226:451, 1984

7. Zagury D, Bernard J, Leibowitch J, Safai B, Groopman JE, Feldman M, Sarngadharan MG, Gallo RC: HTLV-III in cells cultured from semen of two patients with AIDS. Science 226:449, 1984

8. Groopman JE, Salahuddin SZ, Sarngadharan MG, Markham PD, Gonda M, Sliski A, Gallo RC: HTLV-III in saliva of people with AIDS-related complex and healthy homosexual men at risk for AIDS. Science 226:447, 1984

9. Evatt BL, Stein SF, Francis DP, Lawrence DN, McLane MF, McDougal JS, Lee T-H, Spira TJ, Cabradilla C, Mullens JI, Essex M: Antibodies to human T cell leukaemia virus-associated membrane antigens (HTLV-MA) in hemophiliacs: Evidence for infection prior to 1980. Lancet 2:698, 1983

10. Goertler LG, Wernicke D, Eberle J, Zoulek G, Deinhardt F, Schramm W: Increase in prevalence of anti-HTLV-III in haemophiliacs. Lancet 2:1275, 1984

11. 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 312:483, 1985

12. Alter HJ, Eichberg JW, Masur H, Saxinger WC, Gallo R, Macher M, Lane HC, Fauci AS: Transmission of HTLV-III infection from human plasma to chimpanzees: An animal model for AIDS. Science 226:549, 1984

13. Francis DP, Feorino PM, Broderson R, McClure H, Getchell JP, McGrath C, Swenson B, McDougal JS, Palmer E, Harrison A, Barre-Sinoussi F, Chermann JC, Montagnier L, Curran JW, Cabradilla C, Kalyanaraman VS: Infection of chimpanzees with lymphadenopathy-associated virus. Lancet 2:1276, 1984

14. Hirsch MS, Wormser GP, Schooley RT, Ho DD, Felsenstein D, Hopkins CC, Joline C, Duncanson F, Sarngadharan MG, Saxinger C, Gallo RC: Risk of nosocomial infection with human T-cell lymphotropic virus III (HTLV-III). N Engl J Med 312:1, 1985

15. Centers for Disease Control: Update: Prospective evaluation of health-care workers exposed via the parenteral or mucous-membrane route to blood or body fluids from patients with acquired immunodeficiency syndrome—United States. MMWR 34:101, 1985

16. Centers for Disease Control: Provisional Public Health Service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. MMWR 34:1, 1985

17. Johnson RE, Lawrence DN, Evatt BL, Bregman DJ, Zyla LD, Curran JW, Aledort LM, Eyster ME, Brownstein AP, Carman CJ: Acquired immunodeficiency syndrome among patients attending hemophilia treatment centers and mortality experience of U.S. hemophiliacs. Am J Epidemiol 121:797, 1985