Human T cell leukaemia/lymphoma virus infection in pregnant women in the United Kingdom: population study

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Abstract

Objective To assess the prevalence of human T cell leukaemia/lymphoma virus (HTLV) infection in pregnant women in the United Kingdom.

Design Population study.

Subjects Guthrie card samples from babies born in 1997-8. Samples were linked to data on mother's age and ethnic status and parents' country of birth and then anonymised.

Setting North Thames Regional Health Authority.

Main outcome measures Presence of antibodies against HTLV in eluates tested by gelatin particle agglutination assay and results confirmed by immunoblot.

Results Of 126 010 samples tested, 67 had confirmed antibodies to HTLV (59 HTLV-I, 2 HTLV-II, 6 untyped) and six had indeterminate results. Seroprevalence was 17.0 per 1000 (95% confidence interval 9.2 to 28.3) in infants whose mothers were born in the Caribbean, 3.2/1000 (1.5 to 5.9) with mothers born in west and central Africa, and 6.8/1000 (3.1 to 12.9) in infants of black Caribbean mothers born in non-endemic regions. In infants with no known risk (both parents born in non-endemic regions and mother not black Caribbean) seroprevalence was 0.06-0.12 per 1000. Mother's country of birth, father's country of birth, and mother's ethnic status were all independently associated with neonatal seroprevalence. An estimated 223 (95% confidence interval 110 to 350) of the 720 000 pregnant women each year in the United Kingdom are infected with HTLV.

Conclusions The prevalence of HTLV and HIV infections in pregnant women in the United Kingdom are comparable. The cost effectiveness of antenatal HTLV screening should be evaluated, and screening of blood donations should be considered.

Introduction

Human T cell leukaemia/lymphoma virus type I (HTLV-I) is endemic in the Caribbean, Japan, South America, west and central Africa, and isolated pockets elsewhere. It is causally associated with adult T cell leukaemia/lymphoma and HTLV-I associated myelopathy and tropical spastic paraparesis.¹ The association of HTLV-II with neurological and lymphoproliferative disorders is less certain.² HTLV-II is

endemic in some Amerindian groups and in parts of Africa.¹ The epidemiology of HTLV in Europe and worldwide has been reviewed recently.³⁻⁴ Phylogenetic trees based on nucleotide sequencing have thrown further light on the worldwide distribution of HTLV and its origin in simian T cell lymphoma/leukaemia viruses.^{2 5 6}

Both types of HTLV can be transmitted through breast feeding, sexual contact, and blood transfusion and percutaneously.^{1 7} A high prevalence of HTLV, particularly HTLV-II, has been recorded among injecting drug users in the United States⁸ and parts of Europe.³ Blood donors are routinely screened for HTLV in Japan, the United States, Canada, France, the French West Indies, Portugal, Sweden, the Netherlands, Denmark, and Finland.

Rates of transmission from mother to child are 2.7% in formula fed infants, 5% with three months' breast feeding, and up to 20% with prolonged breast feeding.⁹⁻¹¹ Vertically acquired HTLV-I leads to adult T cell leukaemia/lymphoma in 1-5% of infected infants.⁷ Antenatal screening for HTLV, to recommend formula feeding, has been carried out in the Nagasaki prefecture of Japan since 1987¹² and has been proposed in Europe¹³⁻¹⁷ and Jamaica.¹⁸

In the United Kingdom, studies of HTLV seroprevalence in pregnant women have been small, local, and confined to multiethnic inner city areas.^{13 14 16 19-21} This study, based on the presence of HTLV specific antibody in neonates, which is a reliable marker of maternal infection, examines the wider seroepidemiology of HTLV in the North Thames region of south east England. This includes inner London, suburban, and remote rural districts. From this we derive estimates of antenatal seroprevalence in the United Kingdom as a whole and discuss the implications for both antenatal and blood donor screening.

Methods

Population and sources of demographic data

The study included all the 126 010 non-repeat Guthrie card samples arriving over 15 months in 1997-8 in the North Thames neonatal screening laboratory, which serves almost 15% of newborn babies in the United Kingdom. Over the last 12 months of the study, demographic data were linked to samples before irreversible unlinking and testing, as described elsewhere.²²

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Parents' country of birth, recorded at civil registration of births, was obtained from the Office for National Statistics. Maternal ethnic status and age at delivery was available from child health computers in 14 of the 29 districts in the study. Ethical approval was obtained from local committees covering the study population.

Serology

Two 4.9 mm dried blood spot samples were punched into flat bottomed microtitre plates and eluted overnight at 4°C in 170 µl of eluate buffer.²³ Eluates were screened by a modified anti-HTLV gelatin particle agglutination assay, which has been shown to be sensitive to anti-HTLV in simulated dried blood spot samples from patients with HTLV-1 from the United Kingdom, South Africa, and Japan.²⁴ Tests on serial dilutions of a panel of 23 samples from the HTLV European Research Network showed reliable detection of anti-HTLV-I and anti-HTLV-II in dried blood spot eluates derived from serum samples with titres as low as 1:50. Repeat reactive samples were confirmed and typed by immunoblotting (HTLV blot 2.4,

Genelabs Diagnostics, Singapore) at a dilution of 1:50 and according to manufacturer's instructions.

Statistical methods

We used SAS PROC GENMOD for binomial data to perform multivariate analyses with profile likelihood confidence intervals. Additive risk regression was used to assess the effect of parents' region of birth and mother's ethnic status,²⁵ and logistic regression was used elsewhere. Single proportions were compared by Fisher's exact test. We estimated the prevalence of maternal HTLV infection in the United Kingdom by multiplying group specific risks derived from this study and published data into group population sizes estimated from routine birth registration and 1991 census statistics.

Results

Serology and status of indeterminate samples

Of the 126 010 samples tested, 85 were reactive on first gelatin particle agglutination assay and 75 on repeat testing. All 10 samples that were non-reactive on repeat testing gave negative results on immunoblotting. Sixty seven of the 75 repeat reactive samples were confirmed as seropositive (59 HTLV-I, 2 HTLV-II, and 6 HTLV untyped), six were indeterminate, and two were negative. The figure shows the HTLV titres of all 85 initially reactive samples. Six (7%) samples had titres of 1 in 5, the lowest category above the detection limit, suggesting a false negative rate of no more than 2-3%.

Table 1 compares the demographic features of the babies with indeterminate samples with those of babies with confirmed seropositive and seronegative results. Among those with known risk status, only 18% (7558/41 487) of babies with negative results had risk factors for infection compared with 37/39 (95%) of those with confirmed positive results ($P < 0.0001$). Two out of four babies with indeterminate samples had a known risk factor. This proportion was not significantly different from that of babies with negative samples ($P = 0.15$) but significantly lower than in those with confirmed positive samples ($P = 0.037$). In view of the uncertain status of the six indeterminate samples, we assumed for seroprevalence estimates that half the six indeterminate results were HTLV positive. Confidence intervals incorporate this uncertainty.

Table 1 Risk factor distribution of infants with confirmed anti-HTLV positive, indeterminate, and negative eluates. Percentages are given for samples for which presence or absence of risk factors could be determined

Risk factor	Confirmed HTLV				Indeterminate (%)	HTLV negative (%)	Total
	I	II	Not Typed	Total (%)			
Caribbean*	25	0	2	27 (69)	1 (25)	2 898 (7)	2 926
Other endemic area†	6	1	3	10 (26)	1 (25)	4 660 (11)	4 671
No risk‡	1	0	1	2 (5)	2 (50)	33 929 (82)	33 933
Low risk§	11	0	0	11	1	54 951	54 963
No data linkage	16	1	0	17	1	29 499	29 517
Total	59	2	6	67	6	125 937	126 010

*At least one parent born in Caribbean or mother of black Caribbean ethnicity.

†At least one parent born in west or central Africa, Japan, or South America.

‡Both parents born in non-endemic regions, mother not black Caribbean.

§Mother born in non-endemic area, but ethnic status or father's country of birth not known.

Table 2 Maternal prevalence of HTLV infection per 1000 including samples with indeterminate results, by mother's country of birth

Country of birth	Confirmed HTLV			Total HTLV (indeterminate)	Total tested	Prevalence
	I	II	Untyped			
Africa:						
Western*	4	1	2	7 (1)	2 325	3.0-3.4
Central*	1	0	1	2	559	3.6
Rest of Africa	0	0	0	0	4 250	0
America:						
Caribbean*	13	0	2	15 (1)	914	16.4-17.5
South*	1	0	0	1	490	2.0
Central and North	0	0	0	0	801	0
Asia						
Japan*	1	0	0	1	233	4.3
Rest of Asia	0	0	0	0	12 590	0
Europe:						
United Kingdom	22	0	1	23 (3)	69 013	0.33-0.38
Other northern	0	0	0	0	1 948	0
Southern	0	0	0	0	1 143	0
Eastern	0	0	0	0	494	0
Western	1	0	0	1	1 204	0.8
Oceania	0	0	0	0	529	0
Missing	1	0	0	1	272	0.4
No data linkage	15	1	0	16 (1)	29 245	0.58
Total	59	2	6	67 (6)	126 010	0.53-0.58

*Endemic regions.

Seroprevalence in relation to demographic factors

Maternal prevalence of HTLV infection was highest in Caribbean born women, 16.9 (95% confidence interval 9.2 to 28.3) per 1000. Prevalence in women born in western or central Africa was 3.2 (1.5 to 5.9) per 1000. Prevalence was also high in mothers born in Japan and in South America (table 2). These endemic areas accounted for 51% of maternal infection. The remaining 49% of infected mothers were born in Europe, where seroprevalence was 0.36 (0.21 to 0.55) per 1000. The distribution of infection across father's country of birth was very similar.

Maternal ethnic status was known in 40 868 cases. In the 29 confirmed and indeterminate cases where ethnic status was known, 15 (52%) mothers were black Caribbean, five (17%) black African, and six (21%) white. There were no cases of HTLV in babies born to the 7495 mothers recorded as Asian or to 571 British born black African women, but there were four confirmed positives cases and two indeterminate among 26 905 babies born to white women.

Among 32 985 infants with no known risk factors (both parents born in non-endemic areas, mother not black Caribbean) there were two positive and two indeterminate samples (prevalence 0.06-0.12 per 1000). Among infants with a non-black mother born in a non-endemic area, whose only risk was therefore father's country of birth, seroprevalence was 0/352 if the father was born in an endemic area but 2/2347 when the father's country of birth was unknown.

In an analysis of parental country of birth and mother's ethnic status as risk factors for neonatal seropositivity, an additive risk model fitted better ($\chi^2 = 32.6$, $df = 38$, $P = 0.7$) than a logistic regression model ($\chi^2 = 56.3$, $df = 38$, $P = 0.028$) and gave no significant interactions. Table 3 gives the additional risk of being seropositive conferred by each risk factor, relative to a baseline group of infants with seroprevalence 0.098 per 1000 with no parental risk indicators.

Table 3 Additive binomial regression estimates of the contribution of parents' region of birth and mother's ethnic status on neonatal seroprevalence for HTLV. Central estimates are the average, and confidence limits the most extreme, of those obtained including or excluding indeterminate results as seropositive

	Prevalence per 1000 births (95% CI)	χ^2 (df)	P value
Baseline population*	0.098 (0.017 to 0.20)		
Mother's region of birth:			
Caribbean	12.1 (7.5 to 17.7)	42.6 (2)	<0.0001
Other endemic	2.3 (0.9 to 3.0)		
Non-endemic (reference)	0		
Father's region of birth:			
Caribbean	5.4 (2.8 to 8.7)	14.9 (3)	0.0019
Other endemic	0.1 (-0.3 to 0.3)		
Not registered	0.3 (-0.2 to 0.8)		
Non-endemic (reference)	0		
Mother's ethnic status:			
Black Caribbean	3.6 (2.2 to 7.3)	23.0 (3)	<0.0001
Black African	-0.1 (-0.2 to 0.9)		
Not known	0.06 (-0.1 to 0.2)		
Not black (reference)	0		

*Parents born non-endemic region, mother not black.

Anti-HTLV was rare in infants with mothers under 26 years old (table 4), and prevalence increased greatly with maternal age among all groups at risk of HTLV infection ($\chi^2 = 12.6$, $df = 1$, $P = 0.0004$). Prevalence was higher in women born in the Caribbean than black Caribbean women born in non-endemic areas (relative risk 2.9, 95% confidence interval 1.2 to 7.1). This effect was not significant after age was controlled for, but the data remained consistent with a substantial excess risk (relative risk 1.9, 0.8 to 4.9).

Seroprevalence increased from non-metropolitan districts, through outer London, to inner London (table 5). However, this geographical variation can be attributed to distribution of the risk groups. Using only samples for which the presence or absence of risk group was known, we found that the significant trend ($\chi^2 = 11.6$, $df = 1$, $P = 0.0007$) was eliminated after risk

Table 4 Seroprevalence of HTLV per 1000, by mother's age for babies whose mother's country of birth was also known. Samples with indeterminate results (shown in parentheses) are included in seroprevalence estimates

Maternal age	Mother born in Caribbean			Mother born in other endemic region			Black Caribbean mother born in non-endemic region		
	Positive	Total	Prevalence	Positive	Total	Prevalence	Positive	Total	Prevalence
<21	0	42	0	0	108	0	0	142	0
21-25	0	85	0	1	341	2.9	0	226	0
26-30	2	133	15.0	1 (1)	904	2.2	2	408	4.9
31-35	1 (1)	129	15.5	5	898	5.6	6	412	14.6
>35	8	233	34.3	3	409	7.3	1	139	7.2
Total	11 (1)	622	19.3	10 (1)	2660	4.1	9	1327	6.8

Table 5 HTLV seroprevalence per 1000 births by risk group and type of district of birth for samples with known district of birth. Seroprevalence is an average of minimum and maximum estimates

Mother's place of birth and ethnic status	Inner London			Outer London			Non-metropolitan districts		
	Positive*	Total	Prevalence	Positive*	Total	Prevalence	Positive*	Total	Prevalence
Born in Caribbean	7 (1)	460	16.3	7	374	18.7	1	80	12.5
Born in other endemic region	9 (1)	2 362	4.0	1	1 096	0.9	1	149	6.7
Black Caribbean, born in non-endemic region	5	855	5.8	4	418	9.6	0	55	0
Not black Caribbean, born in non-endemic region	2 (1)	14 752	0.17	1	11 982	0.08	1 (1)	10 489	0.14
Region of birth unknown or non-endemic, ethnic status not known	6	11 149	0.54	15 (1)	32 334	0.48	6 (1)	39 104	0.17
Total	29 (3)	29 578	1.03	28 (1)	46 204	0.62	9 (2)	49 877	0.20

*Samples with indeterminate results in parentheses.

Table 6 Estimates of number of pregnancies in United Kingdom each year in which mother is infected with HTLV. Central estimates are an average and confidence limits the most extreme of those obtained including and excluding indeterminate results as seropositive

Risk category	Prevalence per 1000 births (95% CI)	No of births	Expected No of infected women (95% CI)
Born in Caribbean	16.9 (9.2 to 28.3)*	2 750§	46.6 (25 to 78)
Born in other endemic region	3.2 (1.5 to 5.9)*	8 200¶	26.1 (12 to 48)
Black Caribbean, born in non-endemic regions	6.8 (3.1 to 12.9)†	8 000**	54.3 (25 to 103)
Not black Caribbean, born in non-endemic regions:			
Inner London, principal cities	0.35 (0.14 to 0.70)‡	72 000††	25.0 (10 to 50)
Rest of United Kingdom	0.11 (0.01 to 0.32)‡	626 050	69.7 (7 to 201)
Total		720 000	223 (113 to 347)

*Data from table 2.

†Data from table 5.

‡Pooled estimate 9/24 498 based on our figures for inner London 3/14 752 (table 5) combined with 6/9746 previously reported in similar districts.^{13 14 19 20}

§Birth registration statistics.²⁶

¶Based on unpublished birth registration data supplied by Office for National Statistics.

**Assumes that 1.217% births are to black Caribbean women, based on proportion of 0-4 year olds in Great Britain recorded as black Caribbean and 20% of those recorded as black other,^{27 28} and assuming that 87% of black Caribbeans of child bearing age are born in Britain.²⁹

††Office for National Statistics.³⁰

group was controlled for ($\chi^2 = 0.4$, $df = 1$, $P = 0.5$). In inner London, an estimated 90% (22/24.5) of seropositive samples occurred in babies with a maternal risk factor compared with 92% (11/12) in outer London and 57% (2/3.5) in non-metropolitan areas.

Overall prevalence among pregnant women in United Kingdom

To project our seroprevalence findings across the whole of the United Kingdom we multiplied risk group specific prevalence estimates from this study and elsewhere into population estimates (table 6). We assumed that seroprevalence is homogeneous within groups across the country. This assumption is supported by the preceding analysis for North Thames (table 5), although we stratified the low risk into two groups. The overall number of pregnant women in the United Kingdom infected each year with HTLV is predicted to be 223 (95% confidence interval 113 to 347) out of a total 720 000, representing an overall prevalence of 0.31 per 1000 (0.16 to 0.48). The main source of uncertainty is the small numerator in the majority (lowest risk) group, which may account for between 6% and 58% of maternal infection.

Discussion

Our results agree well with what is known about the endemicity of HTLV in the Caribbean, west and central Africa, and elsewhere.^{1 3} The rapid increase in seroprevalence with age and the low seroprevalence in the youngest groups (table 4) point to sexual contact as the primary mode of transmission among women of child bearing age, with only a small fraction attributable to breast feeding. This is also consistent with reports from Africa, Jamaica, and South America.³¹⁻³³ The finding of 1.1 per 1000 seroprevalence in inner London is comparable with estimates of 1.4 to 3.9 per 1000 from smaller studies set in similar areas.^{13 14 16 19-21}

The precise prevalence of HTLV-II remains in doubt. Anti-HTLV-II was detected in two of the 126 010 samples (0.016 per 1000). However, untyped anti-HTLV positive results are more frequent in

samples from Africa than from the Caribbean (table 1), and one or more of the three untyped African samples may be HTLV-II. The gelatin particle agglutination assay is equally sensitive to anti-HTLV-I and anti-HTLV-II.³⁴ However, the serum antibody titre of patients with HTLV-II may be lower than that of patients with HTLV-I,³⁵ and therefore more eluates may have fallen below the detection limit. On the other hand, the 59:2 ratio of HTLV-I to HTLV-II recorded here is similar to the 32:1 reported in a recent study based on serum samples in London.²¹

Screening implications

Several investigators have urged that antenatal screening for HTLV be considered in the United Kingdom in order to prevent vertical transmission of HTLV through breast feeding. The 233 a year nationwide antenatal prevalence of HTLV predicted in this study is comparable to the recent 330 a year estimate for HIV.³⁶ Furthermore, the estimated prevalence of HTLV of 0.06-0.12 per 1000 births among those with no known risk factors in North Thames compares with the prevalence of HIV of 0.10 per 1000 births among United Kingdom born women with United Kingdom born partners reported in the same region.²²

The United Kingdom has recently joined many other countries in recommending universal antenatal testing for HIV,³⁷ but the arguments for antenatal HTLV testing may be less compelling. Although HTLV may be transmitted to 20% of children breast fed for a prolonged period, the transmission rate is only 5% with three months' breast feeding.⁹⁻¹¹ In Britain 34% of mothers do not breast feed at all, and only 35% breast feed for over 3 months.³⁸ Breast feeding may be more prolonged among women born in endemic areas, but these women account for only 32% of prevalent cases (table 6). The rate of vertical transmission of HTLV in the United Kingdom is therefore likely to be under 10% (22/223), which could be reduced to 2.7% (6/223) by formula feeding.⁹ Not only is the burden of preventable infection therefore quite low, but the lifetime risks of HTLV related disease are also small: 1-5% for adult T cell leukaemia/lymphoma,⁷ and 0.25-3% for HTLV-1 associated myelopathy and tropical spastic paraparesis.^{1 39} Maternal infection may therefore lead to disease in only 0.1% to 1% of offspring.

The potentially negative impact of a maternal diagnosis of HTLV on the family's quality of life is a further critical factor, as between 10 and 20 infected women would need to be diagnosed to prevent one paediatric infection, and no effective treatments exist for HTLV infection or HTLV related diseases. A thorough economic evaluation would establish whether there is a net benefit to diagnosing an HTLV infected pregnant woman. If there is a benefit, our findings suggest that targeting high risk women or universal testing in high prevalence areas could identify most women infected with HTLV at relatively low cost.

The conjecture that HTLV may be as frequent in the general United Kingdom population as HIV also has implications for blood donor screening. The prevalence of HTLV infection in women with no risk factors and low risk partners of 0.06-0.12 per 1000 births compares with the 0.05/1000 (5/96 720) prevalence reported in blood donors in north London in 1993⁴⁰ and 0.014 /1000 (1/76 452) in the north of

England.⁴¹ The prevalence of HIV nationally in 1998 was 0.04/1000 in eligible first time blood donations and 0.004/1000 in repeat donations.⁴² Although the risks of infection and disease after contaminated transfusion are less with HTLV than with HIV,⁴³⁻⁴⁴ screening first time donors for HTLV would not be inconsistent with the present policy of screening all donations for HIV.

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What is already known on this topic

Human T cell leukaemia/lymphoma virus (HTLV) type 1 is associated with adult T cell leukaemia and progressive neurological disease; HTLV-II is less common in the United Kingdom but is also associated with serious disease

The viruses can be transmitted sexually, percutaneously, and from mother to child

Antenatal screening is carried out in Japan and many countries screen blood donations for HTLV

What this study adds

The prevalence of HTLV among pregnant women in the United Kingdom is estimated to be 0.31 per 1000, similar to the prevalence of HIV

In inner city areas about 90% of HTLV is associated with birth or ethnic origin in endemic areas, compared to 50% in non-metropolitan areas.

Antenatal HTLV testing is likely to be less beneficial economically and clinically than antenatal HIV testing but should be fully evaluated

Screening of blood donations should be considered

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