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HIV-antibodies in Pediatric Hemophiliacs in Nagasaki

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SUMMARY : Human immunodeficiency virus (HIV) antibodies were assayed in 34 pediatric patients (28 patients with hemophilia A, 3 hemophilia B, and 3 von Willebrand's disease) of Nagasaki Prefecture. Thirteen of hemophilia A patients were positive (46.4%), 2 of hemophilia B patients were positive (66.7%) and 1 of von Willebrand's disease patients was positive (33.3%). Seropositive patients totaled 16 out of 34 and sero-positive rate was 47.1 %.

In Nagasaki University Hospital, HIV-antibodies were detected in 6 of 9 hemophilia A patients, but none in hemophilia B and von Willebrand's disease patients.

When compared with sero-negative patients, sero-positive patients had a depressed helper/suppressor T (OKT4/T8) ratio and a relative increase in serum IgG levels ($p < 0.05$). Absolute lymphocyte counts in sero-positive patients did not differ from sero-negative patients.

The reverse transcriptase activities were detected in the peripheral mononuclear cell cultures in 3 of 4 sero-positive hemophilia A patients from Nagasaki University Hospital by Dr. J. A. Levy in 1985.

The above results suggest that exposure to HIV is widespread in asymptomatic hemophiliacs. Hence, further studies for preventive measures and therapy of Acquired Immunodeficiency Syndrome (AIDS) must be implemented.

INTRODUCTION

Current estimates suggest that in the United States between one and two million individuals have already been infected with HIV, also known as HTLV-III or LAV¹⁾. Most of these individuals are asymptomatic. As of September, 1986, a total of 238 cases of hemophilia-associated AIDS had been reported to Centers for Disease Control (CDC) through state health departments, hemophilia treatment centers and physicians²⁾. The number of hemophilia-associated AIDS cases has been increasing each year.

59 cases of AIDS, including 34 hemophilia patients, have been reported so far in Japan. According to the news paper of late 1987, 688 cases of HIV infected patients were detected by

AIDS surveillance group in Japan. The occurrence of this syndrome has caused a great deal of distress and anxiety among the afflicted patients and has been the subject of concern throughout the society as a whole.

Epidemiological data suggest that AIDS is transmitted by an infectious agent through intimate contact with body secretions, blood or blood products. To maintain hemostasis, many hemophiliac patients depend on commercially prepared clotting concentrates made from large multi-donor plasma pools and are therefore at increased risk of developing the disease³⁾.

Japan has imported coagulation factor concentrates or material plasma mainly from USA. It is supposed that the time of introduction of HIV into Japan was 1980 at the latest or earlier⁴⁾.

MATERIALS AND METHODS

HIV antibody was measured in 34 pediatric hemophiliacs who had been treated in some main hospitals of Nagasaki prefecture.

In Nagasaki University Hospital, samples from eleven pediatric hemophiliacs ; 9 of the patients had hemophilia A and between the remaining two, one had hemophilia B and the other one had von Willebrand's disease, were tested. All hemophilia A patients had moderate or severe disease and received infusions of commercial factor VIII concentrate. The samples were collected since 1981-87 from individuals. All patients were asymptomatic, except for one patient who had clinical AIDS related complex (ARC).

HIV antibody was measured by indirect immunofluorescence assay and radio-immunoprecipitation. Both cellular and humoral immunity were examined. Cellular immunity was examined by using monoclonal antibodies such as OK T4 and OKT8 to analyze T lymphocytes, helper T cells and suppressor T cells by Flow Cytometry. Serum IgG, IgA and IgM were measured as indicators of humoral immunity.

The reverse transcriptase activities were assayed in the peripheral mononuclear cell cultures in 4 sero-positive hemophilia A patients from Nagasaki University Hospital by Dr.J.A. Levy of Los Angels, in 1985.

RESULTS AND DISCUSSION

1) Prevalence of HIV antibodies in Nagasaki Prefecture :

HIV antibodies were assayed in 34 pediatric hemophilia patients in Nagasaki Prefecture. Prevalence of HIV-antibodies of each patient group is shown in table 1. Sero-positive patients totaled 16 out of 34 and sero-positive rate was 47.1%. 13 out of 28 hemophilia A patients were positive, 46.4%, 2 out of 3 hemophilia B were positive and 1 out of 3 von Willebrand's disease was positive.

16 hemophilia patients were sero-positive for HIV. In Japan, prevalence of HIV antibodies has been reported as between 30% and 60%⁴⁾⁻⁶⁾.

Table 1. Prevalence of HIV antibodies in Nagasaki Prefecture

	Patients	Positive	Rate (%)
Hemophilia A	28	13	46.4%
Hemophilia B	3	2	66.7
von Willebrand	3	1	33.3
total	34	16	47.1%

2) Prevalence of HIV antibodies in Nagasaki University Hospital :

In the department of pediatrics, samples from eleven hemophiliacs assayed revealed that 9 of the patients had hemophilia A and between the remaining two, one had hemophilia B and the other one had von Willebrand's disease. HIV-antibodies have been detected in 6 of 9 hemophilia A patients, but none in hemophilia B and von Willebrand's disease as shown in table 2. All of the sero-positive hemophilia A patients had moderate or severe disease and received infusions of commercial factor VIII concentrates. All of the sero-positive patients have been asymptomatic, except for one case. The factor XIII deficiency patient had been treated with domestic fresh frozen plasma and factor XIII concentrates for 4 and 8 years respectively.

Table 2. Prevalence of HIV Antibodies in Nagasaki University Hospital

	Patients	Positive	Rate (%)
Hemophilia A	9	6	66.7%
Hemophilia B	1	0	0
von Willebrand	1	0	0
total	11	6	54.5%

Her serum shows sero-negative to HIV.

3) Changes of HIV antibodies in 11 hemophiliacs :

Figure 1 shows changes of HIV-antibodies in 11 hemophiliacs in Nagasaki University Hospital. The samples were collected from individuals since 1981-87. All patients were asymptomatic, except for one patient, case 5, who had clinical AIDS related complex (ARC). The earliest seroconversion occurred in 1982. Two hemophilia A patients were HIV-antibody positive in 1982 as shown in figure 1. Japanese

scholar, Dr. Nagao had reported that the earliest seropositive samples of hemophilia patients in Japan were found in 1980, two of 19 stored plasma, one hemophilia A and one hemophilia B, showed positive results⁴⁾. Thus, introduction of HIV into Japan is thought to have occurred at the latest, in 1980. According to our results, sero-conversion was noted between 1981 and 1982, in Nagasaki.

In Japan, heat-treated factor VIII concentrates were brought into the market in August 1985, and after they have been in use, sero-conversion has no more been observed.

The mean age of sero-positive hemophilia patients was 14 years, and not significantly higher than that of sero-negative patients. The mean age of sero-conversion was around 10 years. The youngest age of sero-conversion is about 3 years old, case 5. But the sero-negative period could not be confirmed. His stored plasma in early 1983 had already shown sero-positive.

The reverse transcriptase activities were detected in the peripheral mononuclear cell cultures in case 2, 4 and 5 of antibody-positive hemophilia A patients from Nagasaki University Hospital by Dr.J.A. Levy of Los Angeles⁷⁾, in 1985.

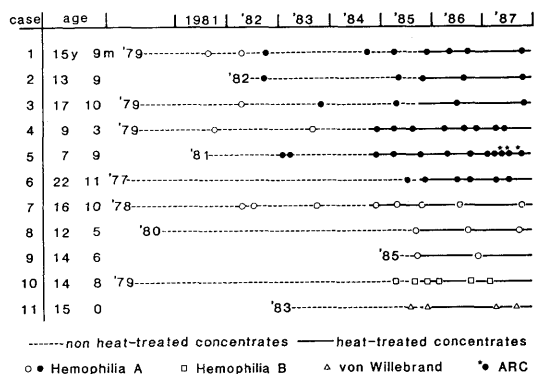


Fig. 1. Changes of HIV Antibodies in 11 hemophiliacs

4) Amount of non heat-treated concentrates in Hemophilia A :

The amount of non heat-treated factor VIII concentrates consumed by the sero-positive patients was compared to the sero-negative patients.

As shown in figure 2, sero-positive patients consumed more amount of factor VIII concentrates than sero-negative patients. However, follow up periods are different from each patient, so expressed by each amount of blood products per year, there is no difference between sero-positive and sero-negative patients in severe hemophilia A. As 2 cases of sero-negative patients have mild and moderate hemophilia A, they did not consume non heat-treated concentrates so much. While, one patient with severe hemophilia A received mainly factor VIII concentrates made from japanese plasma-pools, nevertheless, no sero-conversion was detected. All sero-positive patients who were severe, received imported factor VIII concentrates.

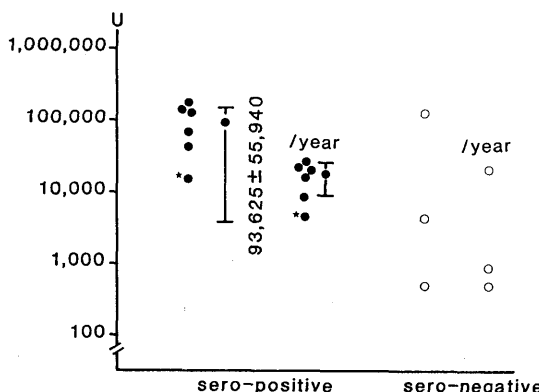


Fig. 2. Amount of non heat-treated concentrates in Hemophilia A

5) Total protein and gamma-globulin Levels in Hemophiliacs :

As hyper gamma-globulinemia was seen in HIV infected patients, the total protein and gamma-globulin levels were compared in sero-positive and sero-negative hemophiliacs. There was no significance in total protein between sero-positive and negative patients. One patient who has ARC showed hypoproteinemia because of malnutrition. Serum gamma-globulin levels of sero-positive patients were higher than those of sero-negative patients ($p < 0.05$), as shown in figure 3.

6) Serum Immunoglobulin levels in Hemophiliacs :

Serum IgG, IgA and IgM were measured as indicators of humoral immunity. Serum IgG

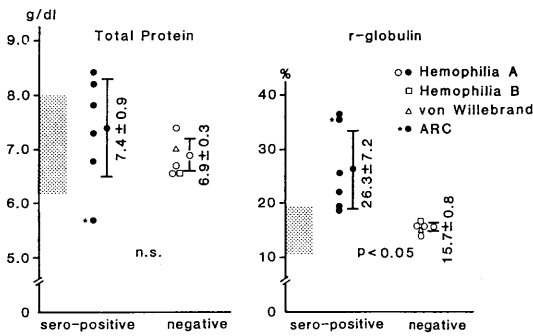


Fig. 3. Total protein and gamma-globulin levels in Hemophiliacs

levels of sero-positive group were slightly higher than those of sero-negative group ($p < 0.05$). There was no significance in serum IgA and IgM levels between sero-positive and sero-negative groups. Serum IgG, IgA and IgM levels in sero-negative group were completely within normal range.

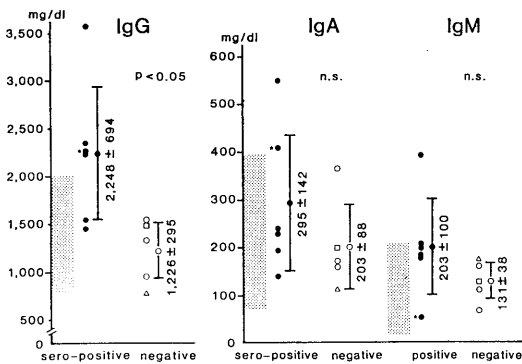


Fig. 4. Serum Immunoglobulin levels in Hemophiliacs

7) WBC and absolute lymphocyte counts in Hemophiliacs :

WBC and absolute lymphocyte counts in sero-positive patients were not different from those of sero-negative patients. ARC patient showed leukopenia and lymphocytopenia as shown in figure 5.

8) OKT4 Positive Lymphocytes in Hemophiliacs :

Cellular immunity which was examined by using monoclonal antibodies such as OKT4 and OKT8 to analyze helper T cells and suppressor T cells by Flow Cytometry, showed that

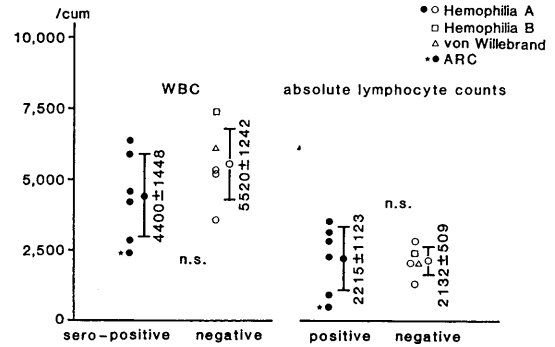


Fig. 5. WBC and Absolute lymphocyte counts in Hemophiliacs

there was no difference in OKT4 positive lymphocyte percent and absolute counts between sero-positive and negative groups (Figure 6).

OKT4 positive lymphocyte percent and absolute counts in ARC patient have been gradually decreasing. As for the OKT4 positive lymphocytes, the sero-negative hemophilia group has slightly lower percent, if compared to that of normal controls.

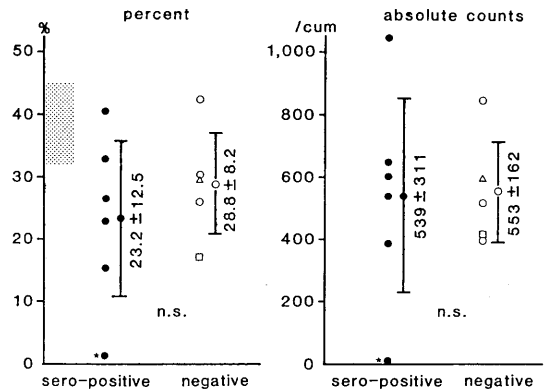


Fig. 6. OKT 4 Positive Lymphocytes in Hemophiliacs

9) OKT8 positive Lymphocytes in Hemophiliacs :

The OKT 8 positive lymphocyte percent in sero-positive group was obviously higher than that of sero-negative group ($p < 0.05$). However, there was no difference in OKT8 positive lymphocyte counts between sero-positive and negative groups (figure 7).

OKT8 positive lymphocyte percent in ARC patient was very high but OKT 8 positive lymphocyte counts was very low due to marked

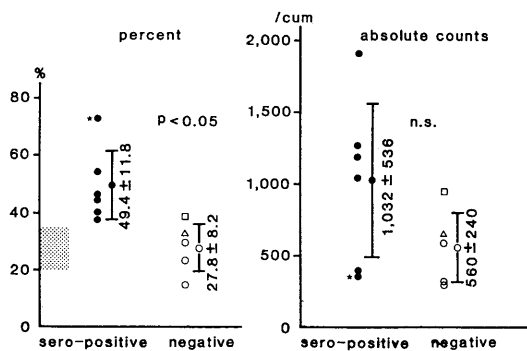


Fig. 7. OKT8 Positive Lymphocytes in Hemophiliacs

lymphocytopenia.

10) OKT4/T8 Ratio in Sero-positive and negative Hemophiliacs :

Figure 8 shows OKT4/T8 ratio, one indicator of cellular immunity, in sero-positive and negative hemophiliacs. OKT4/T8 ratio in sero-positive cases was significantly lower than that in sero-negative cases ($p < 0.05$). 2 out of 6 sero-positive cases showed a marked reversal in OKT4/T8 ratio, showing OKT4/T8 ratios below 0.5 and OKT4/T8 ratio in ARC was markedly depressed.

In sero-negative cases, on the other hand, only 1 case, hemophilia B patient, showed OKT4/T8 ratio below 0.5.

As others have already reported, sero-positive hemophilia patients have lower OKT4, higher OKT8 and lower OKT4/T8 ratio, than sero-negative hemophilia patients.

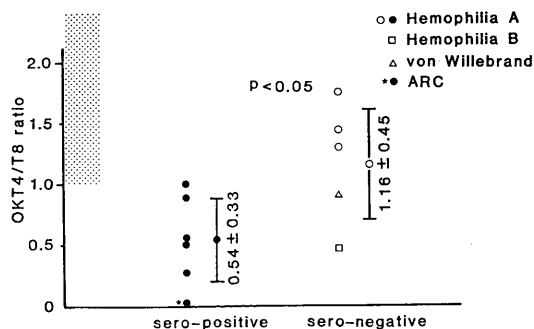


Fig. 8. OKT4/T8 Ration in Sero-positive and negative Hemophiliacs

11) Case Report of 2 Hemophilia A patients :
If someone receives a HIV-contaminated

blood or clotting product, it is estimated that seroconversion will take place within 3-8 weeks.

Case 2 in figure 1 received imported factor VIII concentrates due to joint swelling and hematuria. After 3 weeks, he complained general fatigue. At that time, serum GOT and GPT were elevated more than 1,000 units, so he was diagnosed non A non B hepatitis for blood products. But HIV antibody was positive after 2 months of first factor VIII concentrates infusion. Retrospectively it is supposed that injected factor VIII concentrates were HIV-contaminated clotting products.

Figure 9 shows the clinical course of one patient who was diagnosed ARC. He was 7 years old. Period of sero-positive to HIV was noted in early 1983. He suffered from Herpes Zoster and transient lymphadenopathy in middle 1985. However, he looked well except for joint hemorrhages until January 1987. Serum immunoglobulins have been gradually increasing. He suffered from high fevers of unknown origin in early 1987. During these episodes of fevers, he also developed oral candidiasis and angular stomatitis. These symptoms did not respond to oral antifungal drugs. At the same time, progressive weight loss was prominent due to malabsorption. Furthermore, elevated immunoglobulins levels have been decreasing, as well as WBC and lymphocyte counts.

He was in leukopenia, lymphocytopenia and OKT4/T8 ratio was below 0.01 in late 1987. In the middle of November 1987, he suffered from Herpes simplex virus infection on his right arm. He has been treated with acyclovir, and for prophylaxis of pneumocystis carinii pneumonia he received co-trimoxazole. His weight loss was progressing despite of intravenous hyperalimentation.

CONCLUSION

Human immunodeficiency virus was probably introduced into Japan, by 1980, at latest. And our two patients were confirmed in 1982. After the introduction of heat-treated concentrates, no new cases of sero-conversion have been observed.

The present results suggest that exposure to HIV is widespread in asymptomatic hemop

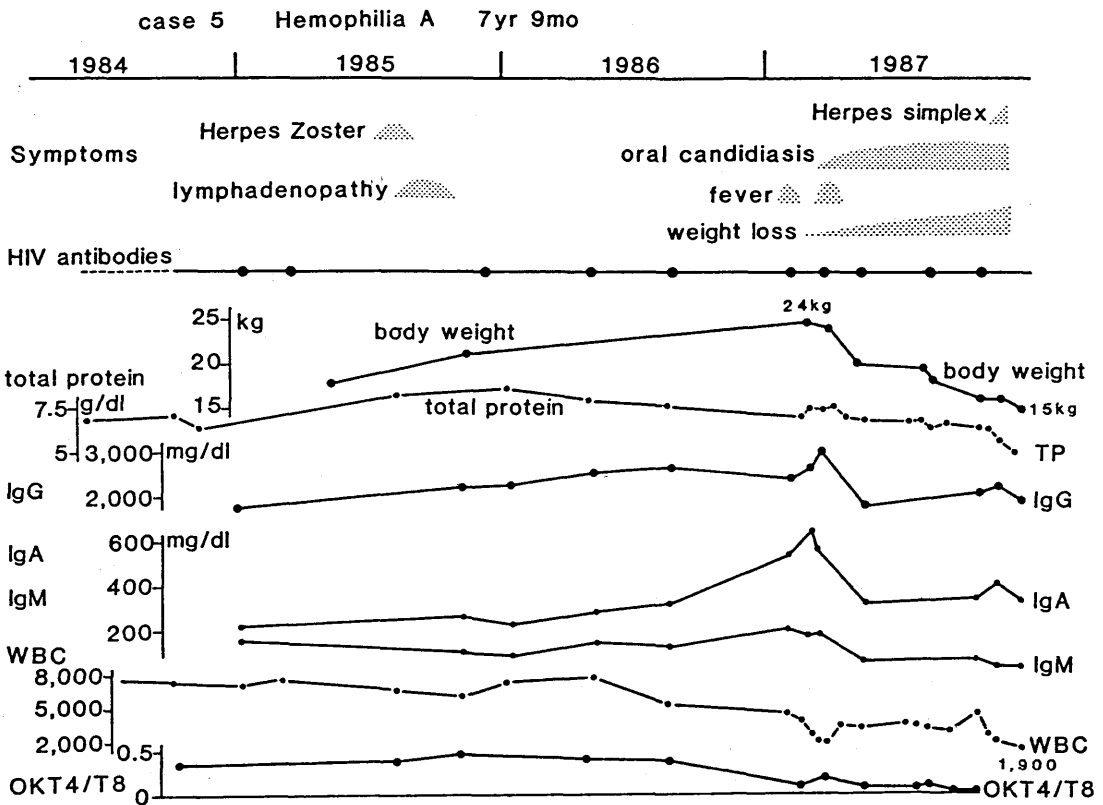


Fig. 9. Case Reports of one Hemophilia A patient

acs. As the incubation period for the development of AIDS following blood transfusion has been estimated to range from 10 months to 5 years, further studies for prophylaxis and therapy of AIDS are require.

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