Adult T-cell Leukemia/Lymphoma (ATL) in Japan

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A specific type of lymphoid malignancy, adult T-cell leukemia/ lymphoma (ATL), which is caused by human T-cell leukemia virus type I (HTLV-I), is highly prevalent and there are also many healthy carriers of HTLV-I in the same areas. Three main routes of HTLV-I transmission are recognized: 1) vertical transmission from mother to child mainly through breast milk, 2) horizontal transmission from man to woman through semen, and, 3) parenteral transmission from carrier donor to non-carrier recipient. The annual incidence rate of ATL among HTLV-I carriers is estimated at 2.0 in males and 0.5 in females, and the cumulative risk for ATL in HTLV-I carriers during a 70-year life span is 2–5%. Possible risk factors for ATL in addition to HTLV-I infection were considered, i.e. genetic factors, environmental factors, nutritional condition, thymus involution and so on. ATL in Japan is an important subject for study in the field of cancer epidemiology, and several trial intervention programs for the prevention of ATL, such as controls of vertical transmission from mother to child through breast milk, are now in progress in ATL-endemic areas in Japan.

Adult T-cell leukemia/lymphoma, Human T-cell leukemia virus type I, Prevention trial

INTRODUCTION

The age-adjusted death rate for malignant lymphomas was much higher in the Kyushu district than in other districts in Japan⁽¹⁾.

The proportion of T-cell malignancies among all non-Hodgkin lymphomas was over 70% in Kyushu, which was very different from Europe and the United States, where the proportion of non-T-cell lymphomas (B-cell lymphoma) was very high. Among the T-cell malignancies in Japan, adult T-cell leukemia/lymphoma (ATL)⁽²⁾ caused by human T-cell leukemia virus type I (HTLV-I)^(3,4) is found mainly in Kyushu and Southern Shikoku. A nationwide survey suggested that the excessive rate of malignant lymphomas in the Kyushu district was due to the high incidence of ATL^(5,6). The geographical distribution of HTLV-I carriers in Japan is concordant with that of ATL patients^(7,8).

In the world, except for Japanese in southeast Asian countries, carriers of HTLV-I are found among Japanese in Hawaii, Melanesians in Papua New Guinea, blacks in central Africa and the Caribbean Basin and indigenous people in South America (Fig. 1)⁽⁹⁾. It is not very easy to explain how HTLV-I could have spread among some limited and isolated groups throughout Japan and in the world. To examine this matter, the author reviewed main epidemiological studies on ATL in Japan.

Clinico-epidemiological features of ATL

ATL patients have been observed throughout Japan, mainly in the coastal areas along the Pacific Ocean and the Japan Sea (Fig 1)^(2,10). The annual incidence of ATL is estimated at 700 or more from 1.2 million carriers of HTLV-I (Table 1)⁽¹¹⁾. More than half of them are distributed in the Kyushu district of Japan and, furthermore, most ATL patients in metropolitan areas such as Tokyo, Nagoya and Osaka were born and raised in Kyushu or Southern Shikoku.

Figure 1 Geographical distribution of ATL patients in Japan (1986-87). Each point indicates one patient. (Ref. 11)

Table 1 Distribution by District of Population in 1985, Estimated Number of HTLV-I Carriers, Annual Incidence of ATL, Number of Patients with ATL by Residential Place and Birth Place Registered by the Fourth Nationwide Surveillance in 1986-1987

District	Population (1,000,000)	Carrier rate* of HTLV-I	Estimated number		Registered number	
			Carrier	ATL#	Residence	Birth@
Hokkaido/Tohoku	15.43(12.8)	0.01	108,000	65 (9.3)	58 (8.8)	62 (9.5)
Kanto	36.65(30.4)	0.005	128,300	77(11.0)	70(10.7)	19 (2.9)
Osaka/Hyogo*	13.52(11.2)	0.015	141,900	85(12.2)	77(11.7)	10 (1.5)
Kyushu	14.46(12.0)	0.06	607,300	364(52.2)	338(51.4)	454(69.8)
Other district	40.66(33.7)	0.005	175,000	106(15.2)	114(17.4)	105(16.2)
Total	120.72(100%)	-	1,160,500	697(100%)	657(100%)	650(100%)

* Estimated from positive rate of anti-HTLV-I in blood donors

Annual incidence of ATL in each district was calculated from the incidence rate of 0.6 per 1,000 adult HTLV-I carriers.

@ Seven cases were excluded because of the lack of information on birth place.

Characteristic clinico-epidemiological features of ATL in Japan are shown in Table 2 and Fig. 2: onset occurred in adulthood over 25 years of age, especially over 40 (average age of 58 years); the age-specific incidence rate increased steeply with age until age 70, and then decreased markedly in both sexes; male predominance (1.3 male to female ratio); familial clustering; leukemia with or without generalized lymphadenopathy (80%); frequent skin involvement (30-40%) and hypercalcemia (30-40%); leukemia cells with peculiar pleomorphic and convoluted nuclei; leukemic cells with peripheral T-cell character (CD4⁺); and diminished cellular immune function and rapid clinical course (6-month 50% survival).

Table 2 Comparison Between Two HTLV-I Associated Diseases (ATL and HAM) in Japan

Items compared	Adult T-cell leukemia (ATL)	HTLV-I associated myelopathy (HAM)
Disease character	Neoplastic disease	Reactive disease
Age distribution (Age modes)	Adults older than 20 (55-65 years)	Children and adults (35-45 years)
Sex distribution (Sex ratio)	Male > Female (M/F=1.3)	Male < Female (M/F=0.5)
Main symptoms	Leukemia/lymphoma Skin lesion Hypercalcemia	Spastic gait Dysuria Sensory disturbance
Transmission route (manifestation)	Vertical (yes) Horizontal (no or rare)	Vertical (yes) Horizontal (yes)
Latent period (transmission)	Longer than 20 years (Vertical transmission)	Longer than 6 years (Natural transmission) Longer than 6 months (Blood transfusion)
Incidence rate (Cumulative risk)	0.5-1.5/year/1,000 (2-5%)	Less than 1.0/year/1,000 (Less than 1%)
Immune reactivity (Antibody titers)	Diminished (Relatively low)	Elevated (Relatively high)
Therapy	No effective drugs (on-going study)	Steroid hormone and its derivatives

Figure 2 Geographical distribution of anti-HTLV-I antibody positives in Japan. The shaded part of each circle represents the percentage of antibody-positives. (Ref. 7)

Epidemiological features of HTLV-I

Epidemiological evidence for a causal relationship between HTLV-I infection and ATL manifestation is as follows: most not necessarily all patients with ATL had an antibody to HTLV-I a high proportion of healthy people in the ATL-endemic areas had an antibody to HTLV-I (Fig. 3), proviral DNA of HTLV-I was detected in the tumor cells of ATL, HTLV-I carriers were seen to develop ATL in a retrospective observation study.

A cross-sectional sero-epidemiological survey on HTLV-I among healthy people in the ATL-endemic areas showed a characteristic age- and sex-specific distribution of HTLV-I carriers (Fig. 4)⁽¹²⁻¹⁴⁾. Several possible explanation for the characteristic age and sex distribution of HTLV-I carriers have been considered, 1) the rate of carriers in the ATL endemic areas might depend on birth cohorts, with earlier generations having a higher infection rate, 2) people at risk are continuously exposed to HTLV-I and infections increase with age, especially in females, and 3) anti-HTLV-I antibody is expressed later in life after infection early in life.

Figure 3 Age- and sex-specific positive rate for anti-HTLV-I in T Island. (Ref. 14)

Figure 4 Age- and sex-specific estimated incidence rate (per 1,000,000 population) of ATL in 1986-87. ■, ●; males and females in the Kyushu district; □, ○; males and females in other districts. The general census population figures for age and sex in 1985 were used as the denominators. (Ref. 11)

Transmission of HTLV-I

HTLV-I is not easily contagious under natural conditions; generally cell-cell contact is required for HTLV-I transmission. Familial clustering of HTLV-I carriers in the ATL-endemic areas suggests two natural transmission routes (Fig. 5)⁽¹²⁾. One is vertical transmission from mother to child (Table 3). Recent studies have shown that breast feeding poses a risk for HTLV-I transmission from mother to child, particularly from mothers with HTLV-I-antigen positive lymphocytes in their breast milk⁽¹⁵⁻¹⁷⁾. The overall infection rate from carrier mothers to their children in recent years was estimated at 10–30% (Table 4). The second

Figure 5 Main routes of natural transmission of HTLV-I. (Ref. 9)

Table 3 Age-specific Positive Rate of Anti-HTLV-I Antibody in Children According to Mother-positivity of Anti-HTLV-I Antibody in the Goto Islands (1984)

Age (years)	Mother (positive) Positive/Tested (%)	Mother (negative) Positive/Tested (%)	Total Positive/Tested (%)
6-19	2/19 (10.5)	1/ 76 (1.3)	3/ 95 (3.2)
20-59	23/49 (46.9)	2/ 57 (3.5)	25/106 (23.6)
Total	25/68 (36.8)	3/133 (2.3)	28/204 (13.7)

Table 4 Risk for HTLV-I Transmission from Carrier Mother to Children

Reporter (year)	Children Positives/Total	Transmission rate (%)	Age (years) of children
Hino (1985)	5 / 30	17	1-9
Tajima (1986)	2 / 19	11	6-19
Kinoshita (1987)	8 / 32	25	3
Kussuhara (1987)	10 / 65	15	3-18*
Total	25 /146	15	1-19

* Followed up for 15 years from 3- to 18-year old

important route of natural transmission is horizontal transmission between men and women through sexual contact^(12,18). A study of married couples strongly suggested that HTLV-I is transmitted mainly from husband to wife (Table 5 and 6). Parenteral infection mainly by blood transfusion is also an important transmission route for HTLV-I⁽¹⁹⁾. It was revealed that the average infection rate of HTLV-I by blood transfusion was around 60% if non-carrier recipients received blood with cell component donated by HTLV-I-carrier donors. Furthermore, fresh blood (within five days) posed a greater risk of HTLV-I infection than blood stored one or two weeks before transfusion.

Table 5 Age-specific Distribution of Positive Anti-HTLV-I Antibody Among Wives over 40 in Married-couples According to Husband-positivity of Anti-HTLV-I Antibody in Tsushima Island (1985)

Age(years) of wives	Husband(positive) Positive/Tested(%)	Husband(negative) Positive/Tested(%)	Total Positive/Tested(%)
40-49	18/29 (62.1)	22/117 (18.8)	40/146 (27.4)
50-59	22/37 (59.5)	32/204 (15.7)	54/241 (22.4)
60-	23/33 (69.7)	20/152 (13.2)	43/185 (22.2)
Total	63/99 (63.6)	74/473 (15.6)	137/572 (24.0)

Table 6 Age-specific Distribution of Positive Anti-HTLV-I Antibody Among Husbands over 40 in Married-couples According to Wife-positivity of Anti-HTLV-I Antibody in Tsushima Island (1985)

Age(years) of husbands	Wife(positive) Positive/Tested(%)	Wife(negative) Positive/Tested(%)	Total Positive/Tested(%)
40-49	15/ 29 (51.7)	9/ 87 (10.3)	24/117 (20.5)
50-59	29/ 64 (45.3)	16/191 (8.4)	45/255 (17.6)
60-	26/ 53 (49.0)	12/181 (6.7)	38/233 (16.3)
Total	70/146 (47.9)	37/458 (8.1)	107/604 (17.7)

Comparative study of ATL and HAM

HTLV-I associated myelopathy (HAM)⁽²⁰⁾ in Kyushu or tropical spastic paraparesis (TSP)⁽²¹⁾ caused by HTLV-I in the Caribbean Basin are distributed in the same endemic areas of ATL in the world. A detailed pathogenesis of HAM has not yet been elucidated but its clinical features are quite different from those of ATL. Several clinico-epidemiological features of HAM and ATL are compared in Table 2. ATL is a neoplastic disease of T lymphocytes (CD4 positive cells), but HAM is a non-neoplastic disease of the nervous system. Although ATL is more prevalent in males, HAM is more often found in females. The onset age for HAM is younger than that for ATL, and child patients with HAM have been observed. It was revealed that horizontal transmission of HTLV-I from men to women and parenteral transmission could lead to HAM manifestation, which is quite different from the conditions of ATL manifestation. General immune response in patients with HAM was elevated. The existence of some haplotype-linked high immune responders to HTLV-I in HAM patients was suggested⁽²²⁾. There may be some difference in the host-specific immune responses between ATL and HAM.

Risk factor for ATL in HTLV-I carriers

Epidemiological observation and virological findings show that HTLV-I infection must be a main causative agent for ATL manifestation. However, many healthy HTLV-I carriers live in ATL-endemic areas in Japan, and so HTLV-I infection alone does not necessarily cause the onset of ATL. Recently, the incidence rate of ATL among 1,000 HTLV-I carriers is estimated at 2.0 in males and 0.5 in females, and the cumulative risk for ATL in HTLV-I carriers during a 70-year life span is 2–5% (Table 2)⁽²³⁻²⁴⁾. As ATL patients were clustered in limited areas and among family members, some possible host factors for ATL may exist. To study this hypothesis, HLA type as a genetic marker was compared between HTLV-I carriers and non-carriers and between ATL patients and healthy controls. It was pointed out that the frequency of several phenotypes is lower or higher in patients with ATL compared with general controls (Table 7)⁽¹⁰⁾.

Table 7 Percentage Frequencies of Selected HLA Antigens Among Patients with ATL, Their Relatives with Positive and Negative Anti-HTLV-I Antibody and Controls Collected from All Japan or Kyushu

Antigen	Japan control	Kyushu control	Patients with ATL	Relatives	
				Anti-HTLV-I(+)	Anti-HTLV-I(-)
Higher*					
A1	0.9	1.1	4.7	0 (0/17)	0 (0/31)
A26	21.2	17.1	34.9	35.3 (6/17)	41.9 (13/31)
B39	7.9	4.9	10.9	11.8 (2/17)	9.7 (3/31)
Lower*					
A24	62.9	69.2	54.7	47.1 (8/17)	45.2 (14/31)
Aw33	16.2	13.3	6.3	17.6 (3/17)	6.5 (2/31)
Bw46	8.8	7.2	1.6	5.9 (1/17)	0 (0/31)
Bw52	22.4	27.8	14.1	11.8 (2/17)	29.0 (9/31)
Bw61	16.8	22.4	12.5	41.2 (7/17)	22.6 (7/31)
DRw6	19.1	9.7	4.7	0 (0/17)	0 (0/31)
DR7	0.6	9.7	0	0 (0/15)	0 (0/30)
DRW53	61.2	-	39.5	20.0 (3/15)	53.3 (16/30)
DQw1	67.4	-	51.2	53.3 (8/15)	66.7 (20/30)

* Higher or lower frequent antigens ($\chi^2 > 3.85$ in patients with ATL compared to those in controls of Japan or Kyushu)

Sanitary and nutritional conditions in Japan have been much improved after World War II, and consequently disease patterns in Japan have changed remarkably; the death rate from communicable diseases, i.e., tuberculosis and other pulmonary pneumonitis, has decreased. According to the national nutritional status of the Japanese by district, per capita consumption of protein and vitamin A in 1966–68 was markedly lower in the ATL endemic districts, Kyushu and Southern Shikoku, compared with other districts. Such relatively poor nutritional conditions in the ATL-endemic areas in the past may have affected the patterns of the spread of HTLV-I and ATL⁽²⁵⁾. It was well known that filariasis, which affects lymphatic vessels and results in several lymphoreticular ailments, had been epidemic in the ATL-endemic areas in southern Japan until 1970. In the Goto Islands, which are typical ATL-endemic islands, the positive rate of anti-HTLV-I antibody among persons with a high antibody titer to filarial antigen was higher than that among persons with a low antibody titer in both sexes⁽²⁶⁾.

These epidemiological findings suggest the hypothesis that repeated filarial infection may have direct and/or indirect effects on promoting HTLV-I infection, HTLV-I proliferation, or both in the hosts in these areas. It was reported that patients with ATL and HTLV-I carriers in Okinawa Prefecture were highly infected with *strongyloides stercoralis*, which is still endemic in Okinawa Prefecture in older people⁽²⁷⁾. From this, it was suggested that ATL patients are more susceptible to opportunistic infectious diseases such as strongyloidiasis than are healthy people, or that *strongyloides stercoralis* itself can modify the progression of ATL in HTLV-I carriers. Although this evidence does not prove a direct causal relation between *strongyloides stercoralis* and ATL manifestation, it cannot be denied that some infectious diseases such as filariasis, strongyloidiasis, and so on, become important modifying factors for persistent HTLV-I infection, ATL manifestation, or both in the southern part of Japan.

Figure 6 A model for the epidemiological hypothesis on the etiology of ATL. (Ref. 9)

Hypothetical model for ATL progression and its risk

From the several examples of epidemiological evidence, a hypothetical model for the progression of ATL can be formed. This is shown in Figure 6. HTLV-I is transmitted from an HTLV-I-carrier mother to her children in infancy, and some (but not all) develop into persistent carriers. Possible modifying factors such as repeated infection and stimulation by non-specific agents may have affected the recent decrease of HTLV-I carrier rate among children. After a long latent period, 2-5% of persistent carriers develop to the clinical stage of ATL, where multiple genetic mutations in the host may be associated with the transformation of infected T-cells, monoclonal progression and blastformation of transformed T-cells.

From a recent cross-sectional study, the overall risk for ATL among children of HTLV-I-carrier mothers is estimated at about 1% under natural conditions.

It is known that there are no cases of childhood ATL, even though most patients with ATL have commonly been infected with HTLV-I by their mother within one year after birth, through breast milk. It is unclear why ATL becomes overt after passing through a long latent period. Generally, T-cells in humans divide, differentiate, and mature in the thymus, which appears in the fetus and reaches its maximum development in children of school age. Maturation of the thymus and the function of cell-mediated immunity are related to nutritional status and health during childhood. It is noteworthy that the thymic organ is mostly involuted after the average age of 40 years, which is most patients contract ATL. There is a possibility that an unknown thymic factor can regulate or control the progression of T-cells transformed by HTLV-I integration, and ATL does not become overt when the thymus functions normally in young adults. It is speculated, therefore, that the age of onset of ATL manifestation may be related to the starting of a wearing-down process of immune regulation of T-cells, such as thymus involution.

Prospects for the prevention of ATL

From follow-up studies on the age-specific distribution of HTLV-I carriers in Japan, it is now speculated that the HTLV-I infection rate may have decreased naturally in the more recent generational cohort groups⁽²⁷⁾ and that HTLV-I carriers could vanish in the future, even in the ATL-endemic areas. Such phenomena may have occurred in the non-endemic areas of the world.

However, ATL in Japan is an important subject for study in the field of cancer epidemiology, and several trial intervention programs for the prevention of ATL, such as control of vertical transmission from mother to child through breast milk, are now in progress in ATL-endemic areas in Japan. Early stages of ATL, such as smoldering ATL or preclinical ATL, can be detected by screening HTLV-I carriers in the ATL-endemic areas. A long-term follow-up study and control of the early stages of ATL cases seem to be important for the prevention of ATL manifestation in the future.

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