Prevention of Mother-to-Child Transmission of Human T-Lymphotropic Virus Type-I

Yoshiro Tsuji, MD, PhD; Hiroshi Doi, MD; Tooru Yamabe, MD, PhD; Tadayuki Ishimaru, MD, PhD; Tsutomu Miyamoto, MD, PhD; and Shigeo Hino, MD, PhD

From the Departments of Pediatrics, Obstetrics and Gynecology, and Bacteriology, Nagasaki University School of Medicine, Nagasaki, Japan

ABSTRACT. Human T-cell lymphotropic virus type I (HTLV-I), an etiologic human retrovirus of adult T-cell leukemia/lymphoma (ATLL), causes approximately 60 new cases of ATLL each year in Nagasaki Prefecture; essentially all cases are fatal, and they account for approximately 0.5% of total deaths in the area. The estimated life risk for an HTLV-I carrier to develop ATLL is approximately 5%. The major transmission pathway of HTLV-I peculiarly endemic in the Nagasaki Prefecture was studied. The prevalence of HTLV-I infection in children of carrier mothers (21%) was significantly higher than that in children in the general population in the area (1%), and more than 85% of mothers of carrier children were carriers. The breast milk of carrier mothers contained HTLV-I-infected cells and was infectious for marmoset via oral administration. A retrospective survey of children of carrier mothers showed that the prevalence of carrier children of carrier mothers was 17 (39%) of 44 and 0 (0%) of 10 when they were given breast milk only or formula only, respectively. These data provide a powerful basis for devising an intervention measure to block the endemic cycle of HTLV-I; ie, if carrier mothers refrain from breast-feeding, the incidence of ATLL will be significantly reduced some 50 years later. *Pediatrics* 1990;86:11–17; *human T-lymphotropic virus, human T-cell leukemia virus, breast milk, mother-to-child transmission.*

ABBREVIATIONS. HTLV-I, human T-cell lymphotropic virus type I; ATLL, adult T-cell leukemia/lymphoma.

Human T-lymphotropic virus type-I (HTLV-I) is the first human retrovirus found to be infectious for $CD4^+$ T lymphocytes via cell-to-cell transmission.[1-3] Antibodies against HTLV-I develop in individuals infected with HTLV-I and they become lifelong carriers.[2] Adult T-cell leukemia/lymphoma (ATLL) develops in HTLV-I carriers only, at a frequency of 1 of 1000 carriers each year.[4,5]

The virus is endemic in southwestern Japan.[2,6] Other endemic areas in the world include the Caribbean Islands,[7] Africa,[8] Australia,[9] northern Japan,[10] Alaska,[11] and South America.[12] In all of these areas, the carrier population seems confined to aborigines or those living in rural areas.

Nagasaki Prefecture, the westernmost prefecture of Japan, has a population of 1.5 million; there is a high prevalence of carriers (approximately 10% of population older than 40 years) and a high incidence of ATLL cases (approximately 60 cases each year).[5] Adult T-cell leukemia/lymphoma is resistant to any currently available treatments and has a poor prognosis—almost 100% of cases are fatal within 2 years.[13,14] At present, the most effective measure to control HTLV-I endemicity seems to be the prevention of infection. These facts prompted us to study the transmission route of HTLV-I.

The previously reported data show that most ATLL cases in nonepidemic areas originated in Kyushu, the southwesternmost island of the four large Japanese islands.[2,6,13,14] There have been no cases of ATLL after infection through transfusion.[15] In the elderly population, the number of female carriers is greater than that of males, indicating the presence of male-to-female sexual transmission in adulthood; however, the male-to-female ratio of ATLL cases is 1.5:1.[4] These findings suggest that HTLV-I infection in adulthood has little effect on the incidence of ATLL. Therefore, we decided to focus our study on events in the early stage of life to analyze the major route of natural transmission of HTLV-I. We conclude that mother-to-child

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Reprint requests to (Y.T.) Dept of Pediatrics, Nagasaki University School of Medicine, 7-1, Sakamoto-machi, Nagasaki, 852, Japan.
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transmission through breast milk plays the major role in the persistence of HTLV-I in the endemic cycle.

MATERIALS AND METHODS

Pregnant Women and Their Children

Thirteen gynecology/obstetrics clinics or hospital departments kindly supplied sera or blood samples obtained from pregnant women during their first prenatal visit. Most of these patients were residing in or around Nagasaki City. Sera of children born to those mothers who were seropositive for HTLV-I were obtained at our Pediatric Clinic of the University Hospital. Sera of children born to seronegative mothers were not obtainable.

Children in the General Population

Serum of healthy children is hard to obtain. We tested 633 pediatric patients (from birth to 19 years of age) hospitalized in the pediatric ward of our University Hospital. Because these samples may have included an iatrogenic bias, we also tested 287 students in a nursing school (aged 18 to 19 years) and 1796 blood donors (aged 16 to 18 years) in Nagasaki City, as young healthy control subjects.

Mothers of Carriers

Some mothers of carrier mothers screened in the Nagasaki City area volunteered for the serum test. We did not actively seek to test these grandmothers because there is, at present, no measure to postpone the development of ATLL, and positive results may simply have caused frustration. The number of subjects in this group was small.

In trying to obtain a population of mothers of carriers independent from that described above, we screened approximately 1600 students (aged 6 to 18 years) in a small town (population, approximately 9000) 50 miles away from Nagasaki City. We also obtained serum samples of approximately 4000 adults in the same town who attended the annual health care program. Familial relations were traced from the official records of residents.

Antibody Testing

We used two independent antibody assay methods, a gelatin particle agglutination assay[16] and an indirect immunofluorescence assay.[2] The particle agglutination assay was performed as indicated in the instructions of particle agglutination assay kits (Serodia-ATLA, Fuji-Rebio, Tokyo). The immunofluorescence assay performed was slightly modified from the original method. We used a 1:4 mixture of HTLV-I-producing MT-2 cells[3] and HTLV-I-uninfected CEM cells on a 10-well slide glass after fixation with acetone. Ten microliters of sera at 1:10 dilution was incubated at 37°C for 30 minutes. After two washings, the slide was stained with anti-human IgG labeled with fluorescein isothiocyanate. The sera of blood donors were screened only by the particle agglutination assay.

Except for the serum of blood donors, we considered a serum anti-HTLV-I-positive if the results were positive in both the particle agglutination assay and immunofluorescence assays to minimize false-positive results, inasmuch as we had agreed to report the results to each individual. Approximately one third of particle agglutination assay-positive sera were immunofluorescence assay-negative. Approximately 0.5% of sera were indeterminate by the immunofluorescence assay; none of these were particle agglutination assay-negative. The nonspecific reactivity in the two combined assays was statistically minimal. We did not use Western blotting in this study because the nonspecific reactivity at p19, p24, and p28 regions corresponding to internal proteins of HTLV-I was controversial.

Detection of HTLV-I-Infected T Cells

Not every cell infected with HTLV-I in the host does express HTLV-I genes. To detect T cells infected with HTLV-I, we prepared a T-cell-enriched fraction by Ficoll-Conray density gradient centrifugation and rosette formation with neuraminidase-treated sheep red blood cells,[17] and we cultured them with RPMI1640 medium fortified with 10% fetal bovine serum and 2 U/mL of interleukin-2 in 96-well culture plates.[18] We sacrificed cultured cells weekly for immunofluorescence assay using a reference negative serum, a reference positive serum of a carrier, and a monoclonal mouse antibody against gp21 (F10).[19] Because even the monoclonal antibody showed some nonspecific reactivity, only cultures negative by the first sera and positive by the last two sera were considered positive for HTLV-I antigen.

RESULTS

Prevalence of HTLV-I Carriers

Pregnant Women and Their Children. Antibody tests on the sera of 18 320 pregnant women in and around Nagasaki City detected 718 (3.9%) pregnant carriers (Table 1). The prevalence was consistent with that of age-matched blood donors in the same area. Of 103 children aged 1 to 13 years born to carrier mothers, we found 22 (21%) carriers (Table 1).

General Population. Of 718 patients hospitalized in the pediatric ward of the Nagasaki University

TABLE 1. Prevalence of Human T-Lymphotropic Virus Type-I in Children and Mothers

Subjects	Age, y	No. Positive/ No. Tested	% Positive	χ^2 *
Children born to carrier mothers	1–13	22/103	21	
Control subjects				
Inpatients†	0–19	17/633	2.7	62
Nursing students	18–19	2/287	0.7	56
Blood donors‡	16–18	29/1796	1.6	164
Pregnant women		718/18 320	3.9	95

* χ^2 test is significant at $P = .05$ with the value over 3.84.
† Twelve carriers (most of them with leukemia) from the inpatient group had experienced multiple blood transfusions before screening of donors was started in Nagasaki. Inasmuch as approximately 5% of blood donors in Nagasaki (aged 16 to 64 years) are carriers, more than one half of these 12 were estimated to have been infected via blood transfusions.
‡ The blood donors were tested only by the particle agglutination assay. One third of the positive results were estimated to be false-positive.

Hospital, 17 (2.7%) were antibody-positive. Transmission of HTLV-I through blood transfusion has been reported in 63% of patients who received at least one infected unit of whole blood (not by plasma).[15] Of the 17 antibody-positive patients, 12 had received transfusions before the screening of blood donors had started. This figure probably overestimates the prevalence in children in the general population.

Of 287 nursing students, 2 (0.7%) had positive results on both the particle agglutination assay and the immunofluorescence assay; of 1796 student donors (aged 16 to 18 years), 2.9 (1.6%) had positive results on the particle agglutination assay. Inasmuch as one third of positive results on the particle agglutination assay are false-positive, the prevalence of HTLV-I carriers in their late teens in the Nagasaki City area was estimated as approximately 1%. This may still overestimate the prevalence of carrier children in the younger age group because the control subjects were not age-matched. Thus, the prevalence of HTLV-I infection in children born to carrier mothers was significantly higher than that in other children in the area. The results suggest that HTLV-I transmits from carrier mothers to their children.

The combination of the prevalence of HTLV-I in pregnant women, 3.9%, and that in children born to carrier mothers, 21%, led us to estimate that 0.9% of the children in the area were infected via mother-to-child transmission. The estimate was closely correlated with the estimated prevalence of carrier children in the general population of this area, 1%, and suggests that most, if not all, cases of HTLV-I infection in children are due to mother-to-child transmission.

Mothers of Carrier Children. If mother-to-child transmission is the major factor in HTLV-I endemicity, the mothers of carrier children should prove to be carriers. We tested two groups in this context. One group consisted of mothers of screened pregnant carriers. Of 19 of these mothers, 17 were carriers. The prevalence was significantly higher ($\chi^2 = 243$) than that of age- and location-matched control subjects (Table 2). Furthermore, both of the remaining two pregnant carriers with seronegative mothers had received blood transfusions before the screening of blood donors started; reasons for the blood transfusion were an open heart surgery in one case and massive bleeding during the previous labor in the other. We considered these two women as having been iatrogenically infected by blood transfusions (Table 2).

The mothers described above were at least one generation older than the pregnant women being screened, and they were associated with the screening. To find mothers of carrier children free from these potential biases, we screened approximately 1600 students in a remote town 50 miles away from Nagasaki City and found 54 carriers. Among adults in the same town who attended the annual health care program, we found 13 mothers of these carrier children. Of the 13 mothers, 12 (92%) were antibody-positive, a significantly higher prevalence ($\chi^2 = 26$) than that in the age- and location-matched control subjects (Table 2).

Thus, most mothers of carriers were carriers. These findings, traced both downward and upward in the family tree, strongly suggest that mother-to-child transmission is the primary route of HTLV-I infection.

Period of Transmission From Mother-to-Child

The presence of IgM antibody against the virus, or the virus in cord blood, is often used as infection

TABLE 2. Prevalence of Human T-Lymphotropic Virus Type-I in Mothers of Carriers

Location/Subjects	No. Positive/ No. Tested	% Positive	χ^2 *
Town 50 miles from Nagasaki			
Mothers of carrier students	12/13	92	
Age-matched women	124/453	27	26
Nagasaki City area			
Mothers of carrier pregnant women	17/19	89	
Age-matched female donors	74/1530	4.8	243

* χ^2 test is significant at $P = .05$ with the value over 3.84.

markers for intrauterine infections. We surveyed 285 cord blood samples of newborns of carrier mother (Table 3). Essentially all (98%) were positive for anti-HTLV-I antibody in IgG class. We considered the antibodies maternal, because they were closely correlated with those of mothers (correlation coefficient = 0.85) and they invariably decreased at a rate of approximately 1/10 every 2 months after birth (data not shown). We tested the presence of IgM antibody using immunofluorescence assay with fluorescein isothiocyanate-labeled anti-human IgM rabbit IgG as a second antibody. This immunofluorescence assay detected anti-HTLV-I in IgM class of reference sera that had been positive in Western blots using anti-IgM antibody. However, we found no case with positive results. Furthermore, we failed to detect any T-cell cultures positive for HTLV-I-bearing cells (Table 3). Inasmuch as the same procedure applied for carriers revealed positive cultures in 2/3 of samples, approximately 40 positive cultures would be expected if the intrauterine infection were the major route. Although we cannot exclude such a possibility by these results, we consider it unlikely.

Children born to HTLV-I-carrier mothers had decreasing antibody titers in the first several months, and essentially all of them became antibody-negative by 6 months after birth. In some of these children anti-HTLV-I antibody in IgG class started to develop at the age of 12 months (data not shown). This finding suggests the possibility of postnatal infection as the major factor. The cell-to-cell nature of HTLV-I infection requires transfer of live cells in fluids. The route should thus be specific to mother-to-child relations. From among the possible routes of postnatal transfer of live cells, we focused on one via breast milk. This hypothesis was strongly supported by our laboratory studies wherein a large amount of HTLV-I-infected cells were identified in breast milk of carrier mothers,[20,21] and marmosets were infected with oral inoculations of ATLL cells[22] and with fresh breast milk samples obtained from carrier mothers.[23]

If breast-feeding is the major factor for mother-to-child infection of HTLV-I, children never breast-fed should not be carriers. We retrospectively analyzed, according to feeding method, the HTLV-I infection rate in children born to carrier mothers (Table 4). The prevalence of infection in children raised on breast milk was only 39%; on a mixture of breast milk and formula, 10%; and on formula only, 0%. The lower infection rate in mixed-fed children may have been due to dose effect. These data indicate not only that milk-borne transmission is significant, but also that prenatal or perinatal transmission is insignificant.

TABLE 3. Infection Markers of Human T-Lymphotropic Virus Type-I (HTLV-I) in Cord Blood of Newborns Born to Carrier Mothers*

Markers	No. Positive/ No. Tested	% Positive
Anti-HTLV-I		
IgG	279/285	98
IgM	0/285	0
HTLV-I-infected cells	0/285	0

* See Materials and Methods for description of particle agglutination and immunofluorescence assays.

Potential Delayed Seroconversion

The prevalence of antibody-positive carriers may increase with age if the appearance of antibody is delayed for years or if horizontal infections take place during childhood. We analyzed the carrier rate of children born to carrier mothers with respect to the first test for each individual. However, there was no significant increase in the carrier rate with age (Table 5). The carrier rates were 32%, 27%, 25%, 25%, and 21% for children aged 1, 1 to 2, 1 to 3, 1 to 4, and 1 to 13 years, respectively. The apparent decrease of the carrier rate in this cumulative classification is within the statistical error. Thus, we conclude that infection takes place during the first year of life and that most infected carrier become antibody-positive by the age of 2. In other words, late seroconversion after the age of 2 seems to be rare. Kusuhara et al[24] have recently reported that no increase in the carrier rate was found in a 15-year follow-up study of children born to carrier mothers in Okinawa Prefecture.

TABLE 4. Feeding Methods and Human T-Lymphotropic Virus Type-I (HTLV-I) Infection in Children Born to Carrier Mothers: Retrospective Analysis*

Feeding Method	Age, y	No. Anti-HTLV-I-Positive	No. Tested	Carriers, %
Breast milk	1–13	17	44	39
Breast milk and formula	1–9	5	49	10
Formula	1–8	0	10	0
Total		22	103	21

* χ^2: breast milk vs breast and formula milk = 10.4 ($P < .01$); breast milk vs formula milk = 5.6 ($P < .05$).

TABLE 5. Cumulative Prevalence of Human T-Lymphotropic Virus Type-I in Children of Carrier Mothers

Age, y	No. Positive/ No. Tested	% Positive
1	11/34	32
1–2	12/44	27
1–3	14/56	25
1–4	16/64	25
1–13	22/103	21

DISCUSSION

The results presented in this paper strongly suggest that infection through the mother's breast milk is the primary route of HTLV-I transmission. The significantly lower carrier rate in children nourished by formula milk indicates that the possibility of prenatal and perinatal transmission of HTLV-I is not a major one.

In Nagasaki Prefecture, infection with HTLV-I is one of our most serious health problems: we have 60 new cases of ATLL per year, accounting for 0.5% of total deaths, and 60 000 carriers. The incidence of fatal ATLL is approximately 1 case per 1000 carriers. Because ATLL seems to develop only in carriers infected early in life, probably via breast milk, and each surviving carrier continues to bear another 1/1000/year risk for decades, the life risk of ATLL in carriers infected via milk-borne HTLV-I exceeds 5%. We have 22 000 deliveries per year, and approximately 900 of these are by carriers. If 21% of children born to carrier mothers become carriers without intervention, we expect approximately 200 new infections each year. Inasmuch as a carrier's life risk of developing ATLL exceeds 5%, the incidence of ATLL 50 years from now will be at least 10 cases every year. The difference between the current incidence of ATLL per year and that estimated 50 years from now is probably due to the cohort effect. Thus, introduction of an effective measure to prevent HTLV-I infection is important.

The screening method for HTLV-I carriers is still not optimal. The sensitivity of assays may not be the major problem, as the screening of blood donors by immunofluorescence assay was sufficient to detect blood-borne infections. In our experience, almost one third of positive particle agglutination assay results are false-positive. Immunofluorescence assay results are ambiguous in some cases. Western blotting has nonspecific reactivities, especially in the regions of p28, p24, and p19. Combinations of two or three different assay systems gave reasonably good results; reliable results were especially important in our program because the results were reported to each subject.

The identification of virus in vivo is difficult in the case of HTLV-I. Because the virus is cell associated, and infected cells are suppressed for viral expression in vivo, we have to culture T-cell-enriched fractions for 2 to 4 weeks to identify the presence of infected cells. The newly developed polymerase chain reaction may help, but we have not solved the problem of false-positive results.

Strong association of carriers in carrier mothers and their children, in both descending and ascending family trees, indicated that the major route of HTLV-I infection in endemic areas is mother to child. Mother-to-child transmission can take place in four stages: genetic, intrauterine, perinatal, and postnatal infections. Genetic infection, an infection due to an endogenous retrovirus present in all human somatic cells as a provirus, was excluded because the virus is not endogenous to human species.[25] Our survey of cord blood of babies born to carrier mothers failed to detect positive evidence of intrauterine infections, IgM antibody, or virus-bearing cells, although there has been a report showing a single case of virus-bearing cells after culture.[26] Most intrauterine virus infection is associated with primary infection of mothers during pregnancy, such as in cases of rubella virus and cytomegalovirus infections. It is not likely that 21% of carrier mothers had primary infection during pregnancy, nor that primary infection would have occurred during two consecutive pregnancies (we found several mothers with more than one carrier child).

We started to detect HTLV-I in children at 12 months of age. Seroconversions by blood-borne in-

fections or by oral infection of marmosets suggest that the antibody in IgG class usually appears within 2 months of infection.[22,23] Hepatitis B virus is representative of perinatal infection, where virus replication and antibody production take place after a latent period of 3 to 5 months after birth, which corresponds to those after horizontal infections in adults.[27] Therefore, perinatal infection is not likely to be the major route for HTLV-I infection. Furthermore, the results of a retrospective study, which showed that none of the formula-fed children were infected, strongly suggest that maternal infection does not take place at the intrauterine or perinatal stages.

Our data, including the presence of infectious cells in the milk of carriers, results of animal experiments, and retrospective analysis of feeding methods and HTLV-I infection rates in children born to carrier mothers, all fit with the conjecture of milk-borne infection as the major route for HTLV-I. Therefore, prevention of HTLV-I infection in Nagasaki seems possible if a large-scale system to screen pregnant women is set up and if the detected seropositive mothers agree to use formula rather than breast milk to feed their babies. An intervention study to have carrier mothers refrain from breast-feeding has been in progress on a small scale since August 1986, and on a prefecture-wide scale since August 1986 (ATLL Prevention Program, Nagasaki).

We had to solve several sociomedical problems before we started the intervention study. In Japan, the vast majority of cancer patients are not informed of their malignancies because doctors believe that most patients would be terrified and would not cooperate for treatment. There were cases of discrimination in Nagasaki against hepatitis B carriers after initiation of a program to notify carriers. In the ATLL Prevention Program, we notify HTLV-I-carrier mothers confidentially; we do not inform family members or doctors not directly in charge.

Pediatricians have been stressing the importance of breast-feeding.[28,29] Theoretically, it is possible to feed breast milk that has been processed (by heating of freezing)[30,31]; however, it is troublesome to continue such processing for months, and this method cannot overcome the disadvantage of the loss of direct contact between mother and baby. We dispense drugs to suppress lactation to obtain more comfortable postpartum periods. So far, most mothers have given their informed consent and have cooperated.

Our intervention study was designed to observe children until 3 years of age because some children change serologic status between 12 and 24 months of age. We are studying 154 children, fed formula only, who were born to carrier mothers; after 12 months follow-up, only 4 (3%) of these children were seropositive. If these babies had been fed mainly breast milk, the expected carrier incidence would be approximately 40 cases; thus 90% of possible infection was interrupted by the intervention. We cannot yet specify the secondary infection route. The outcome of the intervention study will be reported at the end of 1990. A similar small-scale study, from Ando et al,[32] has also been reported.

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CHANCES ARE YOU'RE CODEPENDENT TOO

Instead of a self-help section, my local bookstore has a section called Recovery. . .It's stocked with books about addiction, psychic healing and codependency—a popular new disease blamed for such diverse disorders as drug abuse, alcoholism, anorexia, child abuse, compulsive gambling, chronic lateness, fear of intimacy and low self-esteem. Codependency, which originally referred to the problems of people married to alcoholics, was discovered by self-actualization experts about five years ago and redefined. Now it applies to any problem associated with any addiction suffered by you or someone close to you. This amorphous disease is a business, generating millions of book sales [and] countless support groups. . .

Codependency is advertised as a national epidemic, partly because every conceivable form of arguably compulsive behavior is classified as an addiction. (We are a nation of sexaholics, rageaholics, shopaholics and rushaholics.) "I have a feeling we're soon going to have special groups of third cousins of excessive sherry drinkers," the child psychologist Robert Coles told me. "You don't know whether to laugh or cry over some of this stuff." The codependency movement has "run amok," he said. It's a "typical example of how anything packaged as psychology in this culture seems to have an all too gullible audience."

Kaminer W. Chances are you're codependent too. *The New York Times.* February 11, 1990.

Noted by J.F.L., MD