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Racial and other characteristics of human T cell leukaemia/lymphoma (HTLV-I) and AIDS (HTLV-III) in Trinidad

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Abstract

Adult T cell leukaemia/lymphoma was first recognised as a clinical entity in southwest Japan. Subsequently the Caribbean has been found to be another area where the disease is endemic, and sporadic cases have been identified in different parts of the world. The human T cell leukaemia/lymphoma virus (HTLV-I) is causally related to adult T cell leukaemia/lymphoma. A subgroup of HTLV, designated HTLV-III, has recently been isolated from many patients with the acquired immunodeficiency syndrome (AIDS) and preAIDS, and there is now evidence that this variant is the primary cause of AIDS. This is the first report from Trinidad to describe 12 cases of adult T cell leukaemia/lymphoma and 14 of AIDS. All were in patients of African descent. No cases were seen in subjects of East Indian descent, who, like those of African descent, comprise as much as 40% of the population.

West Indians of African descent may have increased susceptibility to infection with both HTLV-I and HTLV-III.

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Introduction

Retroviruses have been linked to leukaemia in many animal species, and the search for a human retrovirus was first accomplished with the discovery of a type C retrovirus of truly human origin by Gallo and coworkers, which was quite distinct from any known animal retrovirus. This agent, the human T cell leukaemia/lymphoma virus type I (HTLV-I), was initially isolated from two black adults said to have mycosis fungoides and the Sézary syndrome[1 2] but who in retrospect had adult T cell leukaemia/lymphoma.

The link of HTLV-I to this clinical entity was made in serological studies of Japanese patients with adult T cell leukaemia/lymphoma, by the recognition that HTLV-I associated patients in the United States had this syndrome, and by the observation of the clinical syndrome in six black patients in London who originated from the West Indian islands St Vincent, Grenada, and Trinidad and from Guyana,[3] all of whom were shown to be positive for HTLV-I antibodies.[4] Before this, no such cases had been reported in West Indians living in the West Indies.

Subsequently the detection of antibody positive carriers in the region supported the concept that the West Indies are an HTLV-I endemic region.[5] Further support for this concept has come from studies in Jamaica,[6] where 11 (69%) of 16 consecutive patients with non-Hodgkin's lymphoma newly diagnosed between 1 February 1982 and 31 January 1983 had antibodies to HTLV-I in their sera.

A retroviral aetiology for the acquired immune deficiency syndrome (AIDS) was suggested initially by the finding of antibodies to HTLV-I in a high proportion of patients with AIDS, using an HTLV-I membrane antigen assay.[7] AIDS is, however, rare or absent in most areas where HTLV-I is endemic. This discrepancy has been clarified by the recent

discovery of a distinct but distantly cross reactive class of human retroviruses, HTLV-III, which has similar cellular trophism to HTLV-I but with a pronounced cytopathic effect.[8]

Here we summarise the features of the distribution of both these agents in an island (Trinidad) where HTLV-I is suspected to be endemic and their relations to adult T cell leukaemia/lymphoma and AIDS. The first case of adult T cell leukaemia/lymphoma was diagnosed in May 1982 and that of AIDS in February 1983. This case series represents all such patients seen up to June 1984.

Patients and methods

Adult T cell leukaemia/lymphoma—The morphology of the lymphoid cells in the peripheral blood and bone marrow was examined by light microscopy on films stained with the Wright-Giemsa stain. Calcium concentrations were determined using autoanalyser methods. Carboxyterminal parathyroid hormone assays were performed. The presence of T lymphocytes in the peripheral blood was determined in three patients by rosette formation with red cells from sheep after cytocentrifuged preparations had been stained with brilliant cresyl blue. Sera were collected under sterile conditions and stored at −70°C until assayed for HTLV-I antibodies.

AIDS—Patients with AIDS were selected by the diagnostic criteria proposed for defining AIDS by the Centre for Disease Control. Sera were collected under sterile conditions and stored at −70°C until assayed for HTLV-III antibodies.

HTLV antibody assays—All sera were tested for HTLV antibodies by an indirect enzyme linked immunosorbent assay (ELISA) as previously described,[9] using disrupted whole purified virus as the antigen. Antibodies to HTLV-I were confirmed by blocking with virus specific heteroantisera.[10] Antibodies to HTLV-III were confirmed by Western blot analysis[11 12] in samples with binding ratios exceeding 3·0. Titration data were obtained from serial dilutions of test samples using the standard ELISA protocol and an end point value of one to 20 for dilution of standard normal serum.

Results

ADULT T CELL LEUKAEMIA/LYMPHOMA

Table I summarises the main clinical data on the patients with adult T cell leukaemia/lymphoma.

Haematological findings—Anaemia was absent or mild. The leukaemic cells were characterised by pleomorphism, and the nucleic deformities varied in different patients from convolutions to lobulations, indentations, or, sometimes, cerebriform appearances. In one patient (case 8) some of the proliferating cells had features of prolymphocytes. Maximum leucocyte counts ranged from $9{\cdot}2 \times 10^9$/l to 293×10^9/l (mean value 112×10^9/l). The mean proportion of lymphocytes in the peripheral blood was 60·3% (range 9-96%). Bone marrow was affected in eight patients (67%).

Histopathology—All the lymph nodes of the patients examined in this study were of the diffuse lymphoma type, usually diffuse poorly differentiated lymphocytic non-Hodgkin's lymphoma as classified in the Rappaport scheme. One patient (case 3) had a mixed lymphocytic histiocytic picture (mixed small and large cells).

Calcium studies—Seven patients (58%) had hypercalcaemia. One (case 4) presented with bone pain and was found to have widespread osteolytic bone lesions; he died in hypercalcaemic coma. In another patient (case 6) parathyroid hormone assay was 973 pg/ml (normal range 150-450 pg/ml) but no bone lesions were seen. On the other hand, in a third patient (case 7) one osteolytic lesion was found in his skull but the only test for serum calcium concentration done was normal.

Skin lesions—The affinity that the malignant cells of cutaneous T cell lymphomas display for the skin becomes apparent as clinically evident cutaneous infiltrations, present in eight patients (67%). All the biopsies of the skin were diagnostic of lymphoma. Most of these eight patients (table I) had generalised nodular lesions. One patient (case 11) had maculopapular lesions restricted to the palms and soles. Another (case 8) had a diffuse erythroderma. In a third (case 3) the skin lesions presented two years before the appearance of enlarged lymph nodes and a clinically aggressive course.

Immunological cell marker studies—In three patients (cases 5, 10, and 11) E rosette studies were done and the E rosette positive cells represented 92%, 80%, and 92·3%, respectively, of the lymphoid cells.

HTLV-I antibody studies—All the sera from the patients contained antibody to HTLV-I, with titres ranging from 20 to 140 000.

AIDS

Table II gives details of the patients with AIDS. All were homosexual men of African descent. The opportunistic infections of these patients were due to *Cryptococcus neoformans*, *Toxoplasma gondii*, *Candida albicans*, histoplasmosis, tuberculosis, *Herpes simplex*, and *Pneumocystis carinii*. There was only one patient with Kaposi's sarcoma, and one patient had a Burkitt's like lymphoma.

HTLV-III antibody studies—The sera of 11 patients were positive for antibodies to HTLV-III, with titres ranging from 8694 to 791 108. The sera of three patients who died were unavailable for study.

TABLE II—*Characteristics of patients with AIDS. (All patients were black men of African descent)*

Case No	Age (years)	Opportunistic infections	HTLV-III antibody titre
13	25	*Candida albicans* *Cryptococcus neoformans*	NT
14	26	*Toxoplasma gondii*	519 686
15	34	*Candida albicans* *Herpes zoster* Burkitt's like lymphoma	336 182
16	27	*Toxoplasma gondii*	NT
17	25	*Candida albicans* *Histoplasma capsulatum*	791 108
18	45	Kaposi's sarcoma *Toxoplasma gondii*	41 500
19	23	*Histoplasma capsulatum*	NT
20	27	*Candida albicans* *Pneumocystis carinii*	8 694
21	19	*Cryptococcus neoformans*	362 173
22*	44	*Mycobacterium tuberculosis* *Candida albicans*	306 606
23	29	*Mycobacterium tuberculosis*	35 153
24	28	*Pneumocystis carinii* *Candida albicans*	112 730
25	24	*Aspergillus* species	97 992
26*	23	*Cryptococcus neoformans*	213 025

*Still alive.
NT = not tested.

TABLE I—*Clinical and laboratory findings in patients with adult T cell leukaemia/lymphoma. (All patients were blacks of African descent)*

Case No	Age (years)	Sex	Lymphadenopathy	Hepatomegaly	Splenomegaly	Skin lesions	Calcium* (mmol/l)	Bone lesions	Maximum white cell count (×10⁹/l)	Proportion of lymphocytes (%)	Marrow affected	HTLV-I antibody titre	Survival (months)
1	22	F	+	+	+	+	30·9	−	220	87	+	800	1
2	23	F	+	+	−	+	NT	−	209	58	+	1600	5
3	63	M	+	+	−	+	37·2	−	10·2	12	−	140 000	32
4	66	M	+	+	−	−	41·9	+	37·9	9	−	20	5
5	72	M	−	+	+	−	24·7	−	160	96	+	82 000	4
6	46	M	−	+	+	−	37·1	−	293	96	+	2350	3
7	44	M	+	−	−	+	25·2	+	24·7	28	−	1300	1
8	84	M	+	+	+	+	19·2	−	151	89	+	20	9
9	29	M	+	+	+	−	46·7	−	9·2	12	−	5900	9
10	41	M	+	+	−	+	27·0	−	32·9	56	+	82 500	9
11	39	F	+	−	+	+	35·7	−	134	91	+	2560	4
12	60	F	+	+	+	+	21·5	−	58·5	90	+	10 000	4

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml.
*Normal range 21·5-26·5 mmol/l.

Discussion

Adult T cell leukaemia was first recognised as a new clinicopathological entity of T cell malignancy by Takatsuki *et al.*[13] A striking feature of the disease was that it was restricted to the Kyushu and Shikoku districts in southwest Japan. This geographical localisation suggested that some unique factors were involved in adult T cell leukaemia, and an infectious aetiology was postulated. The link, however, to a retroviral aetiology emerged only with the discovery of HTLV-I by Poiesz *et al.*[1 2] A unifying hypothesis linking exposure to this virus to this particular disease has emerged from the recognition of geographical clusters of cases of adult T cell leukaemia/lymphoma not only in Japan but also in blacks from the southern United States and the West Indies. In addition, sporadic cases from widely dispersed geographical areas have been recognised by their characteristic clinicopathological features and the presence of retroviral antibodies.[14]

A study in Jamaica showed that, of 16 consecutive patients presenting with non-Hodgkin's lymphoma, 11 (69%) had antibodies to HTLV-I in their sera and that these 11 patients shared features with those documented in this report from Trinidad as well as those reported from Japan.[6] Thus the West Indies is clearly another area, in addition to southwest Japan, where adult T cell leukaemia/lymphoma is endemic. More recently, nine (20%) of 44 patients with lymphoproliferative diseases in the French West Indies (Martinique) were found to be positive for HTLV-I antibodies.[15]

In the United Kingdom the HTLV-I disease association has to date been restricted to first generation immigrants from the West Indies.[3] Several of these patients had lived in the United Kingdom for as long as 20 years, suggesting a long latent period between infection and overt lymphoma/leukaemia.

Antibodies against HTLV-I have also been found in six (3·7%) of 161 blood donors[16] and in two patients with lymphoproliferative disease in Nigeria.[17] Although suggestive, it is as yet too early to conclude that Nigeria represents another cluster area for HTLV-I associated disease. In all these locales where clusters of adult T cell leukaemia/lymphoma have been found high titres of background infection in the normal population have been detected and persistent infection for over 10 years documented in at least one case without obvious clinical disease.[4] Our findings in these 12 patients with adult T cell leukaemia/lymphoma in Port of Spain, Trinidad, suggest, although this is unconfirmed, that endemic infection with HTLV-I is likely to be found to be widespread. A survey to investigate this is currently under way.

Simple infection per se with HTLV-I is thus not in itself sufficient to induce adult T cell leukaemia/lymphoma as not only do many people without leukaemia manifest persistent antibodies to HTLV-I[4] but in some cases they harbour the virus in some of their peripheral blood T cells.[18] It thus seems important in the future to clarify what, if any, factors are important during the latent period from viral infection to onset of disease and which subjects giving a positive result are likely to develop the disease. The mechanism whereby HTLV-I transforms T cells into tumour cells is also important and may include a process of transcriptional activation of gene transactins as proposed recently by Haseltine *et al.*[19]

Most of the cases reported outside Japan have been in blacks, suggesting that some unique geographical and racial determinants are important in the pathogenesis of this disease. Notably, to date, this disease in Trinidad has been seen only in blacks, and a study of the population prevalence of HTLV antibodies in Trinidad and Tobago is now under way, the results of which should help to confirm whether there is a definite racial predisposition for the virus or associated disease, or both.

In the original study of West Indian immigrants in the United Kingdom four of the six patients were women,[3] and in the Jamaican study 12 of the 19 patients with lymphoproliferative malignancies and positive for HTLV-I antibodies were women.[6] This led Blattner *et al* to comment that in the study in the United Kingdom selective migration patterns would have contributed to the excess of women and that the Jamaican series suggested a true preponderance of women, reflecting either an underlying disproportionate population prevalence of HTLV infection among women or an unexplained susceptibility of women to the disease.[6] On the other hand, our report has shown a distinct male excess (eight men to four women). As these series comprised relatively small numbers of patients larger numbers of patients should help to clarify this pattern.

One of the striking features of adult T cell leukaemia/lymphoma is the tendency of cases to be clustered geographically. This has certainly been noticeable in Japan and may be found in the West Indies as well. There is, however, a tendency for the West Indian islands, strewn as they are over 1700 km, to be considered to have identical disease patterns. As is well recognised with respect to other living conditions, however, the geographical distribution of many diseases is not uniform in these islands so that studies of the prevalence of HTLV antibodies in different locales in the region need to be undertaken. For example, it is interesting that no clinical cases of adult T cell leukaemia/lymphoma have been recognised so far in Barbadians living in Barbados.

None the less the overall data suggest that adult T cell leukaemia/lymphoma is widely distributed in the West Indies with a predilection for affecting blacks. Gallo *et al* suggested that the ancestral origin of HTLV-I was Africa and that the HTLV in the Caribbean, the United States, and South America probably originated from entry of infected Africans to the Americas.[20]

Both adult T cell leukaemia/lymphoma and AIDS have, however, only recently been recognised as clinical entities in Trinidad. The first cases of HTLV-I related disease, adult T cell leukaemia/lymphoma, were diagnosed in May 1982, and in February 1983 Bartholomew *et al* diagnosed the first case of AIDS in Trinidad.[21 22] This was also the first report of AIDS from any of the West Indian islands and now appears to be linked to a new subgroup designated HTLV-III, a cytopathic variant. Since then 14 cases of AIDS have been confirmed in Trinidad, but, to date, no cases have been reported from the other West Indian islands.

All the patients with AIDS in Trinidad were male homosexuals. Only two, however, gave a history of sexual encounters with American homosexuals. There were no Haitian or Zairian connections, and none of them had had any contact with any known patients with AIDS in Trinidad. Antibodies to HTLV-III were found in the sera of all the patients tested.

To date, Trinidad is the only island of the West Indian chain where AIDS and HTLV-I disease have been reported. Unlike adult T cell leukaemia/lymphoma, which affects heterosexual men and women, the AIDS agent in Trinidad appears to be restricted to a single at risk population, in contrast with the pattern in Zaire and Haiti.

It is believed that the small homosexual population in Trinidad spans all ethnic groups, and it is therefore noteworthy that so far all the cases of AIDS in Trinidad have been found only in blacks as have all cases of adult T cell leukaemia/lymphoma. The importance of this becomes more obvious when it is appreciated that this island is the most cosmopolitan of the West Indian chain, with a population of 1·05 million people comprising blacks of African descent (41%), East Indians (40%), people of mixed race (16%), whites (1%), Chinese (1%), and others (1%). This suggests that people of African descent may have some genetic predisposition or other factors explaining the occurrence of HTLV-I and HTLV-III associated diseases in this population. In view of this it is interesting that to date no cases of AIDS or adult T cell leukaemia/lymphoma have been reported from India or in patients of East Indian origin. Much more information, however, is needed before these suggestions can be confirmed.

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Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalised anxiety

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Abstract

A group of patients suffering from anxiety, as assessed by general practitioners and psychologists using research criteria for generalised anxiety, were treated with either diazepam or placebo double blind for six weeks. This active treatment period was preceded by a one week single blind placebo "wash in" period and followed by a two week single blind placebo "wash out" period. The results suggest that diazepam can produce rebound anxiety and withdrawal symptoms when used in moderate doses and for what has previously been regarded as a safe length of time. If replicated these results have implications for the therapeutic use of benzodiazepines.

Introduction

Benzodiazepines are among the most commonly prescribed drugs in the Western world. Each year about 14% of adults in the United Kingdom take a benzodiazepine as an anxiolytic or hypnotic.[1]

In 1977 diazepam was the drug most commonly prescribed by general practitioners, accounting for 4·3% of all prescriptions.[2] These figures reflect the tendency for most anxiety disorders to be treated in primary care, less than 10% being referred to psychiatrists.[3] Few studies assessing the efficacy of benzodiazepines, however, are carried out in a primary care setting; most are carried out with psychiatric outpatients.[4]

Despite the widespread use of benzodiazepines persistent criticisms have been raised about the lack of efficacy after prolonged use,[5-7] "rebound" anxiety,[8] and the emergence of withdrawal symptoms at the end of treatment.[9-11] Studies of the withdrawal of benzodiazepine after the administration of recommended short term therapeutic doses have been few.[6,12] In many cases high doses of benzodiazepines have been used[13-15] or patients have been maintained within recommended doses for prolonged periods (one to 16 years) before withdrawal of the drug.[16-18]

Our study compared the effectiveness of diazepam versus placebo in the management of generalised anxiety over a six week double blind period in a primary care setting. Withdrawal reactions from diazepam were investigated during a two week withdrawal period, when single blind placebo was substituted for the double blind active treatment. The effect of placebo on the state of anxiety at initial presentation was assessed during one week's single blind treatment with placebo before the double blind treatment was started.

Patients and methods

Patients were initially screened for psychological and physical morbidity by their general practitioner and were told the nature of the

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