Low Prevalence of Antibodies against Human Immunodeficiency Virus in Finnish Haemophiliacs

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Abstract. National yearly surveys were carried out between 1985 and 1989 to determine the prevalence of antibodies for human immunodeficiency virus (HIV) in Finnish patients with bleeding disorders. From 192 out of the 214 haemophiliacs (90%) tested, 2 patients were positive for anti-HIV. No seropositivities were found after 1985. Fourteen out of 21 patients (67%) with type III von Willebrand's disease, and 7 out of 8 patients (88%) with factor XIII deficiency were tested with negative results. The low prevalence of anti-HIV (0.94%; 2/213 tested), is mainly due to the self-sufficiency for clotting factors, the low prevalence of HIV in the population, and the use of cryoprecipitate during the critical period.

Introduction

Most haemophiliacs treated effectively with commercial concentrates in the early 1980s have developed antibodies for human immunodeficiency virus (HIV). However, the seropositivity is only 10–15% among patients treated with cryoprecipitate, even in high-risk areas [1]. When locally produced clotting factors are obtained from low-risk donors, even lower prevalence rates have been reported [2], among others in several countries neighbouring Finland [3–7].

Finland has always been self-sufficient for source plasma from voluntary nonremunerated donors for the production of clotting factors. The country is a low-risk area in regard to the prevalence of HIV infection in the population. The prevalence of antibodies for hepatitis B and C virus in haemophiliacs [8] is lower than in most countries where these data are obtainable. Cryoprecipitate was the sole form of factor VIII therapy up to late 1984.

The aim of this study was to establish the prevalence of HIV antibodies among patients with congenital bleeding disorders in Finland.

Patients and Methods

Patients with bleeding disorders have been diagnosed and centrally registered since 1957 in the Coagulation Laboratory of the Finnish Red Cross Blood Transfusion Service. Patients with haemophilia or their families were first contacted by an information letter with the support of the Finnish Haemophilia Association. Those who consented to take part in the study had their blood samples sent to the laboratory. In the registry, there were 193 patients with either haemophilia A or B at the beginning of 1985, and 214 patients at the end of 1989. The distribution of patients in 1989 by severity was: haemophilia A, severe 109, moderate 22, mild 41; haemophilia B, severe 8, mild 34. Seven patients died, and 33 were diagnosed during the 5-year period. One patient moved abroad. Thus, 226 patients with haemophilia were alive during the survey. Twelve patients (5.3%) were excluded: 6 children who were either diagnosed during or after collection of the samples for the fifth survey or who were under the age of 1 year at that time, and 6 other patients with haemophilia exposed to clotting factors for the study.

In 1988 and 1989, 14 of the 21 patients with severe homozygous (type III) von Willebrand's disease, and 7 of the 8 patients with factor XIII deficiency were studied in order to expand the survey to all frequent users of cryoprecipitate.

In addition, frozen and stored serum specimens taken in 1978 and 1979 were available from 113 patients with haemophilia.

Therapeutic Material and Treatment

Cryoprecipitate and factor VIII and IX concentrates are produced by the Finnish Red Cross Blood Transfusion Service. The screening of blood donors for anti-HIV began in the summer of 1985 and has included all donors since the beginning of 1986.

Small-pool cryoprecipitate, from 2 or 8 donors, with a labelled activity of 200 or 800 units and lyophylized since 1969, was the only available factor VIII concentrate from 1967 to the latter part of 1984. A Finnish intermediate purity factor VIII concentrate (AHF-20) was introduced in 1984. AHF-20 became the main product for haemophilia A after being heat treated ($68^{\circ}C/72h$, dry heat) in 1985. It is mainly used by patients with severe haemophilia A in home therapy. Heat-treated cryoprecipitate ($60^{\circ}C/72h$, dry heat) has been used since 1987.

The amount of factor VIII used in the country rose from 6.2 to 9.0 million units during the 1980s. The use in 1989 was 52,300 units per patient with haemophilia A or 1.84 units per inhabitant.

Haemophilia B has been treated with factor IX concentrate since 1969. Heat treatment (68°C/72 h, dry heat) began in 1986. The annual use increased from 846,000 to 1,020,000 units during the 1980s. In 1989 it was 24,300 units per patient with haemophilia B or 0.21 units per inhabitant.

Imported drugs have been used only to treat patients with factor VIII inhibitor. The use of activated prothrombin complex concentrates (Autoplex, Feiba) has varied from 24,800 to 183,000 units per year in the 1980s.

Anti-HIV Assay

Plasma or serum specimens previously stored at -20 °C were tested for anti-HIV by enzyme-linked immunosorbent assays. In 1985, the assay was performed essentially as previously described [9], and later on by different commercial kits: Vironostica anti-HTLV III (Organon Teknika) in 1986, Wellcozyme Anti-HTLV III (Wellcome) in 1987, Wellcozyme HIV monoclonal (Wellcome) in 1988, and Enzygnost-Anti-HIV micro (Behring) in 1989. Repeteadly positive samples were confirmed by Western blot analysis with commercially available strips (HTLV-III Western Blot IgG, DuPont, or HIV Western Blot, Organon Teknika).

Results

From 192 of 214 haemophiliacs (90%), 701 specimens were examined, which gives an average of 3.7 examinations per patient between 1985 and 1989 (table 1). Antibodies against HIV were looked for at least twice in 175 and once in 17 patients. The cumulative percentage of patients studied from all patients has varied from 73 to 92%, and it was 90% in 1989. Two patients were identified as anti-HIV positive in 1985. No new seropositivities were found later. The prevalence of antibodies against HIV in patients with haemophilia A or B was 2 of 192 or 1.0%. The age distribution of patients studied did not differ from that of all the patients.

The overall response rate of the voluntary anti-HIV surveys of patients with haemophilia varied between 72 and 82%. It was highest in 1987 and lowest in 1989. Twenty-two of 214 patients with haemophilia (10.3%) did not respond to our inquiries or participate in the survey. Thirteen of them (59%) have moderate to mild haemophilia A or B; most are adults. The age distribution of these patients did not differ from the patients studied or from all the patients.

Fourteen of the 18 patients with factor VIII inhibitors living in the country have been treated with imported activated prothrombin complex concentrates during the last 10 years. All these, and all except 1 of the 4 other patients, were tested with negative results.

The 7 patients with factor XIII deficiency and 14 with severe von Willebrand's disease tested in 1988 and 1989 were negative for anti-HIV. Table 1. Finnish patients with haemophilia A or B surveyed for anti-HIV between 1985 and 1989

Year	Patients, n		Previously	Cumulative	Anti-HIV
	all	tested	n	coverage, %	n n
1985	193	140 (73)	140	73	2
1986	194	143 (74)	28	87	0
1987	201	147 (73)	14	91	0
1988	204	138 (68)	6	92	0
1989	214	133 (62)	4	90	0

Figures in parentheses are percent values.

The retrospective study of 113 stored frozen haemophiliac blood samples from 1978 to 1979 revealed no seropositivities.

Two adolescent patients were found to have antibodies against HIV in the first survey in January 1985. They had only been treated with Finnish cryoprecipitate until then. Both patients have severe haemophilia A. Both were seronegative in 1979. One of the patients probably received contaminated cryoprecipitate in 1983, as 1 of the 8 donors who contributed to a certain bottle provided a sample some months after that donation which later tested positive. The source of the infection in the other patient has not been located. The patients have no other known risk factors for HIV infection than cryoprecipitate. Their mean annual usages of factor VIII in home therapy were 33,000 and 91,000 units, respectively, at the probable time of infection. Both patients are clinically well.

In conclusion, 2 patients were found to be positive for HIV antibodies among 213 treated patients with congenital bleeding disorders. The prevalence of antibodies against HIV was 0.94%.

Discussion

The prevalence of antibody for HIV in Finnish patients with bleeding disorders treated with clotting factors is <1%. The only 2 infections took place in the first half of the 1980s.

The amount of therapy per patient compares with that of other industrialized countries [10]. The patient groups studied in the five national surveys encompass nearly all regular or frequent users of clotting factors. The compliance to and the coverage of the study were good. Most patients have been tested at least twice. The result is not biased by a lack of high-risk patients, as the majority of the

 Table 2. Epidemiology of HIV infection in Finland between 1980

 and 1989

Year	Population, 1	n	Anti-HIV- positive blood donors, n	Transfusion- related infection, n
	anti-HIV- positive	AIDS		
1980	1ª	_		_
1981	0	-	-	-
1982	2	1	-	-
1983	11	2		2
1984	14	3	-	4 ^b
1985	38	4	3	1
1986	67	7 °	2	0
1987	56	8°	0	0
1988	53	17	2	0
1989	39	15°	1	0
Total	281	57	8	7

^a Figures before 1985 are based on retrospective studies.

^b Including 1 haemophilia patient with uncertain timing.

^c One case related to transfusion.

non-participants suffer from mild haemophilia A. Also, the national register of HIV infections kept by the National Board of Health does not contain other seropositive haemophiliacs than detected in this study. It is reasonable to presume that the situation will remain stable, as the selfexclusion of risk donors, and the anti-HIV screening of donors and virus-inactivated concentrates all keep the future risk of infection with HIV low.

Several factors have contributed to the situation. Finland is one of the very few countries that has been selfsufficient for clotting factors. The donation of blood is voluntary and not remunerated. Anti-HIV positivity is rare in the country; there were 281 cases of HIV seropositivity by the end of 1989 in the population of 4.9 millions, i.e. 5.7 per 100,000 inhabitants (National Board of Health statistics). Eight seropositive blood donors were found after the summer of 1985 during the screening of 1.26 million donations and approximately 250,000 donors (table 2). Cryoprecipitate was long used as the sole form of factor VIII substitution therapy. An intermediate-purity factor VIII concentrate was developed and tested in patients in the latter part of the 1970s. However, the large-pool preparation was not introduced to clinical use because of the increased risk of viral infection, i.e. hepatitis.

The low prevalence of antibodies against HIV in Finnish patients with bleeding disorders is due to conditions which already prevailed during the hidden phase of the spread of the virus. In Finland, the national self-sufficiency for blood product has been decisive for the present favourable situation.

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