Review

HTLV-I transmission from mother to child

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Abstract

Human T-lymphotropic virus type I (HTLV-I), a causative agent of adult T-cell leukemia, (ATL) is transmitted from mother to child. ATL cells originate from the CD4 subset of peripheral T cells. The main route of mother-to-child transmission is postnatal breast-feeding. Refraining from breast-feeding or limiting the duration of breast-feeding can reduce the risk of mother-to-child transmission. Other than postnatal breast-feeding, there seem to be two routes of HTLV-I transmission from mother to child. One is intrauterine transmission, and the other is via saliva. Intrauterine transmission is rare, although proviral DNA is detected in cord blood samples. HTLV-I proviruses in the cord blood may be defective. HTLV-I proviral DNA and antibodies against HTLV-I are also detected in saliva. However, no report has been published so far which showed direct evidence of HTLV-I transmission via saliva. The placenta can be infected by HTLV-I, but infection does not reach the fetus, possibly apoptosis of placental villous cells because it is induced by HTLV-I infection. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. HTLV-I and ATL

Human T-lymphotropic virus type I (HTLV-I) is the first retrovirus to be associated directly with human malignancy. It was in 1977 that adult T-cell leukemia (ATL) was first reported in Japan as a new clinical entity by Takatsuki et al. (1977). This disease was thought at that time to be a distinct entity confined to only the southwest part of Japan. In the USA, in 1980, a type C retrovirus now known as HTLV-I was first identified by Gallo and co-workers in a T-lymphoblastoid cell line that had been established from a patient diagnosed with a cutaneous T-cell lymphoma (Poiesz et al., 1980). The cell line that produced HTLV-I is known as HUT 102. In 1981, in Japan, Hinuma and co-workers demonstrated that another cell line, called the MT-1 cell line, which was derived from a Japanese patient with ATL, also harbored a type C retrovirus (Hinuma et al., 1981; Yoshida et al., 1982). Antibodies against the antigen in MT-1 cells were found in all 44 patients with ATL. The viruses produced from HUT 102 and MT-1 were subsequently shown to be the same and were given the name HTLV-I (Popvic et al., 1982). The patient in the US diagnosed with a cutaneous T-cell lymphoma is now thought to have had ATL. Thus, ATL which was thought to be a distinct entity confined to only the southwest part of Japan is now known to be a world-wide disease.

The overall genetic structure of HTLV-I is similar to that of other retroviruses, that is, 5′-*gag*-*pol*-*env*-3′ in the usual order. However, HTLV-I is unique in that it has a long sequence, named *p*X region, at the 3′ end of the genome. This *p*X region codes for at least two genes, *tax* and *rex*. The *tax* gene encodes a protein responsible for enhancement of transcription of viral and cellular genes (Sodroski et al., 1985; Inoue et al., 1986).

HTLV-I infection is endemic in Japan, West Africa, the Caribbean, parts of South and North America, and Melanesia. In highly endemic areas in Japan, seropositivity for HTLV-I is 6–37% of healthy adults over 40 years of age (Takatsuki et al., 1996), while the seroprevalence of HTLV-I in blood donors in Europe is reported to be low ranging from 0.001 to 0.03% (The HTLV-I European Research Network, 1996).

More than 700 cases of ATL have been diagnosed each year in Japan alone, and the cumulative incidence of development of ATL among HTLV-I carriers in Japan is estimated at 2.5%. Takatsuki et al. (1996) studied 187 patients with ATL. There were 113 males and 74 females (1.5:1), whose age at onset ranged from 27 to 82 years, with a median age of 55 years. The main physical findings of ATL are peripheral lymph node enlargement, hepatomegaly, splenomegaly and skin lesions. The typical surface phenotype of ATL cells are CD3 + , CD4 + , CD8 − , and CD25 + . Chemotherapy to ATL is not effective, and prognosis is poor. The median survival is

8 months, with deaths usually the result of severe respiratory infection or hypercalcemia (Takatsuki et al., 1996). Therefore, prevention of HTLV-I infection is very important.

HTLV-I is transmitted from mother to child (Tajima et al., 1982; Hino et al., 1985; Kusuhara et al., 1987), or from man to woman (Nakano et al., 1984; Kajiyama et al., 1986; Iwahara et al., 1990), or by blood transfusion (Okochi et al., 1983). Among these routes, mother-to-child transmission is most important, because it is considered that ATL develops after a long incubation period since the infection around the perinatal period.

2. Seroprevalence of HTLV-I among pregnant women (Table 1)

In highly endemic areas in Japan, the seroprevalence of HTLV-I in pregnant women is 4–5% (Oki et al., 1992; Hino et al., 1996), while in non-endemic areas in Japan it is 0.1–1.0% (Goto et al., 1997). In Europe, the seropositivity for HTLV-I is reported to be up to 0.6%, and this is 100 times higher than blood donors. In the European studies, most of the HTLV-I-seropositive pregnant women were African-born, or Caribbean-born. However, in the study from the Midlands of England, the seroprevalence of HTLV-I in Caucasian pregnant women was 0.2% (3/1604), and this is the same rate as for Afro-Caribbean pregnant women (1/504) in the study (Tosswill et al., 1990). It seems likely that HTLV-I is spreading into European populations from those who have immigrated to Europe from HTLV-I-endemic areas.

Table 1
Seroprevalence of HTLV-I in pregnant women

Country	No. positive/no. tested	% Positive	Place	Year	Reference
Japan	2484/61 150	4.1	Nagasaki	1989–93	Hino et al., 1996
Japan	885/16 283	5.4	Kagoshima	1986–91	Oki et al., 1992
UK	6/2893	0.21	London	1980	Tosswill et al., 1990
UK	10/3760	0.27	London	1988	Banatvala et al., 1990
UK	5/3522	0.14	West Midlands	1990	Nightingales et al., 1993
France	5/849	0.58	Paris	1987–89	Courtois et al., 1990

3. Mother-to-child transmission of HTLV-I via breast milk and prevention methods against it

HTLV-I is transmitted from mother to child (Tajima et al., 1982; Hino et al., 1985; Kusuhara et al., 1987). HTLV-I antigen was demonstrated in milk from HTLV-I-seropositive mothers (Kinoshita et al., 1984). Moreover, oral inoculation of fresh human milk from HTLV-I carrier mothers to common marmoset leads to HTLV-I infection (Kinoshita et al., 1985). These studies strongly suggest that postnatal breast feeding is one of the main transmission routes of HTLV-I infection from mother to child. In fact, HTLV-I infection is more prevalent among breast-fed children than bottle-fed children (Ando et al., 1987; Hino et al., 1987). Hino et al. (1996) reported that the incidence of seroconversion in children who were breast-fed over 12 months was 15.7% (37/235), while that in children only formula-fed was 3.6% (41/1141) ($P < 0.001$, χ^2-test). The source of HTLV-I in breast milk has been thought to be lymphocytes in the breast milk. Recently there has been a report that basal mammary epithelial cells are also susceptible to HTLV infection and are capable of transferring HTLV infection to normal peripheral blood lymphocytes (LeVasseur et al., 1998). Regardless of which cells in breast milk are responsible for transmitting HTLV-I, refraining from breast-feeding seems to be the best and easiest way to prevent mother-to-child transmission of HTLV-I.

Other than not breast-feeding children, there are a couple of ways for preventing mother-to-child transmission of HTLV-I via breast milk. One is freeze-thawing of breast milk from HTLV-I-seropositive mothers; the infectivity of HTLV-I in breast milk was lost during freezing and thawing processes (Ando et al., 1989). The next possible way to reduce the milk-borne transmission is to limit the duration of breast-feeding (Takahashi et al., 1991; Oki et al., 1992; Takezaki et al., 1997; Wiktor et al., 1997). Takahashi et al. (1991) reported that the seroconversion rates of children who were breast-fed for short term (≤ 6 months), those breast-fed for long term (≥ 7 months) and those bottle-fed were 4.4% (4/90 cases), 14.4% (20/139), and 5.7% (9/158), respectively. Long-term breast feeding yielded more seroconverters than short-term breast feeding (relative risk = 3.68, $P = 0.018$, Mantel–Haenszel test). The difference was not significant between the children who were breast-fed for short term and those who were bottle-fed (relative risk = 0.770, $P = 0.471$, Mantel–Haenszel test). Takahashi et al. (1991) also reported that the addition of HTLV-I-seropositive cord-blood plasma inhibited HTLV-I infection of neonatal lymphocytes in the co-culture with breast milk cells from HTLV-I carrier mothers. Takezaki et al. (1997) reported in their prospective study that short-term breast-feeders (≤ 6 months) showed a statistically significant lower serocon-

version rate than long-term breast-feeders (2/51; 3.9% vs. 13/64; 20.3%, $P < 0.05$, two-tailed Fisher's exact probability test). A similar prospective study regarding the relationship between mother-to-child transmission rate and the length of breast-feeding was reported from Jamaica (Wiktor et al., 1997). Nineteen (32%) of 60 children breast-fed for 12 months or longer were HTLV-I-seropositive, compared with only eight (9%) of 86 children breast-fed for less than 12 months (relative risk = 3.4; 95% CI, 1.7–6.9, Cox proportional hazard models). HTLV-I infection of children who were breast-fed may be abortive if the period of breast-feeding is limited to only during the time when the content of maternal antibodies against HTLV-I which have been transferred to children in utero via placenta is still high. The prophylactic effect of HTLV-I immune globulin against milk-borne transmission of HTLV-I was reported in a rabbit model (Sawada et al., 1991).

There seems to be predisposing factors for mother-to-child transmission of HTLV-I. It was reported that the HTLV-I antigen-producing capacities in culture of peripheral blood and breast milk cells affected the mother-to-child transmission rate of HTLV-I (Yoshinaga et al., 1995). The mother-to-child transmission rate of HTLV-I was 37.5% (6/16) in HTLV-I-seropositive mothers group who produced a large number of HTLV-I antigen positive cells (approximately 10%) in the culture, while it was 3.2% (1/31) in mothers group which produced a small number of HTLV-I antigen positive cells (approximately 0.4%) in the culture. The transmission rate of HTLV-I between the two groups was significantly different ($P < 0.005$, Fisher's exact probability test).

4. Other routes for vertical HTLV-I transmission from mother to child

Three to 4% of children born to HTLV-I-seropositive mothers who had been bottle-fed were seropositive for HTLV-I (Takahashi et al., 1991; Hino et al., 1996). Therefore, although breast-feeding is the major route of mother-to-child transmission of HTLV-I, there must be other HTLV-I transmission routes from mother to children. Intrauterine transmission is one possibility. HTLV-I proviral DNA was detected in cord blood mononuclear cells of neonates born to HTLV-I-seropositive mothers using polymerase chain reaction (PCR). The reported positive rates of HTLV-I proviral DNA in cord blood samples in the literature were 7.5% (3/40 cases, Saito et al., 1990), 0% (0/10 cases, Saji et al., 1990), and 2.5% (18/717 cases, Kawase et al., 1992). Considering the number of cases tested listed above, it seems likely that HTLV-I proviral DNA does exist in the cord blood samples from HTLV-I-seropositive mothers, although the incidence is low.

However, it was reported that when seven children with HTLV-I proviral DNA-positive cord blood were followed up, none of them seroconverted by 24–48 months of age; therefore, cord blood proviral DNA seemed not to be a hallmark of intrauterine infection (Katamine et al., 1994). Recently a paper has been published concerning deleted HTLV-I provirus and the presence of many defective genomes in cord blood samples of babies born to HTLV-I-seropositive mothers (Kazi et al., 1998). Kazi et al. (1998) screened cord blood samples by short PCRs for the *gag* and *p*X regions of HTLV-I. For the samples which had been positive in at least one of the PCRs, a further test was performed by nested long PCRs directed for *gag*-*p*X, *gag*-*pol*, and *pol*-*p*X regions. All of the dually positive samples (positive for both *gag* and *p*X short PCRs) had proviruses harboring *gag*, *pol*, and *p*X priming sites. In contrast, none of the singly short PCR-positive samples (positive for either *p*X PCR or *gag* short PCR) showed the predicted band in the long PCRs. Additional bands which were shorter than the predicted sizes were detected. Therefore, they suggested that HTLV-I proviruses in the cord blood are frequently defective.

Saliva is the next possible transmission route. The HTLV-I *p*X sequence was detected by Miyoshi et al. (1992) in saliva from HTLV-I carriers. HTLV-I proviral DNA was also detected from mouthwash not only by PCR but also by dot blot hybridization assay (Achiron et al., 1996). In both reports, the main cells in saliva or mouthwash were epithelial cells, and there were a few lymphocytes. However, antibodies against HTLV-I are also present in saliva. Antibodies directed to HTLV-I antigens were found in the saliva from 22 of 28 of the HTLV-I-seropositive subjects, and among the 22 subjects, 21 were positive for antibodies directed to the envelope antigens of HTLV-I (Archibald et al., 1987). Yamamoto et al. (1995) reported that the saliva showed a strong tendency to inhibit the cell-to-cell transmission of HTLV-I in vitro, as examined by a syncytium inhibition assay regardless of the presence or absence of antibodies to HTLV-I, and they suggested that HTLV-I-infected cells in the carriers' saliva, which contain neutralizing antibodies in addition to the activity inhibiting cell-to-cell viral infection barely transmit the virus. So far, no study has been published which showed direct evidence of HTLV-I transmission via saliva.

5. HTLV-I infection of the placenta

Although the main target cells of HTLV-I are generally thought to be T lymphocytes, infection of human endothelial cells and other non-lymphoid cells by HTLV-I was reported (Hayami et al., 1984; Hoxie et al., 1984). It was reported that two out of nine placentas from HTLV-I-seropositive

pregnant women were infected with HTLV-I by testing the HTLV-I antigen and HTLV-I proviral genome in cultured placental villous cells (Fujino et al., 1992). On the other hand, the incidence of HTLV-I infection of cord blood lymphocytes from HTLV-I-seropositive mothers is relatively low as described in Section 4. The difference in HTLV-I infection rates between placentas and cord blood samples suggests that there is a placental barrier system against mother-to-fetus HTLV-I transmission.

6. Apoptosis in placentas from HTLV-I-seropositive mothers: a possible defence mechanism against mother-to-fetus HTLV-I transmission

The placenta has long been known as a barrier against mother-to-fetus transmission of many micro-organisms. However, the mechanism how the placenta works as a barrier to infection has not been demonstrated. Reports have been accumulating which suggest that programmed cell death, or apoptosis is involved in defence mechanism against infection (Thompson, 1995; Fratazzi et al., 1997).

It was reported that the incidence of apoptosis-positive cells (nuclei) in placentas from HTLV-I seropositive pregnant women was higher than that from HTLV-I-seronegatives ($P < 0.02$, Mann–Whitney U-test) (Fujino et al., 1999). They counted the number of apoptotic cells (nuclei) per 1000 cells (nuclei) in the placental sections by the terminal deoxynucleotidyl transferase-mediated deoxyuridine nick end labeling method. The number of apoptotic cells per 1000 cells in the placentas from HTLV-I-seropositive women ($n = 8$) was 3–23 with a median of 10, while in HTLV-I-seronegatives ($n = 8$), it was 1–7 with a median of 2.5. They also showed in their study that apoptosis was induced in the placental villous cells in the co-cultivation of placental villous cells with HTLV-I-infected lymphocyte cell line. Although apoptosis may be a coincidental phenomenon, the result may indicate an approach to elucidate the defence mechanism of the placenta against mother-to-fetus viral transmission.

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