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SEROEPIDEMIOLOGIC STUDIES OF HUMAN T-CELL LEUKEMIA/ LYMPHOMA VIRUS TYPE I IN JAMAICA

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The prevalence of HTLV-I antibodies was evaluated in Jamaica among persons with various malignant, infectious, autoimmune and hematologic disorders and in clinically normal persons. Results document that: (1) the prevalence of HTLV-I antibodies in this population increases with age; (2) overall, there is no significant difference in the antibody prevalence between males and females; (3) antibody-positive individuals are born in all major regions of the island and geographical variance in antibody prevalence by place of birth was not prominent; (4) there is further confirmation of the high prevalence of HTLV-I antibody-positive lymphomas in Jamaica; and (5) the prevalence of HTLV-I antibodies in hemophiliacs, patients with chronic lymphocytic leukemia (CLL), myelogenous leukemias, and patients with breast cancer is higher than in the age-matched population without malignancies, although none of these differences were statistically significant. The increased prevalence in hemophiliacs is most likely related to their frequent transfusion with blood products, but it has not yet been determined whether the prevalence in patients with other diseases is related to their diseases or other as yet undefined factors in common.

The human retrovirus HTLV-I has been shown to be etiologically associated with adult T-cell leukemia/ lymphoma (ATL) (Blattner *et al.*, 1983*b*; Robert-Guroff and Gallo, 1983). This virus is endemic in various regions of south-western Japan, the south-eastern United States, northern South America, Central America, Africa, and the Caribbean basin (Blattner *et al.*, 1984; Robert-Guroff *et al.*, 1984*b*; Biggar *et al.*, 1984; Saxinger *et al.*, 1984). Serologic surveys reported from several areas of Japan (Hinuma *et al.*, 1982; Maeda *et al.*, 1984; Tajima *et al.*, 1982), suggest that HTLV-I antibody prevalence: (1) varies markedly by geographic locale, even in viral endemic areas separated by short distances; (2) increases significantly in the population with increasing age; (3) is approximately equal in both sexes up to the age of 40 after which it remains relatively stable in men while continuing to increase in women; (4) is higher in persons with concomitant infection with either filariasis or strongyloides; and (5) is strongly associated with ATL and is increased in some other malignancies where transfusion is a frequent therapeutic intervention. We previously reported the high prevalence of HTLV-I antibody positivity among patients with lymphomas in Jamaica (Blattner *et al.*, 1983*a*). However, to date, no systematic serologic surveys have been reported concerning persons without hematologic malignancies living in Jamaica. In order to determine this prevalence, over the past 2½ years, we have performed serologic surveys of the prevalence of HTLV-I antibodies in various population groups in Jamaica.

MATERIAL AND METHODS

Sera

Serum samples were obtained from the following subjects: (1) Blood bank donors of both sexes in Kingston and Montego Bay seen between September 1983 and February 1984, primarily between the ages of 20 and 55. (2) Patients seen in the outpatient medical clinics of the University Hospital of the West Indies (UHWI) in Kingston during a 4-week period in September and October, 1983. These are general medical clinics serving primarily the population in and around Kingston. This survey was designed to screen at least 10 persons of both sexes in each age group by decade but otherwise randomly selected. (3) Both in- and outpatients with hematologic and other malignancies seen at the UHWI in Kingston between July 1982 and December 1983. (4) Pregnant women attending a prenatal clinic at the UHWI from September 1983 to February 1984.

These samples were collected and frozen at -70°C prior to testing. In addition, serum samples which had been obtained as part of a nutrition and anemia survey of school children in Kingston in 1977 and 1978 and kept frozen at -70°C were also tested. Clinical and pathologic diagnoses were made by physicians at the UHWI. Statistical comparisons were made using a Chi-square test on the comparison of the antibody prevalence rates between men and women, and between the patients with malignancies and the age-matched population. An analysis of covariance was used on comparison of the antibody prevalence rates between the regions (Armitage, 1971).

Immunologic assays

All serum samples were screened for the presence of HTLV-I antibodies by the previously reported enzyme-linked immunosorbent assay (ELISA) technique, using zonal ultracentrifugation-purified detergent-disrupted HTLV-I whole-virus antigen (Saxinger and Gallo, 1983). The specificity of the antibodies for HTLV-I antigens of all reactive sera was determined using competition experiments, and only those sera whose specificity for HTLV-I was confirmed were considered positive (Robert-Guroff *et al.*, 1982; Saxinger *et al.*, 1984).

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TABLE I - HTLV-I ANTIBODY POSITIVITY IN PERSONS WITHOUT MALIGNANCIES IN JAMAICA

Age	Male			Female			Both		
	Number positive	Number tested	% Positive	Number positive	Number tested	% Positive	Number positive	Number tested	% Positive
0–19	4	206	1.9	5	226	2.2	9	432	2.1
20–29	4	112	3.6	14	388	3.6	18	500	3.6
30–39	5	59	8.5	3	55	5.5	8	114	7.0
40–49	4	39	10.3	3	35	8.6	7	74	9.5
50–59	6	39	15.4	6	37	16.2	12	76	15.8
60–69	4	24	16.7	7	37	18.9	11	61	18.0
>70	3	26	11.5	3	30	10.0	6	56	10.7

RESULTS

Prevalence of HTLV-I antibodies by age and sex

The antibody prevalence for each of the 5 groups and their median ages are as follows: blood bank donors—4.5%, median age 25 (n=247); pregnant women—3.2%, median age 25 (n=278); medical clinic outpatients—10.8%, median age 45 (n=269); other clinic outpatients—9.5%, median age 42 (n=179); and school survey—1.5%, median age 10 (n=330). Due to the small number of individuals in each diagnostic group, data from all persons with non-malignant conditions were analyzed together in determining the overall age and sex prevalence of antibodies to HTLV-I (Table I). Although these groups are not strictly comparable, the percentage of antibody-positive individuals in each group, once adjusted for the median age of that group, is comparable to the antibody positivity for that age of the overall combined population tested (above and Table I). All persons with a known history of blood transfusion or who had a primary diagnosis of infection (conditions previously linked to HTLV-I positivity, McLane *et al.*, 1983; Okochi *et al.*, 1984) were excluded from this combined grouping, while individuals unlikely to have been transfused but whose blood transfusion history was not known (n=462) were included in the analysis. As shown in Table I, HTLV-I antibody prevalence increases with age in both sexes, from less than 2% in those under 20 to a maximum of approximately 18% in those aged 60-70 after which it declines slightly to 11%. The prevalence was slightly higher in males than in females for those under 50 whereas it was slightly higher in females than in males in those aged 50 to 70, but neither of these differences was significant ($p=0.65$ and $p=0.79$, respectively, Chi-square test).

Place of birth was known only for the blood bank donors, the persons seen in the outpatient medical clinics in September and October, 1983, and some of the patients with ATL and those seen in the hematology clinic at the UHWI. Evaluation of antibody prevalence by place of birth is based on those groups collected at the UHWI and in the blood banks. As shown in Table II, those born in central Jamaica (8.5%) had a higher antibody prevalence than those born in either eastern (7%) or western (6.1%) Jamaica. The differences are small and are explainable at least in part by the fact that those tested from central Jamaica were somewhat older (median age 39) than those in either eastern Jamaica (median age 35) or western Jamaica (median age 33). After adjusting for the age of the populations studied (Table III), an analysis of covariance using an F statistic showed no significant difference in antibody prevalences between the 3 regions ($p=0.62$). The ages at which persons had migrated from their places of birth, which might affect the likelihood of infection, were not known.

TABLE II - HTLV-I ANTIBODY POSITIVITY BY GEOGRAPHIC REGION IN JAMAICA (NOT ADJUSTED FOR AGE)

Location (county)	Number positive/ Number tested	% Positive	Mean age
I. Surrey (eastern)	18/256	7.0	35
II. Middlesex (central)	16/188	8.5	39
III. Cornwall (western)	12/196	6.1	33

TABLE III - HTLV-I ANTIBODY POSITIVITY IN PATIENTS WITH MALIGNANCIES

Disease	Number positive	Number tested	% Positive
Non-Hodgkin's lymphoma	36 (36[1])	72 (65[1])	50 (55.4[1])
Chronic lymphocytic leukemia	6	26	23.1
Multiple myeloma	3	33	9.1
Acute lymphocytic leukemia	2	16	12.5
Hairy-cell leukemia	0	2	0
Cutaneous T-cell lymphoma	1	2	50
Hodgkin's disease	0	17	0
Malignant histiocytosis	1	2	50
Acute myelogenous leukemia	2	6	33.3
Chronic myelogenous leukemia	1	6	16.7
Breast cancer	6	22	27.3
Other cancer	0	25	0

[1]Over age 15.

Prevalence of HTLV-I antibodies in persons with malignancies in Jamaica

Table III illustrates the prevalence of HTLV-I antibodies in persons with various malignancies. A total of 230 patients with malignancies were screened. There were approximately equal numbers of male and female HTLV-I antibody-positive NHL cases (19 and 17, respectively), although a slightly higher percentage of positive cases was found among females (55% overall and 57% of those over 15) than among males (46% overall and 54% of those over 15). Many of the clinical and pathologic features of these cases were characteristic of ATL (frequent lymphadenopathy, hepatosplenomegaly, skin involvement, leukemic phase, hypercalcemia, aggressive disease, and short survival) as has been reported elsewhere (Blayney *et al.*, 1983). Persons with HTLV-I antibody-positive NHL were born in all 3 regions of Jamaica without a significant preponderance from any of the regions (data not shown).

The prevalence of antibodies in patients with several malignancies was higher than expected for the age-matched individuals without malignancies, although none of these reached statistical significance (Table III). Specifically, patients with CLL (6/26 or 23%, median age = 64; $p=0.57$), breast cancer (6/22 or 27%, median age = 49; $p=0.11$), myelogenous leukemias (3/12 or 25%, median age = 45; $p=0.14$), acute lymphocytic leukemia (ALL) (2/16 or 12.5%, median age = 15; $p=0.12$), mycosis fungoides (MF) (1/2), and malignant histiocytosis (1/2) had a non-statistically-significant increased prevalence of antibodies compared to age-matched individuals without malignancies. The number of cases in each disease category was small and the transfusion status was not known for many of these individuals. We did not detect an increased prevalence of HTLV-I antibodies in patients with Hodgkin's disease, multiple myeloma, or solid tumors other than breast (Table III).

HTLV-I antibody prevalence in persons with hemophilia A or primary infectious diseases

Two of 4 patients with hemophilia A had antibodies to HTLV-I (Table IV). One of 35 patients with viral or bacterial infectious diseases was positive. Two of the 3 patients with a parasitic infection were positive.

DISCUSSION

We have previously reported the occurrence of HTLV-I-associated lymphoreticular malignancy in Jamaica and documented that over half of all adult NHL cases were antibody-positive and frequently had features of the HTLV-I-associated ATL (Blattner *et al.*, 1983*a*; Gibbs *et al.*, 1983). The current study extends these findings and also provides data on the prevalence of HTLV-I antibodies in various groups of Jamaicans without malignancies. The groups without malignant disease available for study (blood-bank donors, schoolchildren, pregnant women, and outpatient medical clinic patients without a primary diagnosis of infectious disease) are not a random sample and do not provide exact proportional representation by age, sex, and geographical location of the general population of Jamaica. However, after taking this into account, there are no clear reasons for expecting this combined group of individuals to have either higher or lower rates of positivity than the general population.

The percentage of antibody prevalence in the adult population seen here (over the age of 20—8.1%) is similar to that previously reported for emigrants from the West Indies to Great Britain [a combination of normal individuals and persons hospitalized for non-leukemic conditions (8%)] (Greaves *et al.*, 1984), for the population of Venezuela which borders the Caribbean on the south (6.8%) (Merino *et al.*, 1984), and for Haitian immigrants to the United States (12%) (Robert-Guroff *et al.*, 1984*a*), all analyzed by an HTLV-I antibody ELISA assay (Saxinger and Gallo, 1983). It is higher than that previously reported from studies in other areas of the Caribbean, St. Vincent Island, BWI (3.3%) (Blattner *et al.*, 1982) and Martinique (1.5%) (Schaffer-Deshayes *et al.*, 1984), both tested by HTLV-I p-24 radioimmunoassay, a highly specific but less sensitive method for detecting antibody positivity. Besides the fact that different population groups were tested in the 3 areas, and that the antibody prevalence rate may vary between Caribbean countries, part of this difference may be explained by greater sensitivity of the ELISA assay in detection of viral antibodies.

Overall, the HTLV-I antibody positivity rate reported here (5.4% overall and 8.1% in those over age 20) is lower than that reported for some endemic areas of Japan (Hinuma *et al.*, 1982; Tajima *et al.*, 1982). However, the rate in adults is very similar to the 8% positivity reported for blood donors aged 16-64 from various centers in Kyushu (Maeda *et al.*, 1984), which may reflect differences in population risk for HTLV-I infection between blood-bank and hospital-based populations. Variation in antibody prevalence on a regional and subregional level within Japan is quite striking (Hinuma *et al.*, 1982; Maeda *et al.*, 1984; Yamaguchi *et al.*, 1983). The current study, although not specifically designed to address the question, did not demonstrate obvious regional variation in seroprevalence. In fact, the preliminary data from multiple locales in the Caribbean suggest a widespread occurrence of HTLV-I, although the actual prevalence of infection may vary significantly between different regions. This widespread occurrence of HTLV-I infection throughout the Caribbean, in contrast to the pattern in Japan, could suggest differences in modes of spread between these locales, a question that needs to be explored in future studies.

As noted in Table I, the prevalence of antibodies in this combined group of individuals increases with age in both sexes up to the age of 70 after which it declines. This pattern is similar to that seen in Japan (Hinuma *et al.*, 1982; Maeda *et al.*, 1984). Unlike the data from Japan (Tajima *et al.*, 1982), these data do not suggest a large divergence between female and male rates in the 50- to 70-year age group (17.6% versus 15.9%, respectively). A recent study in Martinique also showed an increase in antibody prevalence with age, but did not show a significant difference in antibody prevalence between men and women either under or over 60 (Schaffar-Deshayes *et al.*, 1984). However,

TABLE IV - HTLV-I ANTIBODY POSITIVITY BY NON-MALIGNANT DISEASE CATEGORY

Disease category	Number positive	Number tested	% Positive
Outpatient infections	3 (2[1])	38 (3[1])	7.9
Dermatologic conditions	2	26	7.7
SLE	2	43	4.7
Rheumatoid arthritis	0	8	0
Miscellaneous rheumatologic condition	1	3	33.3
(Total rheumatic disease)	3	54	5.6
Hemophilia A	2	4	50

[1]Parasitic infections.

until further population-based studies are done in the Caribbean, it is not clear whether the lack of a significant difference in antibody prevalence between men and women over the age of 40, seen here, truly represents a difference in the epidemiology of infection between Japan and Jamaica, or is somehow due to the small number or the nature of the group of older individuals (hospital outpatients) in the present study.

The increasing prevalence of antibody with age, seen here and in Japan, suggests either that the majority of the infections in the population occur after childhood (possibly as a sexually transmitted disease and through blood transfusions) or that a serologic survey for antibodies does not detect a proportion of children who are infected with HTLV-I but have not produced detectable antibody. Possible explanations for the latter include: (1) infection by virus with insufficient antigen expression for development of a detectable antibody response, until secondary factors stimulating virally infected cells lead to antigen expression later in life; (2) repeated exposure to the virus over the years, leading to a higher percentage of detectable antibody responses with increasing age; or (3) the findings being due to a cohort effect with a decreasing incidence of HTLV-I infection in Jamaica, although this possibility seems unlikely. The exact age at which maternal antibodies against HTLV-I are no longer detectable in an infant's serum is not known. However, on the basis of data for antibodies against most other viral agents, it is reasonable to assume that at least up to the age of 6 months one might be measuring passively transmitted maternal antibody. In the present study the youngest child over 6 months of age and showing detectable antibody was 2 years old; thus it is clear that antibodies against HTLV-I can be produced early in life.

The finding that 55% of the adult (over age 15) patients with NHL in Jamaica are HTLV-I antibody-positive confirms our previous report that HTLV-I infection is a significant etiologic factor for lymphomas in this region (Blattner *et al.*, 1983*a*). The slightly greater number of male HTLV-I-positive cases (19 males versus 17 females) is similar to that reported for Japan although the median age of the Jamaican cases (43.6 years) is younger than that reported for Japan (51 years) (Takatsuki *et al.*, 1979). The most important distinguishing clinical and pathologic features of the HTLV-I antibody-positive cases were: a high frequency of hypercalcemia, leukemia, skin involvement, and histologically pleomorphic or mixed-cell lymphoma, all previously well-characterized features of ATL (Blayney *et al.*, 1983). The clinical and pathological features of the NHL cases have been reported in detail elsewhere (Gibbs *et al.*, 1983).

Although our data suggest that HTLV-I antibody prevalence is higher among patients with certain malignancies (CLL, ALL, myelogenous leukemias, MF, malignant histocytosis, and breast cancer) than in the individuals without malignancies, this is based on a small number of cases and none of these values were statistically significantly different from those pertaining to age-matched individuals without malignancies. Whether the presence of HTLV-I is related to the disease in any of these cases or is a coincidental finding, possibly due in part to an increased number of blood transfusions in patients with malignancies, is still not known. The study of such cases for a possible direct or indirect role of HTLV-I infection in the etiology of the disease is currently under intensive investigation (Gallo and Wong-Staal, 1984).

There was no increase in prevalence of HTLV-I antibodies in patients with autoimmune diseases (primarily systemic lupus erythematosus) or non-malignant dermatologic conditions (see Table IV). The fact that 2/4 hemophiliacs were antibody-positive is most likely due to their frequent transfusion with blood and blood products. HTLV-I has been previously shown to be transmitted by blood (Okochi *et al.*, 1984; Miyamoto *et al.*, 1983) and United States hemophiliacs have a higher prevalence of antibodies against HTLV membrane antigen than the matched population, although it is likely that the majority of these cases represent detection of cross-reactive antigens of HTLV-III (Evatt *et al.*, 1983).

We did not detect a higher than expected prevalence of HTLV-I antibodies overall in patients with a primary diagnosis of infection (Table IV). However, the fact that 2/3 antibody-positive persons with a diagnosis of infection had parasitic infections which are more common in immunocompromised individuals is interesting since there is evidence that HTLV-I alters immune function *in vitro* and HTLV-I infected ATL patients are immunosuppressed (Popovic *et al.*, 1984; Yamada *et al.*, 1983; Sato *et al.*, 1982). Whether HTLV-I infection frequently causes immunosuppression in infected individuals who do not have ATL is not yet known and it is certainly possible that the infections reported here are coincidental. Further studies are needed to determine the possible role of HTLV-I infection in the etiology of diseases other than ATL.

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