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Original Article

Issues of infant feeding for postnatal prevention of human T-cell leukemia/lymphoma virus type-1 mother-to-child transmission

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Abstract ***Background*:** Nationwide antenatal human T-cell leukemia/lymphoma virus type-1 (HTLV-1) antibody screening has been conducted in Japan. The purpose of our study was to clarify the issues related to feeding options to prevent postnatal mother-to-child transmission.

***Methods*:** Of the pregnant carriers at 92 facilities in Japan between 2012 and 2015, 735 were followed prospectively. Among the children born to them, 313 (42.6%) children were followed up to the age of 3 and tested for HTLV-1 antibodies. The mother-to-child transmission rate was calculated for each feeding option selected before birth.

***Results*:** Among the 313 pregnant carriers, 55.0, 35.1, 6.1, and 3.8% selected short-term breast-feeding (≤3 months), exclusive formula feeding, frozen-thawed breast-milk feeding, and longer-term breast-feeding, respectively. Despite short-term breast-feeding, 8–18% of the mothers continued breast-feeding for 4–6 months. The mother-to-child transmission rate with short-term breast-feeding was 2.3% (4/172), and its risk ratio compared with that of exclusive formula feeding was not significantly different (0.365; 95% CI: 0.116–1.145). Because of the small number of children who were fed by frozen-thawed breast-milk, their mother-to-child transmission rate was not statistically reliable.

***Conclusions*:** Pregnant HTLV-1 carriers tended to select short-term breast-feeding in Japan. While short-term breast-feeding was not always easy to wean within 3 months, it may be a viable option for preventing postnatal mother-to-child transmission because the vertical transmission rate with short-term breast-feeding was not significantly higher than that with exclusive formula feeding. Increasing the follow-up rates for children born to pregnant carriers may provide clearer evidence of preventative effects by short-term breast-feeding and frozen-thawed breast-milk feeding.

Key words feeding options, HTLV-1, mother-to-child transmission, nationwide antenatal screening, prevention.

Human T-cell leukemia/lymphoma virus type-1 (HTLV-1) is widely known as the causative agent of adult T-cell leukemia (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Carriers of HTLV-1 are estimated to be at a lifetime risk of 2–7% for the development of ATL[1] and 0.25–3.8% for HAM/TSP.[2] Both of these diseases exhibit serious clinical manifestations, and their associated prognoses remain poor despite therapeutic efforts.[3,4] Mother-to-child transmission (MTCT) can theoretically occur during the intrauterine period or during labor; however, it primarily occurs via breast-feeding.[5,6] A previous study has shown that children infected via MTCT are predominant risk of developing ATL.[6]

In 2010, the Ministry of Health, Labor, and Welfare (MHLW) of Japan decided to conduct a nationwide HTLV-1 antibody screening program for all pregnant women to prevent postnatal MTCT.[7] The following were the justifications for this screening: (i) Japan is the only developed country with more than 1 million HTLV-1 carriers;[8] (ii) they are more widespread throughout Japan due to internal population migration from endemic area such as Kyusyu, Japan to non-endemic area;[8] (iii) more than 4,000 adolescents and adults (77% women) are newly diagnosed annually with HTLV-1 (mainly caused by sexual contact),[9] and (iv) neither an effective vaccine nor antiviral regimens have been developed against this virus.[3]

The ATL Prevention Program (APP) in the Nagasaki Prefecture revealed a marked reduction in MTCT of HTLV-1,

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from 20.3% to 2.5%, by relying on exclusive formula feeding (ExFF).[10] This program also showed that the rate of MTCT with breast-feeding for less than 6 months was higher than that with ExFF, but significantly lower than that with longer term breast-feeding.[10] Hirata *et al*. showed that the prevalence of HTLV-1 antibody among children breast-fed for over 3 months was significantly higher than that of those breast-fed for under 3 months.[11] Thus, in Japan, short-term breast-feeding (STBF) is generally defined as breast-feeding up to 3 months of age.[12]

While some healthcare providers in Japan have recommended STBF[11,13] or frozen-thawed breast-milk feeding (FTBMF)[14,15] as alternatives to ExFF, there is insufficient evidence regarding the effects of STBF and FTBMF on the incidence of MTCT.[12] Despite the increased risk of MTCT from longer term breast-feeding,[11,13] the proportion of mothers who select STBF and refrain from breast-feeding by 3 months remains unknown. Serological testing for the children born to pregnant carriers is not mandatory under the screening program, so we do not know what proportion of the children will undergo serological antibody testing. Our study purpose is to clarify these issues related to feeding options for postnatal prevention of HTLV-1 MTCT.

Methods

Algorithm used for the antenatal HTLV-1 antibody screening test

Human T-cell leukemia/lymphoma virus type-1 antibody screening is usually performed within the first 30 weeks of gestation to ensure that a carrier pregnant woman has enough time to obtain detailed information from healthcare providers and to enable the selection of a suitable feeding option before labor. A confirmatory test by western blotting (WB) was performed for pregnant women with positive screening results. In indeterminate cases, the polymerase chain reaction (PCR) is used as a definite test to diagnose the infection. Its sensitivity of measurement is less than 4 copies/10^5 peripheral bold mononuclear cells.[16] Pregnant women who have either a positive confirmatory test or PCR-positive results are defined as being HTLV-1 carriers.

Study population

From April 2012 until December 2015, we prospectively recruited a cohort of carrier pregnant women at 92 facilities, both inside and outside endemic areas in Japan. The testing statuses of the subjects are shown in Figure 1. Western blot testing was performed for pregnant women with positive screening tests. Of these women, 757 were WB positive and 223 were WB indeterminate. Forty-five of the 757 WB-positive and 108 of the 223 women with a WB-indeterminate result did not participate in the study. Of the 115 women with indeterminate tests, 23 were PCR-positive and 92 were negative; this left 735 carrier mothers who were either WB-positive or PCR-positive were enrolled in the study. After delivery, 313 (42.6%) of the children born to the 735 identified carriers were followed up to the age of 3 and tested for HTLV-1 antibodies. Of the 313 children, there were 29 and 30 preterm and low-birthweight infants, respectively.

Feeding options

Pre-trained healthcare providers at each facility provided subjects with a thorough explanation of ExFF, STBF (≤3 months), and FTBMF. The 27 pregnant carriers selected long-term breast-feeding (>3 months).

Assessment of MTCT

Infants born to carriers were checked at a pediatric clinic at 1, 3, 6, 12, 18, 24, and 36 months after birth. A serum antibody test was performed at the final 36-month visit, because no seroconversion has been reported beyond that age.[17,18] The MTCT rates for the feeding options were calculated based on antenatal feeding selection.

Data collection

The following information was requested by researchers at each facility for database entry: the mother's age, number of births, WB and/or PCR results, antenatal selection of feeding option, gestational age, birthweight, sex, actual feeding methods at 1, 3, and 6 months of life, and the results of the child's serum antibody test at 36 months. This study was carried out in accordance with the recommendations of the Ethical Committee of Showa University (No. 1109, October 7, 2011). The protocol was also approved by the ethics committee at each facility. Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Statistical analysis

Continuous variables were expressed as means ± standard deviations. Categorical variables were expressed as number and percentages. We used the unpaired *t*-test for continuous data and χ^2 tests for categorical data, except when the expected cells were less than 5; in such cases we used Fisher's exact test. All tests were two-tailed and it was determined that there was a significant difference if $P < 0.05$. Risk ratios (RRs) of MTCT on STBM or FTBMF to ExFF are expressed as medians with 95% confidence intervals (CI). SPSS Statistics version 26 (IBM Japan, Tokyo, Japan) was used for the statistical analysis.

Results

Feeding options selected by carrier pregnant women

The distribution of feeding options selected by pregnant women is shown in Table 1. As approximately 41% of the data originated from subjects residing in Kagoshima prefecture

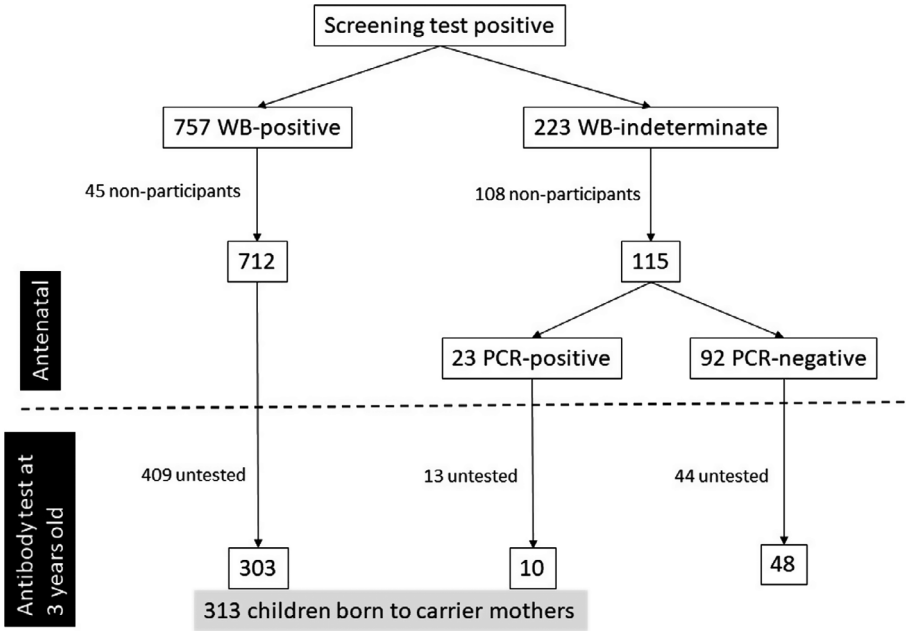

Fig. 1 Subject inclusion based on HTLV-1 testing. WB, western blotting

located in the Japanese endemic area of Kyushu, it is also shown separately for this and other regions. Among the 313 carrier pregnant women whose children was followed up to 3 years of age, the distribution of STBF and ExFF was 55.0% and 35.1%, respectively. It was significantly different between Kagoshima prefecture and other regions (P = 0.001). The selection rate of STBF in Kagoshima prefecture was 77.0%, which was about twice that in other regions.

MTCT rates with respect to the feeding option

The total number of infected children was identified as 14 (4.5%). The clinical characteristics of the children with and without MTCT are shown in Table 2. There were no significant differences between the two groups except for gestational age. The MTCT rates on feeding options selected before labor, not on the actual feeding options, are shown in Table 3. The incidences of MTCT on ExFF and STBF were 6.4% (7/110) and 2.3% (4/172), respectively. Infants with confirmed MTCT in the ExFF group were never breast-fed. The risk ratio (RR) of MTCT for the children born to the women who selected STBF relative to those who selected ExFF was not significant (RR 0.365; 95% CI: 0.116–1.145). The number of subjects who opted for long-term breast-feeding and FTBMF was very small, so those MTCT rates were not reliable.

Breast-feeding changes in the STBF group

Percentages of the infants fed breast milk up to 6 months of age are shown in Figure 2. Approximately 8% of the mothers continued breast-feeding at 6 months of life. We did not have data on what percentage of the mothers in the STBF group

Table 1 The distribution of selected feeding options

	Kagoshima prefecture**			Other regions			F/U n = 313	Lost to F/U n = 422	Total n = 735
	F/U n = 135	Lost to F/U n = 166	Total n = 301	F/U n = 178	Lost to F/U n = 256	Total n = 434			
Long-term breast-feeding (>3 months), n (%)	2 (1.5)	4 (2.4)	6 (2.0)	10 (5.6)	11 (4.3)	21 (4.8)	12 (3.8)	15 (3.6)	27 (3.7)
Short-term breast-feeding, n (%)	104 (77.0)	120 (72.3)	224 (74.4)	68 (38.2)	96 (37.5)	164 (37.8)	172 (55.0)	216 (51.2)	388 (52.8)
Frozen-thawed breast-milk feeding, n (%)	1 (0.7)	0 (0)	1 (0.3)	18 (10.1)	18 (7.0)	36 (8.3)	19 (6.1)	18 (4.3)	37 (5.0)
Exclusive formula feeding, n (%)	28 (20.7)	42 (25.3)	70 (23.3)	82 (46.1)	131(51.2)	213 (49.1)	110 (35.1)	173 (41.0)	283 (38.5)

The distribution of selected feeding options was not significantly different between follow up (F/U) and lost to F/U groups not only in Kagoshima prefecture but also in other regions.

**The distribution of feeding-option selection was significantly different between Kagoshima prefecture and other regions (P = 0.001).

Table 2 Comparison between the clinical characteristics of infected and non-infected children

	Infected children (n = 14)	Non-infected children (n = 299)	P
Mother's age (years old)	33.2 ± 4.9	32.8 ± 4.8	0.751
Primipara (n, %)	9 (64.3%)	150 (50.2%)	0.593
Gestational age (weeks)	38.1 ± 2.3	39.2 ± 1.6	0.021
Birthweight (g)	2,818 ± 403	2,976 ± 417	0.170
Sex (boy) (n, %)	8 (57.1%)	151 (50.5%)	0.627

continued breast-feeding at 4 and 5 months of age. Thus, in order to estimate the rate of breast-feeding at 4 and 5 months, the relationship between postnatal months of life and the proportion of the breast-fed infants was evaluated with second-order polynomial analysis. According to this equation, the rate of breast-feeding at 4 months and 5 months was estimated to be 18.2% and 9.6%, respectively.

Fig. 2 Longitudinal changes of percentages of infants fed breast-milk in the short-term breast-feeding (STBF) group. The relationship between postnatal months (x) and the rate of breast-feeding (y) in the STBF group was shown by the second-order polynomial analysis. The equation obtained is as follows: $y = 3.3639x^2 - 38.858x + 119.83$, ($R^2 = 1.0$).

Discussion

Exclusive formula feeding (ExFF) has been given priority as a means of preventing postnatal HTLV-1 MTCT.[19,20] Nevertheless, approximately half of all pregnant carriers selected STBF, although there were regional variations of 38–74%. One of the reasons may be that not only healthcare providers but also carrier mothers want to obtain the benefits of breast milk.[21,22] Second, there is concern about the psychological consequences for mothers of having to avoid or restrict breast-feeding despite the general promotion of breast-feeding.[23] However, our study indicates that it is not always easy to refrain breast-feeding within 3 months after delivery and healthcare providers should explain this fact to pregnat carriers who select STBF.

Previous studies of HTLV-1 MTCT have been retrospective observational studies, mostly conducted in endemic areas.[10,13-15,18,24-27] In most cases, infants' dietary reports could be inaccurate because the data were obtained retrospectively. There is an additional defect in that the timing of antibody testing for the children varies within and between studies. On the other hand, ours is the first nationwide and prospective study in Japan after the introduction of a nationwide antenatal screening program. Our study suggests that STBF may be a viable option for preventing postnatal MTCT. However, if carrier mothers select STBF without obtaining appropriate support, there is a concern that an increase in the proportion of longer term breast-feeding infants would lead to an increased incidence of MTCT. To minimize MTCT risk, a support system to help mothers to refrain from an extended period of breast-feeding is necessary. The MTCT rate for ExFF (6.4%) in this study appears to be higher than was stated by the APP in the Nagasaki Prefecture (2.5%).[10] The reason for this is not clear, but it may be related to the fact that the number of children born to carrier mothers who selected ExFF was 1/10 in our study compared to that of the ATL prevention program.

Although the detailed mechanisms by which STBF prevents postnatal MTCT remain unknown, antibodies transferred from mother to child *in utero* may have an important role.[24] Frozen-thawed breast-milk feeding (FTBMF) may be associated with the destruction of infected cells by freezing and thawing.[14] It is theoretically an attractive alternative, its effect on the incidence of MTCT could not be evaluated because of the small number of cases in this study. The reason that fewer carrier mothers selected FTBMF may be due to an assumption that daily feeding would be too time-consuming.

The enrolled carriers were told about the serological antibody tests for their children at 3 years of age at each facility but the rate of antibody testing was only about 42%. There are several reasons for this. Most likely, this may be because serological antibody testing is not mandatory in the screening program in Japan. Unlike Latin American reports,[28] the infected children in Japan seem to have few symptoms during

Table 3 Mother-to-child transmission rates with respect to feeding options

	Long-term breast-feeding (n = 12)	Short-term breast-feeding (n = 172)	Frozen-thawed breast-milk feeding (n = 19)	Exclusive formula feeding (n = 110)
Infected children (n, %) (95% CI)	2 (16.7%) (−4.4%–37.8%)	4 (2.3%) (0.0%–4.6%)	1 (5.3%) (−4.8%–15.3%)	7 (6.4%) (1.9%–10.9%)

childhood. Thus, there may be little motivation for mothers to have their children tested for antibodies. From a public health perspective, we argue that antibody testing should be recommended for all children born to the infected pregnant women. This would provide more reliable data on the relationship between the selected feeding options and MTCT rates, allowing us to verify the effects of introducing this screening program in Japan. Moreover, a recent systemic review shows that people with HTLV-1 are at a higher risk of death due to other than two diseases (ATL and HAM/TSP) than their HTLV-1-negative counterparts.[29] This report leads to the recognition of various risks of HTLV-1 infection which have not been given close attention due to the low incidence of ATL and HAM/TSP. Although this article does not mention the timing of infection (MTCT or horizontal transmission), such results may contibute to promote antibody testing of children born to pregnant women in carriers.

Our study suggested that a low follow-up rate for children born to pregnant carriers was a major flaw in the screening program. The limitation in our study is associated with this. More than half of the children born to carriers were not available for follow up, resulting in an antibody testing rate of about 42%. Less confidence can therefore be given to the MTCT rates on feeding options obtained by this cohort study. In particular, it was difficult to evaluate the effects of FTBMF on the prevention of MTCT.

The results of this cohort study showed no statistically significant differences in MTCT rates between STBF and ExFF. It also became clear that STBF does not make it easy to wean within 3 months, so it is necessary to understand this if a pregnant woman desires STBF. Whether a mother selects ExFF or STBF, adequate information and support from healthcare providers is essential. However, there is little evidence to recommend FTBMF at present.

In conclusion, our study revealed that the MTCT rate for STBF was not significantly higher than that for ExFF. There is a concern that it is not always easy to wean within 3 months. In addition, the low rate of postnatal antibody testing is a major issue. To clarify not only reliable feeding options to prevent MTCT but also to evaluate the effects of the screening, antibody testing should be recommended for all children born to infected pregnant women.

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Disclosure

The authors declare no conflict of interest.

Author contributions

All of the authors contributed to the conception, design, and execution of the study. K.I. wrote the first draft of the

manuscript and all of the authors contributed to the manuscript revisions. All authors read and approved the submitted version.

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