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Screening for prolonged incubation of HTLV-I infection in British and Jamaican relatives of British patients with tropical spastic paraparesis

J K Cruickshank, J H Richardson, O St C Morgan, J Porter, P Klenerman, J Knight, A L Newell, P Rudge, A G Dalglish

Department of Medicine and Retrovirus Research Group, Northwick Park Hospital and Clinical Research Centre, Harrow HA1 3UJ

J K Cruickshank, MD, senior registrar
J H Richardson, PHD, research fellow
A L Newell, BSC, research officer
P Rudge, FRCP, consultant neurologist
A G Dalglish, FRACP, head of group

Faculty of Medicine, University of West Indies, Kingston 7, Jamaica
O St C Morgan, FRCP, professor
J Knight, medical student

Medical School, University of Oxford, Oxford
J Porter, medical student
P Klenerman, medical student

Correspondence to: Dr Cruickshank.

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Abstract

Objective—To compare the prevalence of antibody to and proviral DNA of the retrovirus HTLV-I in relatives of 11 British patients with tropical spastic paraparesis who had migrated from Jamaica before they developed symptoms, and to examine factors possibly related to transmission of HTLV-I.

Design—Migrant, family study. Antibody state was determined by several methods and confirmed by western blotting; the polymerase chain reaction was used to detect proviral DNA.

Setting—Britain and Jamaica.

Subjects—All available first degree relatives: those born and still resident in Jamaica (group 1); those born in Jamaica who migrated to Britain (group 2); and index patients' children who were born and resident in Britain (group 3). All had been breast fed and none had had blood transfusions.

Results—Of the 66 living relatives, 60 were traced. Seroprevalence among those born in Jamaica (irrespective of current residence) was 22% (10/46; 95% confidence limits 9 to 34%) compared with zero among British born offspring (0/14) and was higher in group 2 at 33% (7/21; 12 to 55%) than in group 1 at 12% (3/25; 0 to 25%). (Patients in group 1 had the greatest mean age.) Proviral DNA was not detected in any subject negative for HTLV-I antibody, making prolonged viral incubation in those negative for the antibody unlikely.

Conclusion—In this sample factors related to

place of birth and early residence were more important in transmission of HTLV-I than maternal or age effects. In areas with a low to moderate prevalence policies of preventing mothers who are carriers of the virus from breast feeding would be premature.

Introduction

The human T cell leukaemia lymphoma virus type I (HTLV-I) has been aetiologically related to the adult T cell leukaemia lymphoma syndrome¹ and, more recently, to tropical spastic paraparesis.²⁻⁴ Both diseases occur primarily in the major areas where HTLV-I is endemic—south western Japan and the Caribbean—but also develop in migrants from these regions.⁵⁻⁸ The cumulative lifetime risk of developing either disease in otherwise healthy people with antibodies against HTLV-I has been estimated at between 2% and 7% and rises with age.⁹⁻¹¹ Oddly, the risk of adult T cell leukaemia lymphoma is consistently greater in male carriers of HTLV-I than in female carriers, while that of tropical spastic paraparesis is greater in females and reflects the sex ratio of seroprevalence of HTLV-I in the population.

Known routes of HTLV-I transmission include transfusion with infected cellular blood products, sexual activity, and perinatal transmission from mother to child.¹²⁻¹⁴ Whether breast feeding or other perinatal routes are responsible is uncertain but of considerable

importance for public health. There is familial aggregation of HTLV-I infection and poor housing, and proximity to courses of water may increase seroprevalence in endemic areas.^{14 15} As the incidence of HTLV-I seropositivity rises with age it is not clear whether there is a prolonged incubation period of the virus in people negative for the antibody. The generally late onset of HTLV-I associated disease is, however, consistent with a prolonged incubation time between seroconversion and development of disease. These questions can be examined by studying migrants from areas of high prevalence to areas of low prevalence.

Migrant studies also help to dissect out the effects of lifestyle, climate, and other measurable variations (such as exposure to infection) on disease.¹⁶ Our previous studies of West Indian born migrants who developed tropical spastic paraparesis in Britain and had antibodies to HTLV-I suggested an average incubation period of 18 years, ranging up to 34 years, assuming that the patients were carriers of HTLV-I at the time of migration.^{7 8}

Family studies also provide a focus for analysing transmission and information critical to developing strategies to prevent or interrupt viral transmission. In this study we analysed familial aggregation of HTLV-I infection in all first degree relatives of our Jamaican born patients with tropical spastic paraparesis to seek clues to methods of HTLV-I transmission. We aimed at establishing the prevalence of HTLV-I antibodies and of integrated retroviral DNA in these people. We used the polymerase chain reaction, a highly sensitive method for detecting proviral DNA, to test whether seronegative family members might have viral genome sequestered in peripheral blood leucocytes without detectable antibody production.

Patients and methods

Our primary hypothesis was that there would be family clustering of HTLV-I infection. If transmission of HTLV-I occurs primarily in endemic areas such as Jamaica and to a much lesser degree in a temperate climate such as Britain HTLV-I antibodies would be most prevalent in relatives born and living in Jamaica (group 1), present at intermediate rates in relatives born in Jamaica and living in Britain (group 2), and minimal in offspring born in Britain (group 3). If there was excess family transmission the prevalence in each group would be greater than that in the comparable general population of the same age.

Clinical, neuroradiological, and serological details of 21 index patients with tropical spastic paraparesis have been described previously^{7 8}; the 19 women and two men, all positive for HTLV-I antibody, had been born in the West Indies and migrated to Britain an average of 29 years previously. Their mean (SD) age was 56 (6) years and duration of disease 9 (5) years when investigated. We included only the first 11 Jamaican born index patients of the series in this study because they were the only subjects from Jamaica when the sampling for the study was carried out, there were detailed data on the prevalence of HTLV-I infection in Jamaica,¹⁰ and relatives of other patients from the eastern Caribbean islands were precluded from inclusion because of limitations on travel. Rough estimates of the likely prevalence of the antibody to HTLV-I based on Jamaican population studies were 15% for the relatives in group 1, 5-8% for the somewhat younger relatives in group 2, and 1-3% for the offspring in group 3.

The Jamaican born index patients did not differ in basic characteristics from those born in the eastern Caribbean (table I), had also spent about half their lives in Britain, and had the same mean duration of disease. Their degree of disability ranged from minor unilateral leg weakness (but bilateral spasticity) to complete

TABLE I—Details of 11 index patients with tropical spastic paraparesis

Sex	Age (years)	Time in Britain (years)	Age at onset of symptoms (years)	Duration of disease (years)
F	52	26	47	4
M	53	29	49	4
F	55	30	51	4
F	53	26	47	6
F	61	23	54	7
F	48	26	39	9
F	53	25	42	9
F	49	29	37	12
F	65	35	52	13
F	48	26	33	15
F	52	32	36	16
Mean (SE)	53.5 (1.7)	27.9 (1.0)	44.3 (2.2)	9.0 (1.3)

paraplegia and restriction to a wheelchair. In contrast to the symptoms of multiple sclerosis cranial nerve signs were absent and arm involvement rare and minimal.

Details of all first degree relatives (parents, siblings, and children) and spouses or current and recent partners were obtained, with informed consent, from the index patients. The patients contacted their relatives in both Britain and Jamaica and asked permission for us to visit them. Relatives were asked to complete a questionnaire for analysis of risk factors, which included giving information on places and duration of residence since birth, family size, age, history of breast feeding, history of blood transfusion, and number and duration of spouses or partners. Efforts were made to trace all known living relatives, each of whom was visited in his or her home.

With the patients' permission 30 ml of whole blood was taken and mixed with EDTA for subsequent DNA extraction and serum was obtained from 10 ml blood. Whole blood and serum samples were stored at -20°C and then at -70°C until required.

SEROLOGY

The serological methods used have been described previously.^{17 18} Serum samples were considered positive for HTLV-I antibody only if positive results were obtained by using at least two of the following methods: agglutination (Serodia, Tokyo, Japan), immunofluorescence, enzyme linked immunosorbent assay (ELISA) (DuPont, Wilmington, Delaware, United States), and antibody dependent cell mediated cytotoxicity tests. Positive results were then confirmed by western blot analysis.

DNA ANALYSIS

DNA was extracted from whole frozen blood.¹⁹ For the polymerase chain reaction each DNA sample was tested within two sets of primers specific for the gag and X regions of the HTLV-I genome. The gag primers were 5'GTCAGACCTGGACCCCCAAAGAC3' and 3'GTCTCGGTCTCCTTCTACGGGAG5', which amplified the region from 1795 bp to 2030 bp. X region primers were 5'CCTTCTCAGCCCTTGTCTCCAC3' and 3'GCGACGGCTAGTGCTACGCAAAG5', which amplified the region from 6824 bp to 7066 bp. Oligonucleotide probes used to detect the amplified products were 5'CCCCAAATCAGCCGTGCTTC3' (for the gag region) and 5'TACTCAGCGGTCTGCTTTTC3' (for the X region).

Reactions were performed in a 50 μl volume using 1 μg of DNA, 1 unit of Taq polymerase (Perkin Elmer Cetus, Norwalk, Connecticut, United States), and 0.5 μg of each primer. The reaction buffer was potassium chloride 50 mmol/l, magnesium chloride 1.5 mmol/l, deoxynucleoside triphosphate 200 $\mu\text{mol/l}$, TRIS HCl buffer (pH 8.3) 10 mmol/l, and 0.01% gelatin. Samples were denatured for 10 minutes at 95°C and then given 30 and 45 cycles of amplification (at 60°C for 0.1 min, at

72°C for 0.5 min, and at 93°C for 0.1 min). An aliquot of 10 µl of the reaction products was analysed by electrophoresis in 2.5% agarose and transferred to a Zetaprobe membrane (Bio-Rad Laboratories, Richmond, California, United States) in sodium hydroxide 0.4 mol/l. Filters were incubated for 1 hour at 50°C in 6 strength standard saline citrate, 1% sodium dodecyl sulphate, and 0.5% dried skimmed milk and then for two hours in the same solution containing 5 µg/l of oligonucleotide probe end labelled with phosphorus-32 and T4 kinase to a specific activity of 5×10^8 dpm/µg. Filters were washed in 6 strength standard saline citrate with 1% sodium dodecyl sulphate for 10 minutes at room temperature and then 10 minutes at 50°C and underwent autoradiography for 0.5-48 hours at -70°C.

Results

The 11 Jamaican born patients with tropical spastic paraparesis had 66 living first degree relatives and spouses distributed between Jamaica and Britain. Five other relatives lived in the United States or Canada and were not contacted. Of 27 relatives in group 1, 25 were seen; of 24 in group 2, 21 were seen; and of 15 in group 3, 14 were seen. Thus the total response rate was 60 of

TABLE II—Living first degree relatives and spouses of 11 Jamaican born patients with tropical spastic paraparesis

	Group 1	Group 2	Group 3
Mothers	1	1	
Siblings	22	4	
Children	2	9	14
Spouses		7*	
Total	25	21	14
Mean (SE) age (years)	51 (3.8)	46.2 (4.4)	20.2 (3.2)

*Includes one wife.

66 (91%) relatives; of the seven spouses or partners only one was a woman (table II).

Some relatives who were living in Britain (groups 2 and 3) had returned to Jamaica for short visits, the maximum number of visits being four and the maximum length of stay two months. The mean age of relatives born and living in Jamaica (group 1) was similar to that of the index patients; relatives in group 2 were some five years younger and those in group 3 were a generation younger (table II).

All 60 relatives reported having been breast fed as infants and none had had a blood transfusion. The breast feeding history of offspring was confirmed by the index patients.

ANTIBODY TITRES

Geometric mean antibody titres and ranges for the IgG enzyme linked immunoassay and the agglutination method (for all antibody classes) of the seropositive relatives were lower at 1:650 (range 1:64-1:1024) and 1:6800 (1:612-1:10 000) respectively, compared with 1:2825 (1:200-1:6000) ($p < 0.01$) and 1:46 000 (1:10 000-1:100 000) ($p < 0.01$) in the index patients. All seropositive relatives had positive results by at least three methods. A few serum samples that gave weakly positive results on immunofluorescence staining or atypical bands on western blotting but failed to give positive results in the other assays were classified as negative. The figure shows the individual family trees; family size was not associated with transmission of HTLV-I.

Table III gives the prevalence and age distribution of antibodies to HTLV-I in the three groups of relatives. Only three of 25 (12%) relatives in group 1, but seven of 21 (33%) in group 2, were positive for HTLV-I antibody compared with none of the 14 offspring in group 3. These differences among the groups were significant ($\chi^2 = 7.39$; $df = 2$; $p < 0.02$). The seropositive relatives were three siblings and three spouses (two men and the one woman) in groups 1 and 2 and four children in group 2. Thus of the 23 children, four of nine born in Jamaica compared with none of 14 born in Britain were seropositive ($p = 0.034$, Fisher's exact test). Of 38 immediate family members of the same Jamaican born generation (27 siblings and 11 index cases), 14 (37%; 95% confidence interval 21 to 53%) were positive for HTLV-I antibody (see figure). Neither of the two mothers of the index patients was positive. The total prevalence of seropositivity for all relatives and spouses born in Jamaica was 10/46 (22%; 9 to 34%).

CONFIRMATION OF SEROLOGY BY THE POLYMERASE CHAIN REACTION

The polymerase chain reaction for amplifying proviral DNA was used to test whether HTLV-I infection might occur in some people without an antibody response (table IV). After amplification viral DNA could be detected in all of the patients with tropical spastic paraparesis and all seven seropositive relatives tested but not in any of the 37 seronegative relatives

Family trees of 11 index patients with tropical spastic paraparesis

TABLE III—Age specific prevalence of HTLV-I antibody in first degree relatives and spouses of 11 patients with tropical spastic paraparesis

	Age (years)						Total (% , 95% confidence interval)
	10-19	-29	-39	-49	-59	≥60	
Group 1		0/1	0/3	1/7	1/6	1/8	3/25 (12, 0 to 25) 10/46 (22, 9 to 34)
Group 2		1/2	3/6	0/2	2/7	1/4	
Group 3	0/5	0/8	0/1				
Total	0/5	1/11	3/10	1/9	3/13	2/12	10/60

TABLE IV—Analysis by polymerase chain reaction of DNA from patients with tropical spastic paraparesis and their relatives. Figures in parentheses are numbers positive for HTLV-I DNA out of numbers tested

Relatives	No positive for HTLV-I antibody	No negative for HTLV-I antibody
Parents or siblings	3 (3/3)	25 (0/20)
Spouses	3 (1/1)	4 (0/2)
Children*	4 (3/3)	21 (0/15)

*All mothers were positive for HTLV-I antibody.

examined, even with the method being able to detect 10 viral copies per 10⁶ leucocytes.^{19a} In particular, all 14 of the children born and living in Britain were confirmed as being negative for HTLV-I DNA by the polymerase chain reaction.

Discussion

This study has shown that the seroprevalence of HTLV-I of 22% (10/46) in the Jamaican born relatives of 11 patients with tropical spastic paraparesis (groups 1 and 2) was clearly higher than that of 0% in the 14 British born offspring (group 3), particularly as four of the nine Jamaican born children were seropositive ($p=0.03$). In all subjects tested the carrier state was confirmed by the polymerase chain reaction analysis of relatives' DNA, and no subject was positive for HTLV-I DNA and negative for HTLV-I antibody.

The 95% confidence interval (9 to 34%) for the total prevalence of HTLV-I antibody in Jamaican born people overlaps with the 5 to 15% seroprevalence found in community studies of this age group in Jamaica.¹⁰ Thus, from this sample size, this rate would not confirm an excess prevalence in families of index patients with tropical spastic paraparesis compared with the general population in Jamaica. Immediate family clustering in the same generation, however, is clearly shown by including only the index patients and siblings in the prevalence (37%; 21 to 53%) and excluding spouses, who were not exposed to family influences in childhood. Interestingly, the spouses, who were also all Jamaican born, showed a similar rate (3/7). No data for an adequate population sample of Jamaican born migrants in Britain are available, but in a small community study in north west London only two of 81 (2%) randomly sampled Afro-Caribbean subjects (not just from Jamaica) aged 50-69 years were seropositive (JKC and ALN, unpublished data). If this 2% is representative then the family aggregation of HTLV-I in 7/21 (33%) of relatives born in Jamaica and living in Britain is highly significant, but evidence from larger populations and numbers of families is needed for confirmation.

The incubation period from infection to becoming positive for HTLV-I antibody has to be distinguished from that between being positive for the antibody and development of clinical disease. Two main possibilities exist: firstly, that HTLV-I infection is acquired only in endemic regions, in which case the incubation period of tropical spastic paraparesis in our patients is long and the prevalence of seropositivity would be higher in

relatives remaining in the Caribbean compared with those who emigrated (provided acquisition continued in those born and living in Jamaica after the time of emigration of the others). Our data do not support this; if anything, the Jamaican relatives resident in Britain had a higher rate of seropositivity (33%) than relatives still in Jamaica (12%), who were slightly but significantly older (table I), indicating that age does not account for these differences. A second, more likely, possibility that is compatible with our results is that HTLV-I can be acquired in non-endemic countries, in which case the period between infection and disease may be shorter, there should be no difference in HTLV-I seropositivity between relatives resident in Britain and those resident in Jamaica, and the disease should occur in British born people.

A prolonged virus incubation period before seroconversion might explain the negative serology in the British born offspring as well as the increase of HTLV-I seroprevalence with age. But the negative results of the polymerase chain reaction on peripheral blood DNA do not support this hypothesis, although infection of non-circulating cells such as endothelial or fibroblastic cells cannot be excluded. In vitro studies have shown that these and other non-lymphoid cells can be infected with cell free virus.²⁰⁻²²

The absence of HTLV-I antibodies in the 14 British born relatives, all of whom had mothers infected with HTLV-I and were breast fed, argues against maternal transmission as the main route of infection. The route of transmission in the seropositive relatives remains uncertain. Blood transfusion can be eliminated as none of the subjects had had one, though all relatives reported having been breast fed. Japanese and preliminary Caribbean studies show rates of 15-20% for mother to infant transmission,^{13 14 23} which may also be due to exchange of uteroplacental blood perinatally or other forms of direct blood transfer during birth. Hino *et al* found that cord blood of seropositive mothers contained IgG antibody, the concentration of which diminished rapidly after birth, and did not find IgM antibodies (of infant origin) or infected lymphocytes.²⁴ Lymphocytes infected with the virus have been detected by immunofluorescence in human breast milk, and transmission through suckling has been shown in animals.²⁴⁻²⁶ Yet studies have reported that 75-80% or more of infants born to seropositive mothers do not seroconvert in their first three years of life. Seroconversion then levels off until beyond the age of 15 years or so.¹³ Such a plateau throughout childhood has been reported by both Jamaican¹⁰ and Japanese studies²⁷ and is consistent with infection being transmitted from sources other than from the mother—for example, through sexual activity. The negative results in the 14 offspring born in Britain in this study are compatible with relatively inefficient rates of mother to infant transmission because the small numbers have wide confidence intervals. It would be premature to prevent seropositive mothers from breast feeding, particularly in areas of low prevalence of HTLV-I where lifetime disease risks remain low. It has not been confirmed that breast milk was the source of infection in any case of disease; other advantages of breast feeding, particularly in developing countries, currently outweigh the risks.

Sexual transmission (most efficiently from men to women) is generally thought to be the main method of HTLV-I transmission in adults.²⁸ Infectivity by this route seems to be low judging from the slow rate of seroconversion in wives of infected men¹⁴ and from the low rate of infection with HTLV-I in promiscuous homosexuals whose partners are infected.²⁹ It may not be an adequate explanation for the significant difference in seroprevalence in this study between Jamaican born children (4/9) compared with British born offspring (0/

14). Rather some factors related to place of birth and early residence, perhaps close cohabitation in poor housing with an index patient, seem to promote HTLV-I infection. Improvement in such conditions was a prime reason for migration; indeed in 1897 the first Jamaican account of a tropical spastic paraparesis-like syndrome reported that many cases were found among the poor, as was found later.^{31 32}

In conclusion, our data suggest that place of birth and early residence rather than maternal or age effects are the important factors in HTLV-I infection. No evidence of prolonged seronegative incubation of HTLV-I has been found.

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Absorption of glycine irrigating solution during transcervical resection of endometrium

Ralf Baumann, Adam L Magos, Jonathan D S Kay, Alexander C Turnbull

Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU
Ralf Baumann, MD, research fellow in gynaecological endoscopy
Adam L Magos, MRCOG, clinical lecturer
Sir Alexander C Turnbull, FRCOG, professor

Nuffield Department of Clinical Biochemistry, University of Oxford, John Radcliffe Hospital
Jonathan D S Kay, MRCPATH, consultant chemical pathologist

Correspondence to: Mr Magos.

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We recently described transcervical resection of the endometrium as a less invasive alternative to hysterectomy for menorrhagia.¹ The operation is similar to transurethral resection of the prostate in terms of technique and the use of liquid media such as 1.5% glycine solution for distension and irrigation. As absorption of large volumes of such fluid can cause fluid overload, hyponatraemia, cerebral oedema, haemolysis, and even death² we assessed the risk of these complications associated with the operation.

Patients, methods, and results

We studied 10 women aged 34-51 who were undergoing endometrial resection for symptoms of menorrhagia. They were otherwise healthy, and none took drugs that affected renal function. All women were starved for six hours preoperatively, and intravenous fluids were not used during the operation. The operative technique was as described previously¹ and

included careful monitoring of inflow and outflow of the uterine irrigant. Haemoglobin concentration, packed cell volume, plasma osmolality, lactate dehydrogenase activity (an indicator of haemolysis), and plasma concentrations of sodium, potassium, creatinine, total protein, albumin, and glycine were measured before, during (at 10, 20, and 30 minutes), and after (at two, four, six, and 24 hours) resection.

The mean operating time was 39.2 minutes (range 20-80). Vital signs remained normal in all cases, and the mean estimated blood loss was 133 ml (80-200). A mean of 4948 ml irrigant was infused into the uterus (1750-8900), the mean deficit of fluid at the end of the operation being 643 ml (100-2030). The volume of fluid absorbed was smallest (100 and 200 ml) in two patients who had been sterilised.

There was a negative linear correlation between the volume of irrigant absorbed and the change in plasma sodium concentration ($r = -0.717$, $p < 0.02$); hyponatraemia of 125 and 130 mmol/l occurred in two women within 10-30 minutes of the start of the operation, both women having absorbed more than 900 ml of irrigant. Changes in plasma sodium concentration were paralleled by falls in total protein, albumin, and haemoglobin concentrations and packed cell volume, but only minor fluctuations occurred in potassium and creatinine concentrations (table). Lactate dehydrogenase activity increased after the operation in the two women with hyponatraemia. Only two out of nine women monitored showed an increase