

Role of HTLV-I in development of non-Hodgkin lymphoma in Jamaica and Trinidad and Tobago

Angela Manns, Farley R Cleghorn, Roni T Falk, Barrie Hanchard, Elaine S Jaffe, Courtenay Bartholomew, Patricia Hartge, Jacques Benichou, William A Blattner and the HTLV Lymphoma Study Group

Summary

Human T-cell lymphotropic virus type I (HTLV-I) has been implicated in the aetiology of adult T-cell leukaemia/lymphoma in Japan and elsewhere, particularly the Caribbean. We have carried out parallel case-control studies in Jamaica and in Trinidad and Tobago to quantify the role of HTLV-I in the development of non-Hodgkin lymphoma (NHL).

135 cases of NHL were enrolled in Jamaica and 104 in Trinidad and Tobago. Controls were selected from patients treated in the same wards or clinics at the same time as the cases. Overall, patients with NHL were 10 times more likely than were controls to be seropositive for HTLV-I (Jamaica odds ratio 10.3 [95% CI 6.0-18.0]. Trinidad and Tobago 14.4 [7.6-27.2]). In both countries the association between NHL and HTLV-I was greatest for T-cell lymphomas (18.3 [9.5-35.6] and 63.3 [25-167]). Among T-cell lymphomas especially, there was no significant difference between men and women in the association between NHL and HTLV-I, but there was a significant inverse relation between age and likelihood of HTLV-I seropositivity. B-cell lymphomas were predominant in the older age groups and were not associated with HTLV-I seropositivity.

These findings are consistent with the hypothesis that early life exposure to HTLV-I is important for risk of subsequent ATL. Prevention of vertical transmission of HTLV-I could reduce by 70-80% cases of NHL in people under 60 years in this region.

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Introduction

Non-Hodgkin lymphoma (NHL) is a lymphoproliferative neoplasm, which derives much of its heterogeneity from the range of T and B lymphocytes that are the target of malignant transformation. Although the aetiology is multifactorial, insights gained from classification of the tumours by cell types have generated new approaches for investigation.¹ Such studies led to the identification of a new clinical and pathological entity, adult T-cell leukaemia/lymphoma (ATL) in Japan.² Its aetiological agent, human T-cell lymphotropic virus type I (HTLV-I), the first human retrovirus,³ was subsequently discovered and implicated in the causation of ATL in many parts of the world, particularly in the Caribbean.⁴⁻⁶ World wide, there is close concordance between areas of HTLV-I endemicity and ATL occurrence but systematic analyses of comparative features and risk factors outside Japan are lacking. In this investigation, parallel case-control studies with similar designs were undertaken in Jamaica and in Trinidad and Tobago to quantify the risk associated with HTLV-I infection in the development of NHL.

Subjects and methods

The protocol was approved by the institutional review boards of the University of the West Indies, the Caribbean Epidemiology Center, and the National Cancer Institute. In Jamaica, all incident cases of NHL reported to the Jamaica Cancer Registry and the Department of Pathology at the University of the West Indies between May, 1984, and July, 1987, were eligible for enrolment. We believe that most cases diagnosed in Jamaica were included, since the University Hospital is the main site of pathology review and cancer treatment for the whole country. In Trinidad and Tobago, the study took place at two general hospitals, which are the main referral centres for diagnosis and treatment of haematological malignant disorders for the whole country. All incident cases of NHL reported between October, 1985, and June, 1992, were eligible for enrolment.

Case ascertainment initially included all cases of haematological malignant disorders, because at the start of the study, the clinical range of ATL in relation to other NHLs and leukaemias was not known for Jamaica or Trinidad and Tobago. Each lymphoma case was clinically staged by the Ann Arbor Classification and histologically classified based on the recommendations of the National Cancer Institute Working Formulation⁷ and the Lymphoma Study Group of Japan.⁸ Lymphoma cases were immunophenotyped and classified as T or B cell by study of peripheral blood lymphocytes if circulating malignant cells were present, of fresh tumour tissue, or of paraffin-embedded tumour tissue.^{9,10} Cases that could not be classified as T-cell or B-cell phenotype by these methods were designated indeterminate or unclassified. Patients for whom appropriate material for typing was not available, but who were histologically confirmed as having NHL, were included for analysis.

In both study sites, controls were selected from patients treated in the same hospital ward or outpatient clinic at the time of the case diagnosis, and matched by sex and age within 10 years. The case and control groups were limited to subjects aged 14 years and above. Because NHL was related to human immunodeficiency

Epidemiology and Biostatistics Program, Division of Cancer Etiology (A Manns MD, F R Cleghorn MD, R T Falk MS, P Hartge MD, J Benichou MD, W A Blattner MD), and Laboratory of Pathology (E S Jaffe MD), National Cancer Institute, Bethesda, Maryland, USA; Department of Pathology, University of the West Indies, Kingston, Jamaica (B Hanchard FRCP); and Department of Medicine, Port-of-Spain, Trinidad (Prof C Bartholomew MD)

Correspondence to: Dr Angela Manns, Viral Epidemiology Branch, National Cancer Institute, 6130 Executive Blvd 434, Rockville, Maryland 20852, USA

virus infection and HTLV-I was linked to tropical spastic paraparesis after the study was set up, subjects with these diagnoses were later excluded from the control groups.

Serum was stored at -70°C until analysis for antibodies to HTLV-I at the National Cancer Institute, initially by whole virus enzyme-linked immunosorbent assay (ELISA; Dupont, Wilmington, Delaware, USA) and recombinant gp21 envelope ELISA (Cambridge-Biotech, Rockville, Maryland). Seropositive samples were confirmed with western blot (Cambridge-Biotech). The definition of seropositivity on western blot, required the presence of *gag*, anti-p24 and *env*, anti-gp46 or anti-rgp21.¹¹ Serum from a subset of lymphoma patients who were seropositive for HTLV-I was also tested by the polymerase chain reaction to distinguish HTLV-I from HTLV-II; we found no evidence of HTLV-II (data not shown).

The odds ratio estimate of the relative risk was used to measure the association between NHL and HTLV-I and 95% CI were calculated. Unconditional logistic regression models¹² were used to obtain odds ratios with adjustment for age, race (for Trinidad and Tobago), sex, and study site. In most instances, adjustment for these factors did not affect the odds ratio so, unless indicated, crude odds ratios are reported. Data were classified by race, sex, and age group to assess age-specific differences in development of NHL. The population attributable risk was estimated to measure the proportion of NHL related to HTLV-I infection by the method described by Bruzzi et al¹³ for case-control data and corresponding 95% CIs were obtained.¹⁴ Differences in means were tested by Student's *t* test and differences in proportions by the chi-square test or Fisher's exact test. A chi-square test for homogeneity was used to compare odds ratios.

Results

In Jamaica, HTLV-I results were available for 135 cases of lymphoma, 80 of other haematological malignant disorders, and 380 controls. 4 controls with a diagnosis of tropical spastic paraparesis were withdrawn from the study. The seroprevalence of HTLV-I among the 376 remaining controls was 7%, which is similar to the 6% prevalence reported from population survey data.¹⁵ In Trinidad and Tobago, HTLV-I results were available for 104 cases of lymphoma, 89 of other haematological malignant disorders, and 355 controls. The seroprevalence of HTLV-I among controls was 6%, which was somewhat higher but not significantly different from the 3% prevalence reported in an occupational cohort.¹⁶ To rule out the possibility that haematological malignant disorders other than T-cell NHL might be linked to HTLV-I, we looked at several other classes of disease (table 1). HTLV-I was not associated with other haematological malignant disorders overall (odds ratio 0.7 [0.2-2.0] for Jamaica, 1.4 [0.5-3.7] for Trinidad and Tobago), or independently. We separated cases of

chronic lymphocytic leukaemia from other NHL because of previous reports¹⁷ of an HTLV-I association with this disease; no case was HTLV-I seropositive. Among T-cell lymphomas a higher proportion was HTLV-I seropositive in Trinidad and Tobago than in Jamaica (34 [79%] of 41 [59%], $p=0.03$). Most of the cases of lymphoma enrolled in this study were T cell (65% and 55% of lymphomas with immunophenotyping available in Jamaica and Trinidad and Tobago, respectively).

Overall, NHL patients were at least 10 times more likely to be HTLV-I seropositive than were controls. B-cell lymphomas were not associated with HTLV-I infection; only 1 B-cell lymphoma patient in each country was seropositive for HTLV-I. In both countries, the strongest association with HTLV-I was for T-cell lymphomas. The association of HTLV-I infection with T-cell lymphomas was significantly stronger ($p=0.02$) in Trinidad and Tobago than in Jamaica.

Only 10% of lymphomas in each country were classified as indeterminate or were not classified; they resembled T-cell lymphomas in their relative risk of HTLV-I infection. Cases that were histologically classified as NHL, but not immunophenotyped, had odds ratios intermediate between B-cell and T-cell lymphomas, which suggests that lymphomas of both origins were represented.

Although the distribution of NHL was similar in Jamaica and Trinidad and Tobago, racial or ethnic risk differences for the populations were postulated. Jamaica and Trinidad and Tobago have distinct sociodemographic features. Jamaica has a population predominantly of African descent, whereas Trinidad and Tobago have a more racially diverse population—40% people of African descent, 40% people originating from the Indian subcontinent, and 16% mixed race.

Since the prevalence of HTLV-I infection is highest in people of African descent,¹⁸ we expected to find fewer HTLV-I-positive cases among other racial groups in Trinidad and Tobago. We found that 85% of patients with NHL in Trinidad and Tobago (especially those who were HTLV-I positive) were of African descent. Among the other racial groups, only 2 of 34 (6%) patients were HTLV-I seropositive, and both had T-cell lymphomas with features histologically and clinically distinct from most of the lymphomas in individuals of African descent. In Jamaica, 97% of NHL cases were among people of African descent.

There was a slight male predominance of NHL in both Jamaica and Trinidad and Tobago, whereas for T-cell

Group	Jamaica			Trinidad and Tobago		
	HTLV positive	HTLV negative	Odds ratio (95% CI)	HTLV positive	HTLV negative	Odds ratio (95% CI)
Controls	27	349	1.0	20	335	1.0
Other malignant disorders						
CLL	0	13	0.4 (0.5)	0	8	0.0 (0.6)
Myeloma	0	71	0.2 (0.7)	3	21	2.4 (0.4-9.1)
Hodgkin's	1	11	1.0 (0.03-6.7)	0	13	0.6 (0.1)
Other*	3	31	1.3 (0.2-4.4)	4	40	1.7 (0.4-5.4)
NHL						
B-cell	1	23	0.5 (0.01-3.3)	1	24	0.7 (0.02-4.5)
T-cell	41	29	16.3 (9.5-33.6)	34	9	63.3 (25-167)
Indeterminate	7	6	15.1 (4.0-57.6)	4	6	11.2 (2.1-50.8)
Not†	11	17	6.4 (3.3-21.3)	9	17	8.9 (3.2-24.5)
All lymphomas	61	74	10.3 (6.0-15.0)	48	56	14.4 (7.6-27.2)

CLL = chronic lymphocytic leukaemia.

*Acute or chronic myelocytic leukaemia, acute lymphocytic leukaemia. †Typing not available. ‡No exposed case, leading to null estimate of odds ratio.

Table 1: Odds ratios for HTLV-I infection among patients with haematological malignant disorders and in hospital controls

Age group (yr)	Odds ratio (95% CI) for HTLV-I seropositivity*	
	All lymphomas†	T-cell lymphomas
<40	35 (15-82)	93 (34-259)
41-59	9 (5-17)	26 (11-62)
≥60	5 (2-11)	6 (2-17)

*Among subjects of African descent; adjusted for sex and study area. Includes T-cell, B-cell, indeterminate, unclassified, and untyped cases.

Table 2: HTLV-I risk estimates for NHL in Jamaica and Trinidad and Tobago

NHL women were as likely to have HTLV-I-associated disease as were men. There was no significant difference between men and women in the likelihood of HTLV-I infection in Jamaica (odds ratios 25.7 [9.1-73] for men and 15.8 [6.8-37] for women) or in Trinidad and Tobago (58.9 [17.7-196] for men and 53.1 [11.3-251] for women). Patients with T-cell, HTLV-I-seropositive lymphomas were more likely to be female in Jamaica than in Trinidad and Tobago, but this difference was not significant.

Age was a significant determinant of HTLV-I-associated NHL. For all NHL, the mean age at diagnosis was 46 (range 14-79) years in Jamaica and 52 (15-84) years in Trinidad and Tobago; the mean age at diagnosis was lower for HTLV-I-positive, T-cell lymphomas (39 in Jamaica and 46 in Trinidad and Tobago), but not significantly so. To assess the effect of age on HTLV-I risk, patients and controls of African descent from Jamaica and Trinidad and Tobago were analysed together (table 2). There was an inverse relation between age and likelihood of HTLV-I seropositivity. NHL patients under 40 years were 35 times more likely than controls were to be seropositive, whereas for patients and controls over 60 years old, the increase in risk was only 5-fold. Among T-cell lymphomas, the association with HTLV-I was very strong in the youngest age group, less strong but significant in the age group 40-59 years, and weakest in the oldest age group. B-cell lymphomas, rather than T-cell lymphomas, were predominant in the older age group and were not associated with HTLV-I.

The attributable risk percentage, or the aetiological fraction, of NHL and T-cell NHL due to HTLV-I infection was calculated from the data collected in this case-control study. The attributable risk takes into account the strength of association between HTLV-I and NHL as well as the prevalence of HTLV-I. Among all patients with lymphomas enrolled in this study, 41% and 44% of cases in Jamaica and Trinidad and Tobago, respectively, can be explained by HTLV-I infection. HTLV-I accounts for even higher proportions of T-cell lymphomas—56% in Jamaica and 78% in Trinidad and Tobago. Consistent with

	Population attributable risk (95% CI)			
	Jamaica		Trinidad and Tobago	
	All lymphomas	T-cell lymphomas	All lymphomas	T-cell lymphomas
Overall	41 (32-52)	56 (43-68)	44 (32-53)	78 (62-88)
By sex				
Male	33 (23-45)	45 (30-66)	45 (32-57)	79 (59-91)
Female	50 (36-64)	62 (44-77)	39 (32-57)	75 (46-91)
By age group				
<40 yr	53 (36-67)	71 (53-85)	45 (29-61)	83 (58-95)
41-59 yr	45 (30-61)	60 (39-78)	49 (32-67)	75 (49-91)
≥60 yr	16 (6-36)	2 (0-99.8)*	27 (11-54)	69 (27-92)

Overall estimates adjusted for age (according to age groups presented) and sex; sex-specific estimates adjusted for age; age-specific estimates adjusted for sex; in addition for Trinidad and Tobago, all categories adjusted for race. *Based on only one exposed case.

Table 3: Population attributable risks for HTLV-I-associated NHL

the decline in HTLV-I risk observed with age, most lymphomas, especially T-cell lymphomas in subjects younger than 60 can be accounted for by HTLV-I infection (about 80%). In Jamaica, HTLV-I exposure explained more of the NHL case load among women than among men, despite the similar magnitude of association (odds ratios 10.3 [5.8-20.9] and 14.9 [6.3-35.3], respectively). This difference accords with the finding from population surveys that HTLV-I is more prevalent among women in this age group.

Discussion

World wide, NHL incidence has increased during the past 15 years. The increase has come mainly in B-cell lymphomas in developed countries.¹⁹ Rates in the Jamaica Cancer Registry remained stable between 1958 and 1987,²⁰ which suggests that exposure to important aetiological factors has remained relatively constant. Our study identified HTLV-I as an important factor in the aetiology of NHL in Jamaica and Trinidad and Tobago.

The features of our patients²¹ resemble those of ATL syndrome reported by Takatsuki et al² from Japan and, as such the pattern of NHL differs from that in the USA and Europe.^{22,23} Patients in the West Indies tend to present at a more advanced stage and are likely to have hypercalcaemia, skin infiltration by malignant cells, leukaemic manifestations, and a rapidly progressive clinical course with overall poor survival.²¹ Our results confirm the predominance of T-cell NHL and the clinical and virological features of most T-cell NHL were consistent with lymphoma-type ATL.²⁴ Japan, by contrast, has predominantly acute-type ATL. It is possible that racial, ethnic, or environmental factors may influence the pattern of disease manifestations.

Elimination of the risk of NHL due to HTLV-I infection in Jamaica and Trinidad and Tobago would prevent nearly half the lymphomas in susceptible hosts, and the distribution of lymphoma immunophenotypes would then resemble that seen in the USA and Europe.²² The incidence of NHL in Jamaica and Trinidad and Tobago increases with age and is higher among men than women.^{20,21} Although HTLV-I seroprevalence also increases with age, women are twice as likely as men to be seropositive at all ages.¹⁵ HTLV-I risk did not differ by gender, but because of the higher prevalence in women, viral exposure explained a higher proportion of female cases in Jamaica. Other exposures, through occupation or environment, may contribute to the lymphoma case load in Jamaican men and will be examined elsewhere.

Early-life exposure to the HTLV-I virus, through mother-to-infant transmission, has been postulated to pose the greatest risk for subsequent development of ATL.²⁵ We found that the HTLV-I association with NHL was strongest in people under 40 years old at diagnosis and declined with age, especially among patients with T-cell lymphoma. It has been suggested that many other oncogenic "stimuli" are involved in the process leading to malignant transformation.²⁶ Assuming a 10-40-year latent period between childhood HTLV-I exposure and development of a malignant disorder, our findings are consistent with this hypothesis. Further, the declining risk for HTLV-I-associated malignant disorders in the oldest age group suggests that there is a finite latent period between exposure and ATL development. Our findings have important public health implications, since elimination of HTLV-I could lead to as much as an 80%

reduction of lymphoma cases under the age of 60. Studies to find out the best approaches to interrupting mother-to-infant transmission where breastfeeding is unavoidable should have high priority. Clarification of the intervening steps of malignant transformation and strategies to reverse this process are needed to help people already infected.

Although animal models have not been developed to support the HTLV-I early exposure hypothesis, the feline leukaemia virus, an animal retrovirus, proves this hypothesis in the pathogenesis of leukaemia and lymphoma in cats.^{27,28} The latent period between virus exposure and subsequent development of leukaemia depends on the age of the cat, time of virus exposure, strain of virus, virus dose, and serological status of the cat. These factors presumably operate to determine the immunophenotype and characteristics of leukaemias and lymphomas among cats. In kittens infected immediately after birth, lymphoma develops at 9 weeks, whereas kittens inoculated at 8 weeks develop lymphomas between 5 and 24 months. Other human cancers linked with virus exposure,²⁹ such as hepatitis B in hepatocellular carcinoma and Epstein-Barr virus in Burkitt's lymphoma, are also postulated to have a critical period for virus exposure during early life as a major determinant in subsequent development of the malignant disorder. A multi-step model for lymphomagenesis in the subsequent development of ATL is likely,³⁰ with early life exposure to HTLV-I serving as an initiator of the malignant process, and other intermediate factors that are host or environmentally determined.

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