transformation of infected CD4+ T cells. These differences partly explain the distinct spectrum of diseases caused by these 2 retroviruses.

DISEASE ASSOCIATION WITH HTLV-1 INFECTION

Although most infected individuals remain asymptomatic, HTLV-1 may result in 2 major diseases, adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy (HAM)/tropical spastic paraparesis (TSP). ATLL results from clonal proliferation of CD4+ T cells, which contain HTLV-1 provirus randomly integrated in to their genome. Four clinical variants of ATLL are described: acute, lymphoma-type, chronic and smoldering, with different clinical manifestations and prognosis. The clinical course of acute and lymphoma-type ATLL is quite aggressive, and overall median survival is 7.7 months despite aggressive treatment. In Japan, >1000 cases of ATLL are diagnosed annually, and the lifetime risk of ATLL in HTLV-1 infected individuals is approximately 5%. ATLL is extremely unusual before 30 years of age. ATLL develops after a long incubation period (a median age of onset is 67 years), and is unlikely to develop if HTLV-1 infection acquired in adult life. Risk factors for the development of ATLL include high viral load and family history of ATLL.

In contrast, HAM/TSP is a slowly progressive disorder characterized by unilateral or bilateral lower limb weakness and spasticity, lumbar pain and detrusor instability. The lifetime risk of HAM/TSP is estimated to be 0.25% in Japan and 1.9% in Jamaica and Trinidad. In a US prospective study, 3.7% of HTLV-1 carriers were diagnosed with HAM/TSP. HTLV-1-infected individuals with higher proviral load and/or particular genetic background may be at greater risk of developing HAM/TSP. HAM/TSP may develop after an incubation period of several years to decades.

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the first to demonstrate transmission in breast milk (summarized in Hino et al8), a finding subsequently confirmed by other studies. The data supporting the importance of breast-milk transmission included 1) the demonstration of HTLV-1 antigen in breast milk derived from infected mothers; 2) oral administration of fresh human milk derived from HTLV-1-infected mothers to uninfected marmosets led to HTLV-1 infection; 3) a significantly increased HTLV-1 infection rate in breastfed children compared with bottle-fed children and 4) long-term prospective studies showing that MTCT rates were 20.5% in infants breastfed for 6 months or more, 8.3% in those breastfed for <6 months and 2.4% in infants exclusively formula-fed (Fig. 1).10 These data indicate that breastfeeding is the most prevalent, but not the sole route of MTCT of HTLV-1, and that a longer duration of breastfeeding increases the risk of MTCT.

Transmission of HTLV-1 infection to exclusively formula-fed infants indicates that other largely unknown routes of MTCT. Transplacental infection or placental microtransfusion are less likely, as proviral HTLV-1 DNA in cord blood of infected mothers is not transplacentally transferred or transferred only at low and high proviral loads in breast milk, respectively.11 Transplacental infection or placental microtransfusion is a maternal health problem that is only achievable by restricting transmission. In Japan, seroconversion after 2 years of age is infrequent, and most infected infants became seropositive by 12 months.9,17 A prospective study in Jamaica showed that 32% of children breastfed for >12 months were infected, compared with 9% of those breastfed for <12 months (relative risk 3.4; 95% confidence interval: 1.7–6.9).18 An estimated median time of HTLV-1 infection in those children was 11.9 months.18 A number of small Japanese studies in Japan suggest that short-term breastfeeding (<3 months) was as effective as exclusive bottle-feeding in reducing MTCT of HTLV-1.

FIGURE 1. MTCT rates by feeding methods in Nagasaki Prefecture, Japan, between 1987 and 2000 are shown (modified from reference10). There are statistically significant differences between the 3 groups.

FIGURE 2. A flow chart showing a national program for prevention of MTCT of HTLV-1. The details are described in the text (modified from Moriuchi20). PA indicates particle agglutination; CLEIA, chemiluminescent enzyme immunoassay; PCR, polymerase chain reaction; WB, Western blotting.

PREVENTION OF MTCT OF HTLV-1

It is not possible to prevent the development of ATLL or other HTLV-1-associated disorders in HTLV-1 carriers, and primary prevention is the only strategy likely to reduce disease. No HTLV-1 vaccine has reached clinical trials, and therefore, prevention is only achievable by restricting transmission. As the majority of HTLV-1 infection follows MTCT and ATLL develops only after MTCT, prevention of milk-borne transmission is the most efficient and feasible way to reduce the disease burden.

Exclusive formula-feeding is the most reliable and easiest method to prevent milk-borne infection, although the manifold advantages of breastfeeding would also be lost. An expected outcome of withholding breastfeeding is reduction of MTCT rate from 15%–20% to 2%–3%. Since lifetime risk of ATLL is approximately 5%, exclusive formula-feeding will reduce incidence of ATLL patients among individuals born from HTLV-1 carrier mothers from 0.75%–1% to 0.1%–0.15%. In contrast, breastfeeding can reduce perinatal mortality rates for >20% in some developing countries.15 Therefore, this preventive strategy may only be justified in developed country like Japan and even so is likely to be controversial.

There are 2 alternative methods to reduce breast-milk HTLV-1 transmission—freeze-thawing and reducing the duration of breastfeeding. Freeze-thawing effectively destroys HTLV-1-infected cells in breast milk in vitro and small-scale field studies demonstrated significant reduction of MTCT,16 although it is laborious and may be impractical for many mothers. Expressed breast milk should be frozen at –20°C or below for >12 hours. MTCT can be reduced by limiting the duration of breastfeeding.10 In Japan, seroconversion after 2 years of age is infrequent, and most infected infants became seropositive by 12 months.9,17 A prospective study in Jamaica showed that 32% of children breastfed for >12 months were infected, compared with 9% of those breastfed for <12 months (relative risk 3.4; 95% confidence interval: 1.7–6.9).18 An estimated median time of HTLV-1 infection in those children was 11.9 months.18 A number of small Japanese studies in Japan suggest that short-term breastfeeding (<3 months) was as effective as exclusive bottle-feeding in reducing MTCT of HTLV-1.
CURRENT STRATEGY IN JAPAN TO PREVENT MTCT OF HTLV-1

Since 2011, it is recommended that all pregnant women in Japan are screened for HTLV-1 antibody by particle agglutination or chemiluminescent enzyme immunoassay, with Western blotting and/or polymerase chain reaction for confirmation (Fig. 2). Particle agglutination and chemiluminescent enzyme immunoassay have high sensitivity and specificity, but still give a substantial number of false-positive results, especially in nonendemic areas. Western blotting is also sometimes inconclusive. Polymerase chain reaction is both sensitive and specific. Pregnant women with HTLV-1 infection receive detailed information about HTLV-1, MTCT and infant feeding strategies. Unless they give birth to high-risk infants (e.g., premature babies), they are advised to undertake exclusive formula feeding, freeze-thawing of expressed breast milk or breastfeeding for a maximum of 3 months. Ongoing support is critical, especially for those who have chosen the latter 2 options. We recommend anti-HTLV-1 antibody testing of the offspring at 3 years of age.

PERSPECTIVES IN OTHER ENDEMIC COUNTRIES

HTLV-1 causes ATL or HAM/TSP in only a minority of carriers after a long incubation period. Withholding breastfeeding significantly reduces MTCT of HTLV-1, but will increase infantile mortality rate in developing countries, and therefore, the overall benefit is unclear. Long-term results from the current nationwide MTCT prevention program in Japan will be important in informing preventative strategies in other settings.

REFERENCES


