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Acquired Immunodeficiency Syndrome (AIDS) in Hemophiliacs

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From mid-1977 to mid-1983 the Centers for Disease Control (CDC) has received reports of more than 2,100 cases of acquired immunodeficiency syndrome (AIDS). These cases had either biopsy confirmed Kaposi's sarcoma or a biopsy or culture confirmed life-threatening opportunistic infection, without an identifiable cause of immunosuppression. Reports of AIDS in hemophiliacs began to appear in January 1982. As of October 6, 1983, CDC has confirmed 18 reports of AIDS in United States (U.S.) hemophiliacs and 5 outside the U.S. Two had other known risk factors for AIDS. Seventeen of these cases had *Pneumocystis carinii* pneumonia. (PCP). The mortality rate for the 23 hemophiliac cases was 70 percent. Immunologic findings included lymphopenia, a decreased ratio of T helper/T suppressor lymphocytes, and hypergammaglobulinemia. Most hemophiliac cases did not reside in areas of high risk for AIDS. All cases had received factor and, often, other blood products in the 5 years prior to the AIDS diagnosis. The racial distribution of hemophiliac AIDS patients resembled that of transfusion-associated AIDS patients. Hemophiliac AIDS patients resembled both transfusion-associated and IV-drug abuser AIDS patients and differed from homosexuals with AIDS in regard to associated diagnoses. The epidemiology of these cases is consistent with the possibility that AIDS is caused by an agent transmissible through blood products. These data support the need for current blood product related precautions issued by the National Hemophilia Foundation and by the Public Health Service.

Key words: Acquired immunodeficiency syndrome (AIDS), Hemophilia, Plasma derivatives, Factor VIII concentrates, Factor IX concentrates, Transfusions

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On June 5, 1981, the Centers for Disease Control (1981) published a report of five cases of *Pneumocystis carinii* pneumonia in homosexual males, which occurred between October 1980 and May 1981. This proved to be the beginnings of what is now called an epidemic of the acquired immunodeficiency syndrome (AIDS), with United States cases reported to the CDC totalling 2,157 as of August 22, 1983. By CDC criteria, all cases had either biopsy confirmed Kaposi's sarcoma at less than 60 years of age or a life-threatening opportunistic infection confirmed by culture or biopsy, and no underlying cause of immunodeficiency (Jaffe et al 1983). Patients who were subjected to appropriate immunologic studies were found to have a similar pattern of immune dysfunction, associated with a decreased number of T helper lymphocytes, a low ratio of T helper cells/T suppressor cells, and polyclonal hypergammaglobulinemia (Rogers

et al 1983).

Several factors have implicated a transmissible agent as the cause of this syndrome. These have included the sudden appearance of cases in specific geographic localities, the association with a prolonged prodrome of generalized lymphadenopathy, recurrent fever, and weight loss, and the occurrence of epidemiologic case clusters which suggest that the syndrome may be sexually transmitted among homosexual men (CDC 1981, 1982a, Curran et al 1983). The concurrent appearance of AIDS in the intravenous drug abuser population (Wormser et al 1983) suggested that the syndrome may also be transmitted through an intravenous route and that hepatitis B might be a useful model for the transmission pattern of any proposed AIDS agent (CDC 1982a, Jaffe et al 1983). Consistent with this model, CDC received a report of AIDS in a hemophiliac in January 1982 and found two further cases in June and July 1982, through intense surveillance of requests for a drug used to treat PCP and which is available only from CDC. Since then, a total of 23 cases of AIDS in hemophilia patients have been identified, 18 in the United States and 5 in other countries (CDC 1982b, Ehrenkranz & Rubini 1983, Davis et al 1983, Poon et al 1983, Elliott et al 1983, Eyster et al 1982, CDC 1982c, Lissen et al 1983). In all but 2 cases, data from inquiries about patients' sexual activities, drug usage, ethnicity, and travel or residence have provided little evidence that the disease could have been acquired by contact with homosexuals, with illicit drug abusers, or with Haitian immigrants. On the other hand, all of these AIDS patients had been exposed to some form of blood product. This report summarizes the epidemiologic findings in these reported cases of AIDS in hemophilia patients.

MATERIALS AND METHODS

Case reports on U.S. hemophiliacs with AIDS were obtained through the ongoing AIDS surveillance system (Jaffe et al 1983), interviews of attending physicians, reviews of reports of suspected AIDS patients in hemophiliacs obtained from the CDC-National Hemophilia Foundation Hemophilia Treatment Center Surveillance program, or by routine reviews of requests to CDC for pentamidine isethionate to treat *Pneumocystis carinii* penumonia. Non-U.S. cases were confirmed by follow-up on reports to CDC by other sources. Data on non-hemophiliac U.S. persons with AIDS were obtained through the ongoing AIDS surveillance system (Jaffe et al 1983). Transfusion-associated AIDS cases (TA-AIDS) were defined as cases of AIDS that on thorough CDC investigation had no identifable risk factor for AIDS and had received a blood product in the five years prior to their AIDS diagnosis.

Once a case of AIDS was identified, a CDC staff member interviewed the patient and/or the attending physician by telephone or in person, and reviewed all obtainable clinical information, including, types of illnesses, dates and methods of diagnosis, dates of onset of signs or symptoms, history of predisposing conditions, types of therapy, dates and types of blood transfusion and/or blood product therapy, and demographic data such as age, race, marital status, sexual prefer-

ence, travel history, and residence. Attempts were made to obtian pertinent laboratory data on all suspected cases of AIDS in patients with hemophilia, including complete blood counts, differential counts, platelet counts, lymphocyte subset enumeration, lymphocyte helper to suppressor subset ratios, *in vitro* lymphocyte responses to mitogens and antigens, skin tests, and immunoglobulin levels. When these were not available from the patients' recores, tests were performed when possible at CDC using standard techniques (Hoffman et al 1980, Chan et al 1982, McDougal et al 1979, Zubler et al 1976).

RESULTS

AIDS was documented in 23 hemophiliacs between January 1, 1982 and October 6, 1983. Eighteen of the cases were in the United States, 4 in Europe (Spain and Wales), and 1 in Canada. One of these patients had symptoms of immunodeficiency prior to the onset of the current AIDS epidemic and a history of misuse of prescription intravenous medication. Another case was a homosexual and thus had another risk factor for AIDS.

Twenty-two of the 23 patients had hemophilia A; one had hemophilia B. Only one patient with hemophilia A was known to have had a factor inhibitor. This was present in low titer and the patient was treated during bleeding episodes with high-doses of factor VIII concentrate. All U.S. hemophilia A patients were known to have received factor VIII therapy in the 5 years and the hemophilia B patient, factor IX. At least 5 U.S. patients had received cryoprecipitate. At least 6 had received some other type of blood product in the 5 years prior to their AIDS diagnosis.

The number of diagnosed hemophiliac cases increased through the first quarter of 1983. Five U.S. and one non-U.S. cases were diagnosed in the second quarter of 1983, and one, thus far, in the third quarter. This decline may well correspond to a delay in the reporting of an AIDS case to CDC after the diagnosis is made. The 18 U.S. cases were reported from 14 states: Alabama, Colorado, Connecticut, Florida, Georgia, Illinois, Iowa, Kentucky, Maryland, Missouri, New Jersey, New York, Ohio, and Pennsylvania. Non-U.S. cases were from Spain, Wales and Canada. Thirteen of 18 U.S. cases came from relatively low-risk areas for AIDS. Approximately 66 percent of all the reported non-hemophiliac AIDS cases have been in New York City, San Francisco, and Los Angeles, whereas none of the hemophilia cases have occurred in those 3 cities.

The ages of the 23 hemophiliac AIDS patients ranged from 9 to 74 years with a median of 35 years. Twenty-one were white and 2 were black. The racial distribution of U.S. hemophiliac AIDS cases was similar to that of CDC-investigated transfusion-associated AIDS cases (TA-AIDS) (Table 1).

As of October 6, 1983, sixteen of the patients had died; 12 of these were U.S. cases, giving a U.S. mortality rate of 67 percent and a non-U.S. rate of 80 percent. Sixteen of the 18 U.S. patients had *Pneumocystis carinii* penumonia (PCP) and 5 had more than one infection. One of the five non-U.S. cases was reported as having PCP and three had multiple infections. Other opportunistic infections

TABLE 1.

Race of AIDS cases, by risk group.*

Race	Heterosexual AIDS	TA-AIDS	Hemophiliacs
White %	22	73	89
Other %	78	27	11
Total%	100	100	100
n	319	11	18

* All U.S. heterosexual cases reported to CDC as of April 5, 1983; transfusion-associated AIDS cases (TA-AIDS) investigated by CDC as of May 12, 1983; all U.S. hemophiliac cases reported to CDC as of October 10, 1983.

TABLE 2.

Percent of AIDS cases with Pneumocystis carinii pneumonia (PCP) or Kaposi's sarcoma (KS), by risk group, **.*

Risk group	n	PCP %	KS%
Hemophiliacs	18	89	0
TA-AIDS	11	91	9
IV drug abusers	217	77	5
Homosexuals	933	55*	46*
Haitians	64	42*	9*

* Signifies that difference between hemophiliacs and designated group was significant at at least the .01 level, by Fisher's exact test.

** Data on hemophiliac cases as of Oct. 6, 1983; data on IV drug abusers, homosexuals, and Haitians as of April 5, 1983; data on transfusion-associated AIDS cases (TA-AIDS) as of May 12, 1983.

included *Myobacterium avium intracellulare,* histoplasmosis, disseminated cytomegalovirus, cerebral toxoplasmosis, cryptococcal meningitis, and esophoegeal candidiasis. In one instance, *Mycobacterium tuberculosis* occurred before PCP. The proportion of hemophiliac AIDS cases having PCP was similar to the proportion of reported TA-AIDS and IV-drug abuser cases having that diagnoses (Table 2). This proportion differed significantly from that for homosexual cases ($p = .003$) and for Haitian cases ($p = .0004$). No U.S. hemophilia patients had Kaposi's sarcoma (KS), a finding that was significantly different from that for homosexual AIDS cases ($p = .00003$) (Table 2).

Hemophilia patients with AIDS had a complex illness identical in its clinical manifestation with AIDS seen in other affected groups. The majority have had a prodromal episode lasting for a few weeks to months, characterized by malaise, weight loss, fever, and lymphadenopathy. After the onset of opportunistic infections, most of the patients did poorly. Of the 16 patients who are known to have died, survival time after the date of diagnosis of opportunistic infection was a few days to 11 months. Most survived no longer than 2 months.

Laboratory results show that three of the patients have had thrombocytopenia (<100,000/ul) at the time of diagnosis. The most consistent laboratory finding in the patients had been a markedly depressed lymphocyte helper to suppressor ratio. In 20 of 22 cases tested, this ratio has been less than 0.6. In addition, all but one of the patients have developed lymphopenia with their illness. In 19 of the 20 cases with recorded absolute lymphocyte counts, these counts ranged from 100 c/mm^3 to 1,200 c/mm^3 at the time of diagnosis of the initial opportunistic infection. The *in vitro* lymphocyte functions in 7/7 cases tested were abnormal, and skin tests to common antigens suggested anergy in 10/11 persons tested. Seven of 15 patients tested had elevated IgG; 14/15, elevated IgA; and 6/15, elevated IgM. Five of 15 tested had elevations of IgG, IgA, and IgM.

DISCUSSION

It might reasonably be asked whether these reported cases of opportunistic infections in hemophiliacs represent an unusual or new phenomenon. Although the number of reported cases of AIDS in hemophiliacs is low, it represents an attack rate of about 1 per 1,000 for the 12,000 to 17,000 hemophilia patients in the United States (Aledort & Goodnight 1981). All but six of the hemophilia patients with AIDS had *Pneumocystis carinii* pneumonia. The annual incidence of PCP in the United States has been estimated to be about 0.30 cases per 1 million population (Walzer et al 1974). The present attack rate of PCP among the hemophilia patients, therefore, represents about a 5,000-fold elevation over the general population. Further, we can find only 1 report of a case of *P. carinii* pneumonia in a hemophiliac before 1981 (Muller 1960). The patient was a 7-1/2 year old boy with hemophilia A who had *Pneumocystis carinii* pneumonia after a 2-month couse of high-dose corticosteroids for joint problems. The immunosuppression produced by the extended steroid treatment may have been responsible for his PCP, and he would not presently be classified as an AIDS case. Finally, an extensive review of requests for pentamidine isethionate in the period 1967–1983 for treatment of patients with *Pneumocystis carinii* pneumonia failed to reveal a single patient with underlying hemophilia. Thus we may conclude that the reported hemophiliac AIDS cases reported here are new and are a part of the current AIDS epidemic.

The AIDS epidemic initially involved male homosexuals and intravenous drug abusers, suggesting that the disorder could be infectious in nature, and transmissible through sexual or intravenous routes (Curran et al 1983, CDC 1982a, Wormser et al 1983), as is hepatitis B. The evidence for increased incidence of hepatitis B infection in the populations which have a high risk of contracting AIDS, i.e. male homosexuals, intravenous drug abusers, and recent Haitians entrants to the United States, suggest hepatitis B could be used as a model for transmission of the disease (Rogers et al 1983 and unpubl. observations). A hepatitis B model for the transmissibility pattern of AIDS implies low infectivity, but does suggest that persons receiving blood products could be at heightened risk of the disorder, if those blood products happened to contain the AIDS agent. Indeed, the transfusion of blood products is known to be associated with transmission of other viruses, especially hepatitis B virus, non-A non-B hepatitis virus(es), cytomegalovirus, and Epstein-Barr virus. Hemophilia patients have a significant risk of developing hepatitis; in fact, approx. 85 percent of these patients will eventually have serum markers for an infection with hepatitis B (White & Lesesne 1983). All the reported cases of hemophiliacs with AIDS had received some form of blood product during the time period pertinent to the AIDS epidemic. They resemble AIDS cases suspected of being infected via an intravenous route, i.e., drug-abusers and TA-AIDS cases, in regard to associated diagnoses and to TA-AIDS, in regard to racial distribution. Thus, when hepatitis B is used as a transmission model for the AIDS agent, the appearance of AIDS in persons with hemophilia is not surprising, albeit of concern, and may be related to their

receipt of blood products.

For hemophilia patients, the initial part of the epidemic curve resembles the early phase of the epidemic that was seen for the other groups affected by AIDS. For the period from October 1981 to July 1982, 3 patients were found, from July through December 1982, 6 more were reported, and from January through June 1983, 13 were reported. An extensive review of the 7,600 patients seen in U.S. hemophilia treatment centers with 10 or more patients failed to uncover other patients in 1978–1982. There is an apparent lag phase of 2 to 2-1/2 years between the original epidemic beginning with the homosexual population (mid-1979) and the appearance of AIDS in hemophilia patients (January 1982). If these two epidemics are related, and if AIDS is indeed transmitted by an agent found in blood or blood products, then the lag time may represent, in part, latency after the introduction of the agent into blood products, plus any processing time of the blood products before they then reached a susceptible population. The 2 to 2-1/2 years would be compatible with what is known about the latency seen after possible exposure (7-14 mo.) in sexually transmitted AIDS in homosexual men (Auerbach et al in press) plus the average processing time of plasma factor concentrates from blood acquisition to consumption (12–15 mo., personal contact, Dr. Michael Rodell).

Hemophilia patients, of course, receive other blood products besides plasma factor concentrates. These include blood and plasma transfusions at the time of bleeding episodes. The possibility that some or all of the AIDS cases in hemophilia patients may be related to transfused blood rather than plasma factor concentrates cannot be ruled out, especially in light of reports of transfusion-associated AIDS cases (CDC 1982 d, Ammann et al 1983, Curran et al in press). However, most of the blood used for transfusion is obtained in the region where it is used, and any diseases produced by possible transmissible agents would be expected to appear in that region, i.e., an area having high endemic rates with respect to AIDS, therefore, New York, San Francisco, and Los Angeles would be expected to have the highest incidence of AIDS associated with a blood transfused agent. The random geographic distribution of AIDS in hemophiliac patients is inconsistent with this expectancy, while a transmissible agent spread by plasma factor concentrates manufactured in a few locations and then widely distributed would by consistent with the geographic location of cases.

It has been suggested that immunologic abnormalities in hemophiliacs may be caused by a biochemical component of factor VIII, and not an infectious agent transmitted in the factor (Lee et al 1983, Richard et al 1983). We do not feel this is a reasonable or complete explanation for the appearance of AIDS in hemophiliacs. While a non-infectious agent may explain laboratory abnormalities found in clinically healthy hemophiliacs, it is not compatible with the temporal aspects of these reported hemophiliac AIDS cases. Plasma factor concentrates first became widely used in the late 1960s; therefore, if a non-infectious agent were responsible for AIDS, the appearance of the syndrome might have been expected

before 1982. Although one might postulate the need for prolonged exposure to the proposed non-infectious agent to explain this temporal pattern, AIDS has occurred in young hemophiliacs who have only received plasma factor concentrate during the last few years. Furthermore, the recent appearance of AIDS in patients who have received blood transfusions but who otherwise have no known risk factors suggests that a single exposure may be all that is necessary to transmit the disease (CDC 1982d, Ammann et al 1983, Curran et al, in press).

The evidence to date suggests that it is prudent to take measures to reduce the risk of acquiring and transmitting AIDS via blood and blood products. This may be especially pertinent to the hemophilia patient. Most hemophilia AIDS patients have died a few months after onset of opportunistic infections. Clinically they represent a more difficult patient to manage because any invasive procedure is complicated by their bleeding diathesis. Specific recommendations concerning the treatment of hemophiliacs with blood and blood products have been issued by the Medical and Scientific Advisory Committee of the National Hemophilia Foundation (1983). The Public Health Service is requesting that high-risk persons refrain from donating plasma and/or blood and that an extensive effort be undertaken to develop and evaluate the use of laboratory tests for screening out blood or blood products obtained from individuals in high-risk groups (CDC 1983). These interim measures are reasonable ones to persue until the cause of AIDS is found.

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