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REVIEW

The epidemiology of HTLV-I infection

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It has been 10 years since the discovery of the human T-cell lymphotropic virus type I (HTLV-I), the first human retrovirus. During the past decade, significant progress has been made in understanding the transmission of the virus and defining its geographic distribution. It has been shown conclusively that HTLV-I is a causal factor in the induction of both adult T-cell leukemia/lymphoma and HTLV-I-associated myelopathy. However, the pathogenesis of each of these conditions is not clear, and in the light of the evidence of immune dysfunction seen among carriers of the infection, it is likely that other associated diseases will be identified. The challenge in the next decade will be to develop and implement therapeutic interventions among carriers to prevent such diseases as well as to curtail transmission within endemic populations.

Key words: Adult T-cell leukemia, epidemiology, HTLV-I, lymphoma, viral oncogenesis.

Introduction

It has been 10 years since the human T-cell lymphotropic (or leukemia) virus (HTLV-I) was isolated and characterized as the first known human retrovirus. Subsequent research has demonstrated conclusively that the virus plays a causal role in the etiology of adult T-cell leukemia/lymphoma (ATL) and HTLV-I-associated myelopathy (HAM). However, the natural history of the infection is not well understood. Although the virus is transmitted by the same routes as some other infections—perinatally, sexually, and by blood—the epidemiology of the infection itself is highly unusual, marked by extreme geographic restriction and a high degree of microepidemicity. The purpose of this paper is to review current knowledge of the epidemiology and natural history of HTLV-I infection.

The HTLV-I

The isolation and characterization of HTLV-I was accomplished independently and in parallel by two groups of investigators, American and Japanese. In 1980, Poiesz *et al*[1] isolated a new retrovirus (called HTLV) from two T-lymphoblastoid cell-lines established from biopsied tissue from an American black male with cutaneous T-cell lymphoma. This work was preceded by the recognition in 1976 by Takatsuki *et al*,[2] of a distinct malignancy—ATL—occurring in southern Japan. In 1980, Miyoshi *et al*[3] established a cell line from leukemic white cells obtained from an ATL patient, from which a retrovirus (called ATLV) was isolated and characterized in 1982.[4] Miyoshi *et al*[5] demonstrated the oncogenic potential of the virus by transformation of cord lymphocytes by co-cultivation with ATL leukemia cells. Gallo *et al*,[6] in 1983, identified additional foci of ATL among Caribbean blacks. In 1982, Watanabe *et al*[7] demonstrated that the ATLV and HTLV were identical and, by consensus, the virus was later designated HTLV-I.

HTLV-I is an RNA-containing C-type virus with the general structure common to that of the known animal retroviruses. These include coding areas of the 'gag' internal proteins, the 'pol' polymerase proteins, and the 'env' envelope proteins.[8] The polymerase, reverse

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transcriptase, synthesizes a DNA transcript of the RNA genome, resulting in its integration as a provirus into the host genome. At each end of the genome are long terminal repeats which code for transcription initiation signals. In addition, two regulatory genes are coded in the 'pX' region. The first gene codes for the protein, p40/p42 ('tax'), which is responsible for the transactivation of virus transcription. Tax also transactivates several host genes, leading to sustained production of interleukin 2 (IL-2) and of IL-2Rα which combines with IL-2Rβ to form a high affinity receptor for IL-2 on T-cells.[9-11] It also transactivates the gene for granulocyte-macrophage colony-stimulating factor,[12] but transrepresses the β-polymerase gene, which is involved in host cell DNA repair.[13] A second regulatory protein, p27 ('rex'), appears to control gag mRNA levels.[14]

Sera from persons infected with HTLV-I—healthy carriers as well as ATL and HAM patients—react specifically with virus-encoded polypeptides. Most commonly these include two glycoproteins (gp61 and gp45) encoded by the env gene and p24, p19, and p15 encoded by the gag genes.[15,16] Reactivity to tax is present in about half of carriers,[16] while that to rex appears to be extremely rare.

An unusual feature of HTLV-I is that it establishes a highly cell-associated infection, with no serologically detectable free virus. This property likely accounts for the extremely low level of person-to-person transmission. The apparent reservoir of latent infection is the peripheral blood T-lymphocytes.[17] Immortalization of T-cells by HTLV-I *in vitro* leads to cell growth in the absence of IL-2. The immortalized cells are generally of an activated T-helper phenotype, marked by the presence of the surface antigens CD4 (a marker for T-helper) and CD25 or 'Tac' (both of which react with IL-2Rα) in cell typing assays.

Shortly after the identification of HTLV-I, a closely-related retrovirus—HTLV-II—was isolated from an American white male with a T-cell variant of hairy cell leukemia.[18] Unlike HTLV-I, few additional isolates of HTLV-II have been reported.[19] The two HTLVs share 50 percent nucleic acid homology[20] and have extensive cross-reactivity with env gene products.[21] This property has created confusion in seroepidemiologic studies since most assays cannot distinguish between the two.[22] (For the purpose of this review, the term 'HTLV-I' will be used for simplicity unless the presence of type II has been established in the specific data quoted.)

Of interest, HTLV-I is much closer to a simian retrovirus, STLV-I, with 90 percent nucleic acid homology, than to HTLV-II.[23] STLV-I was identified by Miyoshi *et al*,[24] who examined sera from 20 Japanese macaques with an antibody assay for HTLV-I and found that 18 were seropositive. They then isolated the STLV-I by cultivation of lymphocytes of a seropositive monkey. The virus was found to be prevalent in a range of Asian and African primates, but not among New World monkeys.[25-27] As does HTLV-I in humans, STLV-I can cause lymphoma and leukemia in naturally infected monkeys.[28,29] It has been speculated that HTLV-I infection originated from a cross-species infection with STLV-I. If true, this must have happened centuries ago, as, at present, the seroprevalences of the two infections are geographically distinct both within and outside of Japan.[27]

A remarkable feature of the epidemiology of HTLV-I infection is its highly restricted geographic seroprevalence. The most thorough documentation has been in Japan, beginning with a nationwide survey of blood donor populations in 1982.[30] This comprehensive study determined that the 'highly' endemic populations were restricted to the southern islands of Kyushu, Shikoko, and Okinawa which corresponded to the areas where ATL occurred. Subsequent surveys have confirmed these findings[31-42] with the additional observation of a high infection rate among the aboriginal Ainu people in northern Hokkaido.[43] However, the infection appears to be rare in the rest of Asia,[44-49] with the interesting exception of the finding of 17 seropositives among 746 Aeta, an isolated aboriginal population in the Philippines.[48]

A second endemic area was identified in the Caribbean, primarily in Jamaica[50,51] and in Trinidad.[52,53] The infection has been reported in Martinique,[54] Barbados,[55] and French Guiana,[56] but is absent in Puerto Rico.[57] The infection has also been found among Caribbean migrants to the United Kingdom.[58] A lower level of endemicity has been found in Columbia[59] and Brazil.[60] A pocket of high seropositivity among Guaymi Indians in Panama has recently been shown to be due to HTLV-II infection.[61,62]

Emerging data from Africa also point to HTLV-I endemic populations,[49,63] primarily in French-speaking West Africa. These include Gabon,[64] Cameroon, Southern Chad, Equatorial Guinea,[65] Ivory Coast,[66,67] and Nigeria.[68]

The most controversial data concern seroepidemiologic studies in Papua New Guinea. Kazura *et al*[69] reported high positivity rates (26 percent) in a study in rural areas. Further, on prospective follow-up of 87 seronegatives over one year, they reported that 11 (13 percent) seroconverted. Babona and Nurse reported similar findings.[70] These reports were challenged by several investigators because of the lack of a confirmatory assay as well as the evidence of a high level of false positivity in this population.[71-73] However, Brabin *et al*[74] recently reported finding high rates of seropositivity in a sample of women from the area using a standard assay with

confirmation. Relatively high seroprevalence has also been reported for the Solomon Islands[70,75] and among Australian aborigines.[76]

Finally, in the United States, HTLV-I infection has been detected among Japanese-Americans (both first and second generations) in Hawaii[77] and among American blacks.[78-80] Among intravenous drug-abusing populations a relatively high prevalence has been reported, primarily in older black Americans,[81,82] involving both HTLV-I and HTLV-II.[83-85] Among native American populations, two pockets of infection have been reported: among Florida Indians[49] and Alaskan Eskimos.[86]

The emerging patterns of endemicity of HTLV-I infection are shown in Table 1. This picture must be considered provisional for three reasons. First, data are only available on selected populations; as such, they may be biased or nonrepresentative. Second, the validity of assays has been evolving and, in some populations, a high level of false positivity has been found.[87,88] Last, the present picture is based on assays for HTLV-I which do not distinguish between type I and II, and additional sub-types may also be present.[88] New techniques are being developed to distinguish between I and II and it is likely that within the next year the epidemiology of HTLV-II will be delineated.[85] In the present review, most of the analytic studies are reported in populations which are clearly infected with HTLV-I (Kyushu) or presumably so (Jamaica).[85]

The origin of HTLV-I infection has been a question of lively discussion for some time. Gallo *et al*[89,90] have asserted that the virus originated in Africa and was introduced into Japan by African sailors on Portuguese trade ships in contact with Kagoshima in the 16th century. This view was supported by the observation of Hino *et al*[91] of a strong correlation between the incidence of ATL and the proportion of Catholics in various areas of Nagasaki Prefecture, reflecting early contact with Portuguese missionaries. In addition, the STLV-I isolate which shows the greatest nucleic acid homology with HTLV-I is from an African green monkey.[20]

However, a counter-argument has been put forward by Ishida *et al*,[43] who note that the Ainu people of Hokkaido are regarded as descendants of the pre-agricultural native population of northern Japan and share some physical and genetic traits with the Ryukyuan populations, the original natives of the extreme south. In light of the almost total lack of infection among the Wajin (the predominant Japanese population) who migrated from the Asian continent between 300 BC and 600 AD, these observations suggest that the infection was already present in Japan more than 2,300 years ago. Further, Ishida *et al*[48] also identified a pocket of infection among the Aeta people, an aboriginal population of the Philippines, which had been isolated in remote mountainous areas since their arrival 12,000 to 15,000 years ago until quite recently.

Taguchi[92] has suggested that the distribution of the infection along the coast of Kyushu was facilitated by the movement of fishermen. More recently, Zaninovic *et al*[93] have pointed out that HTLV-I infection in South America occurs not only among blacks, but also among isolated Indian populations. Given the presence of the infection in aboriginal populations in the southern Pacific, they argue that early migration from Asia (or the Pacific Islands) brought the virus to the Americas. Although this dispute may never be resolved, it is clear that HTLV-I is an ancient infection, of highly conserved structure, which has established a stable accommodation with its human host over millennia.

In view of the early origin of this infection, it is surprising that HTLV-I has such a limited distribution and that it does not appear to saturate a population. This is quite different from other known, latent human viruses such as the herpesviruses or the papillomaviruses. Many authors have noted that even within HTLV-I endemic populations, there is a high level of microepidemiology, in that the infection tends to be concentrated within geographically or socially self-contained population pools. This fractal quality is apparent even within small endemic villages, where significant variation occurs.[94] This phenomenon likely reflects the very low infectivity of the virus and its high degree of clustering within families, reflecting perinatal and sexual transmission.

Within highly endemic populations, an unusual age-specific seroprevalence curve is characteristically

Table 1. Emerging patterns of HTLV-I seroprevalence among population groups by apparent level of endemicity

Highly endemic (≥15%)[a]
Japan: Kyushu, Shikoku, Okinawa, Ainu Aborigines
South Pacific: Papua New Guinea, Solomon Islands, Australian Aborigines
Intermediately endemic (5 – 14%)
Caribbean: Jamaica, Trinidad, Martinique, French Guiana
West Africa: Gabon, Cameroon, Equatorial Guinea, Ivory Coast
Low seroprevalence (1 – <5%)
Carbibbean: Barbados
South America: Panamanian Guayami Indians (II), Columbia, Brazil
West Africa: Southern Chad, Nigeria
America: Alaska Eskimos, Florida Indians
Philippines: Aeta Aborigines
Very low seroprevalence (<1%)
American blacks (I and II)

[a]Among adults ≥ 40 years of age in the general population.

seen.[95,96] A typical example is that derived from our own prospective cohort study based in two highly endemic villages in southern Miyazaki Prefecture (Figure 1). These data are from 1,694 persons who were seen in conjunction with a free government-sponsored annual health examination. Blood samples were collected from 1984 through 1988 and tested by the particle agglutination test (Fuji Rebio, Tokyo, Japan) with confirmation by indirect immunofluorescent staining with acetone-fixed Hut102 cell antigen, or by immunoblot and radioimmunoprecipitate assay. In this population, there is a gradual increase of seroprevalence between age 30 and 55 with a slight female predominance. Among older persons, the seroprevalence tends to plateau among men but continues to rise among women.

Data from other Japanese populations indicate that the seroprevalence among children is low and stable. In the study on Tsushima Island by Tajima[39] the seroprevalence among 700 children less than 15 years of age was about two percent. Kusuhara *et al*[97] studied 311 mother/child pairs in Okinawa followed over 18 years and found that no child had seroconverted by age 18 other than those infected perinatally, *i.e.*, those who had antibody by age three and a mother who was seropositive at the birth. Ten of 65 children born to seropositive mothers seroconverted, but none of the children born to the 246 seronegative mothers did. (Of interest, three of the 65 positive mothers seroconverted after the birth of their child; none of their three children seroconverted.) The increase in seroprevalence beginning in young adulthood, in our and other similar endemic populations, is then, presumably due primarily to sexual transmission, since blood transfusion appears to account for relatively few infections.

If true, this characteristic age-seroprevalence pattern (Figure 1) is unexpected since, for other sexually transmitted infections, there is a rapid 'shoulder' of increase during the period of life when sexual activity begins. Here, there is only a gradual increase of seroprevalence between the third and sixth decade of life. The fact that the rates diverge between the sexes after age 50 is also unexpected.

One possible explanation for the apparent increase in the oldest ages as evidenced by cross-sectional studies is that it reflects a cohort effect, where earlier-born cohorts had higher baseline rates, presumably because of a higher rate of perinatal transmission.[39] Evidence to support this hypothesis comes from a series of cross-sectional surveys between 1966 and 1988 among young adult women from Okinawa.[98] In these data there was a decrease in seroprevalence for later-born cohorts. A decrease in seroprevalence among pre-adolescent children between 1973 – 76 and 1981 in Nagasaki also has been reported.[99] However, in two other populations in Okinawa, sampled over all ages between 1968 and 1984, no consistent or substantial change in seroprevalence was evident.[100] Thus, there is at present no consistent evidence of a cohort effect nor any other explanation for the excess prevalence among older women from descriptive epidemiology.

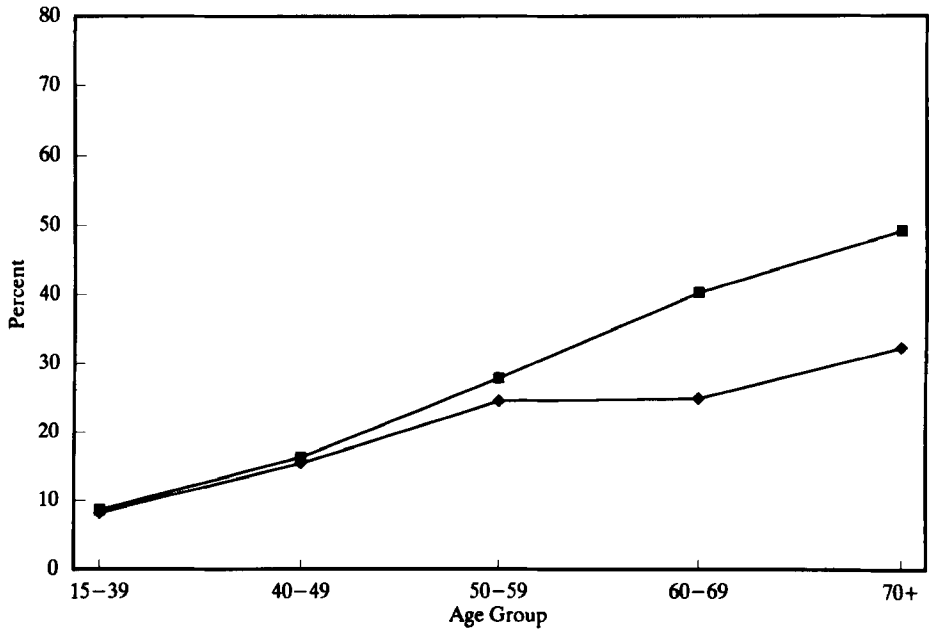

Figure 1. Age-specific seroprevalence curve in Miyazaki study population by sex; 994 women and 700 men. (■) Females; (◆) males.

Transmission studies

Analytic studies on transmission provide further insight into these observations. It was recognized almost immediately that ATL clustered in families in Japan,[101] and the concordance of antibody status between mother and child was clearly documented in Okinawa by Kajiyama *et al.*[102] This group first surveyed 4,649 adults of whom 719 were seropositive and then traced and obtained blood samples from the children (including adults) of the carriers. In an analysis of data from 434 children for whom both parents' status was known and at least one parent was positive, they found only those children whose mothers were seropositive were themselves seropositive (86 of 352), but none of the 82 children were positive whose mothers were negative and whose fathers were positive.

Because of the highly cell-associated nature of the virus and absence of evidence of free virus in serum, the mechanism of perinatal transmission became a matter of speculation. In 1984, Kinoshita *et al*[103] and Nakano *et al*[104] demonstrated the presence of virus in cultured lymphocytes isolated from breast milk of carrier mothers, suggesting that breast milk was a vehicle for transmission. Subsequent research has focused on the validity of this hypothesis and on evaluating whether such transmission is associated with various indices of virus status, as evidence of the level of infectiousness of carrier mothers.

The evidence indicates that being breast-fed by a seropositive mother is a significant risk factor for perinatal transmission of HTLV-I, but neither sufficient nor necessary. In data from Nagasaki, Hino *et al*[105] reported that among children born to seropositive mothers, five of 32 children who were only breast-fed had seroconverted by 18 months of age, compared to four of 47 children who were 'partly' breast-fed and to none of eight children who were only bottle-fed. Ando *et al*[106] reported one seroconversion among 11 bottle-fed children of carrier mothers.

In terms of the virus status of breast-feeding mothers, those carrier mothers whose breast milk lymphocytes were culture positive were more likely to transmit the infection (four of six) than those who were culture negative (one of 14), (relative risk [RR] = 9.3).[107] Carrier mothers with high antibody titer were more likely to transmit (14 of 46) than those of medium titer (six of 46) or those of low titer (zero of 14); no breast-feeding data were given.[108] Finally, in a study of 225 children (aged two to five years) born to 121 carrier mothers, 67 of 132 whose mothers were currently seropositive for antibody against the tax protein were themselves seropositive, compared to 17 of 93 children whose mothers did not currently have detectable antibody against tax (RR = 2.8). No data on breast-feeding were given.[109]

A question which complicates the interpretation of these obsevations concerns the possibility of antibody-negative infection. The seroconversion of infected children following the decay of maternal antibody takes about 12 to 18 months.[105] Nakano *et al*[110] reported in 1986 that of 16 children born to carrier mothers, 13 had detectable virus-bearing lymphocytes nine to 18 months after birth but only four were antibody positive. More recently, Saito *et al*[111] reported that five of 22 antibody-negative infants born to carrier mothers were positive by polymerase chain reaction for the HTLV-I genome. Thus, the possibility exists that more children of carrier mothers are infected perinatally than are detected by antibody studies.

Several intervention studies are currently underway to interrupt transmission via breast-feeding in endemic areas of Japan.[108,112] The efficiency of these programs is not presently established; however, preliminary results are promising.[113] Since breast-feeding patterns have changed over time in Japan with a substantial decrease in the length of breast-feeding,[112] the observed decrease in seroprevalence among some younger Japanese[98,99] may also provide evidence of an effect of length of lactation.

A second route of transmission which has been well documented is via transfusion of whole blood or cells from a carrier. In 1984, Okochi *et al*[114] reported a retrospective cohort study of 307 antibody-negative transfusion recipients followed for more than 50 days. They documented 26 (63 percent) seroconversions in 41 recipients of a blood transfusion containing cells from an HTLV-I-positive donor, but none in 14 recipients who received fresh frozen plasma from a carrier, nor any in 252 recipients of blood from antibody-negative donors. In these subjects, the seroconversions were first evident beginning 20 days after transfusion. This finding has been corroborated in a Jamaican population.[96] In both Japan and Jamaica (and in other endemic populations as well as the US), donors are now being screened and positive units discarded. The effect of this intervention on the age-specific seroprevalence remains to be seen, although it is likely to be minor. However, blood exposure among intravenous drug abusers will continue and is associated with a significant risk in American black populations.[81-83]

Evidence of sexual transmission of HTLV-I comes from several types of study. A case report highly suggestive of sexual transmission was recently published by Gout *et al.*[115] They reported a case of HAM diagnosed in a 41-year-old white Frenchman, subsequent to multiple transfusions following a heart transplant. In a 'look-back' at 59 donors of blood components which he received, one was found to be an HTLV-I carrier. The seroconversion was documented in the patient, and virus was

Table 2. Distribution of couples by concordance for antibody status (by sex) and by age-group of husband in Miyazaki study population

Age	M+/F+	M+/F−	M−/F+	M−/F−	Total
<40[a]	1 (0.03)[b]	3 (0.10)	2 (0.06)	25 (0.81)	31
40 − 49	16 (0.15)	10 (0.10)	9 (0.09)	69 (0.66)	104
50 − 59	34 (0.20)	12 (0.07)	26 (0.15)	102 (0.59)	174
>59	37 (0.30)	3 (0.02)	16 (0.13)	68 (0.55)	124
Total	88 (0.20)	29 (0.06)	53 (0.12)	264 (0.61)	433

[a]Age at first screen.
[b]Proportion.
Note: Status defined prior to seroconversion, from Ref. 95.

isolated from his cells. A blood sample drawn six months later in his wife was weakly antibody-positive, and her antibody response to p24 shifted from IgM to IgG after nine months, most likely reflecting infection from her husband.

In cross-sectional analyses, the clustering of carrier-status within married couples has been clearly documented.[39,102] We have found this also to be true in our own prospective cohort study. As previously reported,[95] 433 married couples were identified in the first four years of this study. The distribution of these couples by antibody status is shown in Table 2. In this follow-up period, five seroconversions occurred among these couples. These included four women (ages 50, 60, 63, 63) and one man (age 54). In further analysis of these data, we found that four of these seroconversions occurred among the 61 seronegative spouses of discordantly-infected couples, compared to only one among 378 spouses in doubly-negative couples (RR = 24.8, $P = 0.002$). Of the four seroconversions in discordant couples, three occurred among the 21 wives of carrier husbands, compared to one of 40 at-risk husbands with carrier wives (RR = 5.7, $P = 0.11$). Further, of the three 'exposed' wives, two seroconversions occurred in eight women-years of observation defined as having a positive husband who was aged 60 years or more, compared to one seroconversion in 34 women-years 'exposed' to a younger (less than 60 years of age) positive husband (RR = 8.5, $P = 0.10$). Thus, the highest risk of seroconversion occurred among older women married to carrier husbands—consistent with the cross-sectional seroprevalence curves, but the age-group in which this occurred is inconsistent with our concepts of sexually transmitted infections.

Of interest, in a more recent analysis which included an additional seroconversion of a 58-year-old woman married to a 60-year-old positive man, more detailed serologic assays were done on the sera from the 'exposing' partners. For comparison, blood samples from carrier partners in discordant couples of the same age but without seroconversion were analyzed. All 'exposing' partners of seroconverters had antibody to recombinant tax protein compared to 50 percent of the control carriers ($P = 0.001$), and also had somewhat higher antibody titers.[116] These findings are similar to those reported for perinatal transmission.[108] Blattner[96] has also noted that wives of carrier husbands with high antibody titers were more likely to be also seropositive than wives of carrier husbands with lower antibody titers, within the Hawaiian migrant population.

An analogy for these observations can be drawn from the findings of Goedert *et al*[117] who have been following couples discordant for HIV status. These investigators have observed seroconversions occurring in conjunction with the infected partner's advancing immunosuppression and apparent viremia. This suggests by analogy that there are two periods of infectivity for HTLV-I: (i) during initial viremia, as in the case reported above;[115] and (ii) after an extended latency with progression of the natural history of the infection, since antibody titers increase with age.[118] Our data would suggest that infectiousness relatively late in life is much more common in older seropositive men than women. This predominance of seroconversions among older 'exposed' women could be explained if the potential for women to transmit the virus is attenuated following menopause, perhaps due to physiologic changes in the vagina. It also may be that these seroconversions reflect transmissions which occurred years before, but without sufficient viral expression to induce antibodies. The fact that the seroconversions do not occur randomly, but are significantly clustered in the discordant couples, argues against silent perinatal infection as their source.

Additional risk factors associated with sexual behavior have been identified. These include male homosexual activity (duration and number of partners) in Trinidad[119] and female prostitution in the US.[120] Murphy *et al*,[121] in a detailed analysis of data from a sexually transmitted disease clinic population in Jamaica compared to that from a food-handler population, found

Table 3. Average age, sex ratio, and frequencies of abnormal clinical findings on admission in patients with each type of ATL

Clinical features and laboratory findings	Clinical type of ATL (number of cases)			
	Pre[a] (16)	Chronic (25)	Acute (102)	Lymphoma (38)
Average age (years)	47.9	65.1	56.3	57.2
Age range (years)	34 - 63	40 - 84	24 - 90	31 - 81
Sex ratio (male *vs* female)	1.7	0.9	1.6	1.2
Leukocytosis (>10,000/mm^3)	31.2	76.0	79.8	35.1
Atypical cells in blood (>5%)	53.3	86.4	86.6	30.6
Swollen superficial lymph nodes	0.0	12.0	19.6	36.8
Skin lesions	50.0	40.0	27.5	18.4
Hypercalcemia (>5.5 mEq/l)	0.0	0.0	21.6	23.7

[a]Pre-clinical stage including smoldering ATL and pre-leukemia; table adapted from Ref. 124.

that, for women, risk factors for HTLV-I seropositivity included: the presence of venereal disease (RR = 1.8); having more than 10 lifetime sex-partners (RR = 3.5); and having a current diagnosis of syphilis (RR = 2.1). For men, a history of penile sores (RR = 2.1) and a current diagnosis of syphilis (RR = 3.6) were risk factors.

All these data support the role of sexual exposure as a major route of transmission of HTLV-I. The age and sex distribution of the seroconverters are consistent with those predicted from the cross-sectional age curve, suggesting that the curve, in itself, is valid, and not likely explained by a major cohort effect. The fact that a similar curve pertains for monkeys naturally infected with STLV-I also argues for the validity of the curve.[26]

ATL

The most serious disease known to result from infection with HTLV-I is ATL. The epidemiolology of ATL and its clinical features have been carefully described in a series of four reports from the T- and B-Cell Malignancy Study Group in Japan, published between 1981 and 1990.[122-125] The group was established to study the nature and etiology of the 'endemic' ATL which Takatsuki had first recognized.[2] These reports are based on standardized reporting of all incident cases of non-Hodgkin's lymphoma and lymphocytic leukemia in 24 major cancer treatment facilities.

The first report[122] reviewed data on 673 lymphoid malignancies and documented the excessive incidence of T-cell malignancy in those areas of Japan which subsequently were shown to be endemic for HTLV-I infection.[30] It also documented the common clinical features of ATL including hepatosplenomegaly, skin lesions, hypercalcemia, elevated serum glutamic pyruvic transaminase and lactate dehydrogenase, poor prognosis, and immunosuppression—as evidenced by anergy to purified protein derivative (PPD) skin-testing and the occurrence of opportunistic infections. In addition, seasonality of clinical onset was noted, as was the risk factors of family history of hematopoietic malignancy and of employment in primary industry (agriculture, forestry, fishing) which is more common in the endemic areas.

The second report in 1985[123] summarized the results from a new incidence series of 1,040 lymphoid malignancies. Of these, 197 were identified as ATL, with the added diagnostic criterion of HTLV-I seropositivity. The report characterized the pathologic features of the lymphoma as diffuse non-Hodgkin's lymphoma, usually large cell or pleomorphic sub-type. The result of a case-control comparison of data on ATL patients with those with other lymphoid malignancies confirmed the previous findings of an association with employment in agriculture and fishing and of a family history of lymphoid malignancy. No associations were found with history of raising animals in childhood or of eating raw meat, evidence against the virus being an epizootic infection.

The third report in 1988[124] focused on family studies involving 181 incident cases and noted the high seropositivity among family members and several differences in HLA haplotypes among patients as compared to healthy controls, but little difference in comparison to their relatives. The report noted that history of transfusion was not a risk factor for ATL. This report included a summary of abnormal clinical findings for each of the sub-types of ATL: acute and chronic leukemia; lymphomia; and pre-ATL (including 'smoldering' ATL). These are summarized in Table 3.

The most recent report came out in 1990[125] with an expanded database drawn from 1,287 hospitals nationwide; data on 754 cases of ATL were included. This report reconfirmed the original finding on the geographic distribution of cases. In addition, the investigators sought

to estimate the annual incidence of ATL by district and documented the unimodal age distribution of the disease in Kyushu (Figure 2), with a male to female ratio of about 1.2. The occurrence of ATL has also been described in other endemic populations,[126-129] with similar clinical features.

The natural history of HTLV-I-induced ATL is not presently known. Essentially all antibody-positive ATL cases have monoclonally integrated provirus in their malignant cells, but no common site of integration or oncogene has been identified. Yoshida[130] has proposed the following model:

> HTLV infects helper T cells and expresses the viral antigens. A pX gene product $p40^x$ abnormally induces the growth of the infected T cells, however, viral antigen-positive cells are rejected by antibodies against the env gene products . . .. In healthy virus-carriers, these cycles of reinfection, atypical growth and rejection are infinitely repeated. As a very rare event, a cell which is negative in viral antigen expression but which retains the growth abnormality, can escape from immunological surveillance, thus establishing smoldering ATL, an initial clinical stage of ATL.

This model emphasizes the role of transactivation in oncogenesis induced by expression of the tax gene product of the integrated HTLV-I provirus. The validity of this model can be evaluated by prospective follow-up of HTLV-I carriers by determination of a variety of intermediate markers. These include antibody assays including anti-tax, clonality studies of viral integration, and the presence of circulating atypical lymphocytes.

In the few prospective studies which have been published, the most relevant hematologic marker for progression to ATL is the presence of atypical ('flower-like') lymphocytes, very similar to ATL leukemia cells, on peripheral blood smear. These cells are phenotypically CD4- and Tac-positive, and are thought to contain HTLV-I provirus.[131,132] Of interest, very similar cells are seen in the STLV-I-infected monkeys.[133] These cells are found in a small proportion of healthy carriers but are characteristically present in a spectrum of pre-leukemic states. In the initial characterization of smoldering ATL as a pre-leukemic state, Yamaguchi[134] reported on five seropositive patients with skin lesions and a low level of circulating atypical lymphocytes (0.5 – 2.0 percent). Of these, two developed ATL (after five and 13 years); four had concurrent evidence of immunosuppression. The same group later described 15 individuals with polyclonally integrated HTLV-I provirus and a low level of circulating atypical lymphocytes (less than three percent).[135] All showed some level of immune dysfunction. Follow-up extended up to three years. During that time,

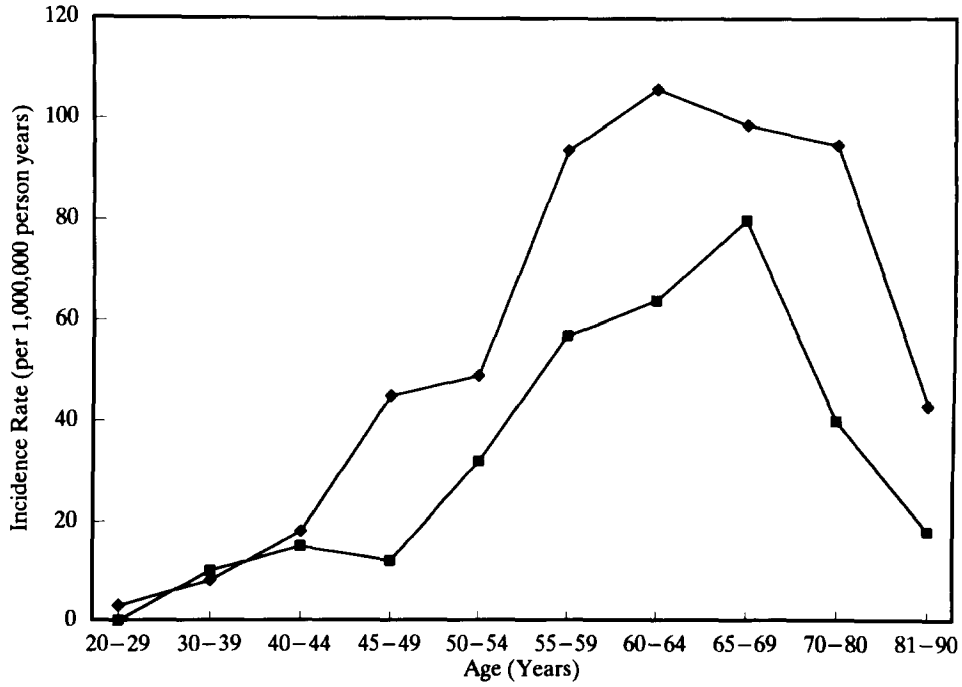

Figure 2. Age-specific incidence rate of ATL in 1986 – 87 in Kyushu Prefecture, by sex. Adapted from Ref. 125. (■) Females; (◆) males.

one patient progressed to ATL. Kinoshita[136] reported on 18 persons with relatively high levels of atypical lymphocytes (10 – 40 percent) and T-lymphocytosis; 14 had monoclonally integrated provirus. Of 13 patients followed from one to seven years, three developed ATL, three had persistent T-lymphocytosis, and in seven there was a regression in the level of atypical lymphocytes with their lymphocyte count becoming normal.

Suppression of cell-mediated immunity has consistently been a feature of smoldering ATL. For example, Nakada *et al*[137] reported on 36 patients with strongyloidiasis who were HTLV-I carriers. Of these, 28 (78 percent) had detectable atypical lymphocytes (0.1 – 2 percent), 14 (39 percent) had monoclonal integration of HTLV-I proviral DNA, and an additional seven (19 percent) had polyclonally integrated virus.

This suppression may be mediated by functional changes induced by the clonal expansion of HTLV-I-infected T-cells. It has been shown that infected cells *in vitro* release immunosuppressive factors or lose specific cytotoxic activity.[138-140] In the Miyazaki cohort, we have found evidence of immunosuppression in asymptomatic carriers which increases with age. Upon measurement of delayed-type hypersensitivity to PPD in 126 consecutively seen subjects, we found that the HTLV-I carriers were much more likely to lack a response to PPD than the seronegative residents (RR = 6.3). This effect was greater among persons 60 years or older.[141] In a subsequent study among 56 elderly hospitalized patients without immunosuppressive or HTLV-I-associated diseases, we tested response to both PPD and phytohemagglutinin (which directly stimulates T-cells). Again, the HTLV-I carriers showed a significantly reduced level of response to the two antigens.[142]

Additional evidence of diminished cellular immunity among HTLV-I carriers comes from serologic studies of antibody response to the Epstein-Barr virus (EBV), a common latent herpesvirus infection. Imai and Hinuma[143] evaluated the profile of antibody response to 103 ATL patients, 99 HTLV-I carriers, and 143 seronegatives. All subjects showed evidence of an EBV infection. As expected, the ATL cases had a profile consistent with some level of immunosuppression; that is, they had higher titers against the capsid antigen, a higher prevalence of antibodies against the early antigen, and a diminished level of response to the nuclear antigen —a pattern seen in therapeutically immunosuppressed patients.[144] The healthy carriers had a pattern intermediate between that of the ATL patients and the seronegatives. Thus, a hallmark of the progression of HTLV-I infection is a reduced level of cellular immunity.

Similar to what is seen serologically prior to the development of other virus-associated cancers (such as chronic hepatitis-B virus infection and hepatoma), we would anticipate that evidence of virus activation would be a risk factor for ATL. Although free virus has not been detected in carriers, some evidence of virus activity has been reported. Schüpbach and Kalyanaraman[145] have reported the detection of circulating immune complexes containing p24 in one of eight asymptomatic carriers. Kinoshita *et al*[146] reported the detection of polymerase chain reaction of an mRNA from the pX region in four of eight healthy carriers.

Serologic evidence of virus replication may be inferred by the presence of antibody against the tax protein, as this is correlated with infectiousness. However, in a case-control study which we conducted comparing the serologic pattern of antibodies against the HTLV-I of 64 prevalent ATL patients and 105 healthy carriers, we found that the ATL patients were significantly more likely to lack antibody to tax by radioimmunoprecipitation than the carriers (RR = 3.4).[147] Kamihara *et al*[148] have reported three cases of ATL developing in a follow-up study from the Gotoh Islands in Japan. Two of these cases had lacked antibody to tax by an ELISA assay and the third had a low response prior to their diagnosis. This was not different from the expectation of 50 percent seropositivity. They also reported that ATL cases had somewhat higher prevalence rates of anti-tax antibody than did healthy carriers. Overall, there is no consistent evidence regarding the predictive role of antibody against tax or against the gag proteins.[147,149]

Since only a small proportion of carriers—probably less than five percent—ever develop ATL, it is important to identify cofactors which modify this risk. Tajima and Hinuma[150] have proposed that perinatal infection may be an important modifier of risk, since the sex ratio among ATL cases is nearly equal, similar to that among children following perinatal infection, and quite different from that seen among infected adults.[51,151,152] Further, the age-incidence curve of ATL is unimodal, peaking at about age 65 years and decreasing thereafter (Figure 2). This distribution suggests that the cases share a very early etiologic exposure.[153] Among the naturally occurring animal models of virally induced malignancy such as leukemia/lymphoma induced by the feline leukemia virus, early age at infection is generally associated with an increased risk of cancer.[154]

Genetic factors should also be considered, as immune response can be related to HLA haplotype. Epidemiologic studies have found that ATL patients are more likely to have a family history of lymphoid malignancy.[101,122,123] However, since the infection itself clusters within families, this observation may simply reflect the micro-epidemicity of the infection. Although certain HLA haplotypes have been found to be more common among ATL patients, this is also true among healthy carriers.[124,155]

HAM

The second disease recognized to be induced by HTLV-I infection is HAM, a myelopathy of gradual onset marked by mild sensory and sphincter disturbance, leading to paraparesis. In 1985, Gessain *et al*[156] reported that 10 of 17 patients with tropical spastic paraparesis (TSP) in Martinique were HTLV-I seropositive. Similar findings from Jamaican and Colombian TSP patients followed shortly, with the additional observation of HTLV-I antibody in cerebrospinal fluid (CSF) of patients.[157] In 1986, Osame *et al*[158] reported that all patients with a spinal spastic paraparesis which appeared to be endemic in Kagoshima were HTLV-I seropositive, and termed the condition HAM. A national survey in Japan subsequently found that the geographic distribution of HAM cases superimposed that for ATL cases.[159] Typical cases from other populations in which HTLV-I is endemic were identified, and it was agreed that HTLV-I-associated TSP and HAM were identical.[160]

The ages of onset of HAM are younger than those for ATL and there is a strong female predominance (3:1). HAM is a less common condition than ATL, with only 589 prevalent cases identified in Japan in two national surveys.[161] Yoshida *et al*[162] and Imamura *et al*[163] have shown that the viruses from ATL and HAM are identical. However, characteristics of the infection differ between the two groups of patients. In HAM, the virus itself can be isolated from CSF[163] and patients have high antibody titers in both serum and in CSF.[164] Molecular analysis of lymphocytes from HAM patients shows polyclonal integration of HTLV-I rather than monoclonal as is true of ATL.[165,166] Nearly all HAM patients have antibodies against the tax protein.[148]

These observations suggest that a hyperimmune response to HTLV-I infection plays a role in the development of HAM, which is also supported by the finding that patients respond to immunosuppressive treatment.[167] Genetic factors may also play a role in this pathogenesis. Usuku *et al*[168] have undertaken HLA typing studies of both HAM and ATL patients and report that there are distinct genotypes for the two diseases. Further, the peripheral blood lymphocytes from HAM cases *in vitro* responded to HTLV-I antigen while those from ATL cases showed little or no response.[168]

An additional difference between HAM and ATL is that history of blood transfusion is a risk factor for the former, but not the latter. As first noted by Osame *et al*,[169] nine of 23 HAM patients gave a history of blood transfusion compared to one of 23 ATL patients (RR = 14.1). In a later report of 85 cases of HAM, the 18 (21 percent) with a history of transfusion had a later age of onset than those without. Of six cases diagnosed at age less than 14 years, all had a seropositive mother, indicating perinatal infection.[170] The onset of HAM following blood transfusion has been observed to be rapid; in one case, 18 weeks.[115] This is substantiated by the national survey in Japan where the median interval between transfusion and HAM diagnosis was 3.3 years. Further, there has been a substantial decrease (16 percent) of newly reported HAM cases in Japan in the first two years of nationwide screening of blood donors.[161] If the rapidity of onset from infection is also true for non-transfused cases of HAM and most cases (85 percent) occur after childhood, it appears that infection in adulthood is a risk factor. Thus both the mode and age of infection, as well as host response, appear to be important in the pathogenesis of HAM, and differ from that of ATL. There are cases reported who have both ATL and HAM, but this occurrence appears to be quite rare.[171-173]

In addition to ATL and HAM, there are a number of other diseases which are associated with HTLV-I infection. The most commonly reported of these is chronic lymphocytic leukemia (CLL). In a hospital-based survey in Nigeria, Fleming *et al*[174] reported that four of nine CLL patients were HTLV-I seropositive, with an expected seroprevalence of less than one case. In Jamaica, six of 17 CLL patients were seropositive with HTLV-I and evaluation of one of these cases showed that the CLL was of B-cell origin.[175] More recently, Mann *et al*[176] established CLL-hybridoma cell lines using cells from two HTLV-I seropositive CLL patients in Jamaica. Both cell lines produced antibody specific to an antigen of HTLV-I, but lacked the HTLV-I genome. These findings imply that the CLL cells are malignantly transformed, HTLV-I antigen-committed B-cells which are induced secondarily to HTLV-I infection.

A second set of patients with a higher than expected HTLV-I seroprevalence are those with chronic renal failure. Uematsu *et al*,[177] who first noted this relationship, have reported that 34 percent of 260 such patients were HTLV-I carriers, and that the association held regardless of history of hemodialysis or of transfusion.[178] This finding was quite consistent with a report from Kumamoto by Lee *et al*.[179] One possible explanation of this finding is that carriers have circulating immune complexes, leading to kidney damage.[145,180] Finally, HTLV-I has been found to be associated with polymyositis,[181] with chronic inflammatory arthropathy,[182] and with a T-lymphocyte alveolitis.[183]

Future research

In the past 10 years, a substantial amount of information has been obtained concerning the HTLV-I. Intervention programs are now in place in some endemic populations

to interrupt transmission by blood transfusion and from mother-to-child. The strategy to interrupt perinatal transmission may become more focused by incorporation of more specific markers of infectivity—such as antibodies against tax. Policies for counseling discordant couples need to be developed and to incorporate both the evolving understanding of the health risks associated with seroconversion at various ages, as well as the cultures of the endemic populations, in order to minimize the impact on family life.

Risk factors for the development of ATL in a subset of carriers are becoming somewhat clearer, and therapeutic interventions are being considered.[184,185] The STLV-I model should be of utility in evaluating the efficacy of various treatments. Strategies for vaccine development[17] should be illuminated in parallel with those for HIV-I. Finally, in view of the effects on immune dysfunction by HTLV-I, it is likely that additional diseases will be identified as occurring at a higher than expected frequency among carriers.

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