

Antenatal survey for the seroprevalence of HTLV-1 infections in the West Midlands, England

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SUMMARY

The sera of 3522 women who attended an antenatal clinic in Birmingham, England were tested anonymously for antibodies against HTLV-1. Samples from 5 women (0·14%) were positive, one serum showed indeterminate reactivity. Two of the women (0·06%) were born in the West Indies (of Afro-Caribbean ethnic origin), one (0·03%) in Africa (of African ethnic origin), and three (0·09%) were white Caucasian women born in the UK. Thus, HTLV-1 infection in pregnant women in the UK, though comparatively rare, is not negligible. As transmission of HTLV-1 to the newborn via breast milk has been observed and as seropositive mothers can be advised to refrain from breastfeeding or to treat their milk, the question of routine screening for HTLV-1 infection during antenatal care is discussed.

INTRODUCTION

The human T cell leukaemia/lymphoma virus type 1 (HTLV-1), a member of the Oncovirinae subfamily of the Retroviridae, has been recognized as the causative agent of adult T-cell leukaemia/lymphoma, ATL [1, 2], and has been found to be closely associated with a chronic neurological disease termed tropical spastic paraparesis, TSP [2, 3], or HTLV-1 associated myelopathy, HAM [4]. However, there are many apparently healthy carriers [1, 5]. The virus is endemic mainly in Southern Japan and the Afro-Caribbean islands [6–8], but has also been found in regions as diverse as the Arctic [9], Papua New Guinea [10] and the South Western Pacific islands [11].

In the United Kingdom HTLV-1 infection has been described as mainly prevalent in immigrants from Afro-Caribbean countries [12–14]. The virus has been found to occur in remarkable intrafamilial clusters [15]. Transmission of the virus by blood or sexual contact is the most common mode of infection [16, 17], and universal screening of blood donations for HTLV-1 has been recommended by

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a Public Health Service Working Group [18] in the United States. However, besides this horizontal mode of transmission, vertical transmission from mother to infant during intrauterine life, perinatally via blood, or postnatally via breast milk, has been suspected, and evidence for this, especially the last, has been accumulated [19–22].

Epidemiological evidence [6, 15], and more recently the use of molecular techniques for the investigation of carrier mothers and their children [22], have indicated that transplacental infection of HTLV-1 is rare and that postpartum infection via breast milk is likely to be the major mode of transmission. The possibility of milk-borne oral infection has also been experimentally confirmed in marmosets [23]. High titres of specific HTLV-1 antibody in carrier mothers may be linked to increased risk for their infants [20, 24, 25]. It has been shown that if carrier mothers refrain from breast feeding, postnatal transmission is prevented [25]. Alternatively, heating to 56 °C for 30 min [26] or freeze-thawing [27] of milk of HTLV-1 carrier mothers was reported to eliminate HTLV-1 infectivity.

We have determined the HTLV-1 seroprevalence in a subpopulation of pregnant women by unlinked anonymous screening in an English antenatal clinic. Such serosurveys are needed in order to make rational decisions about national antenatal screening programmes and possible interventional measures.

MATERIALS AND METHODS

Subjects and collection of sera

The subjects were 3522 pregnant women attending an antenatal clinic in Birmingham, England, from February 1990 to January 1991. These women represented almost all those who attended the clinic during that time; a few were missed due to various technical circumstances. Sera were collected in an unlinked fashion, i.e. an aliquot was obtained from blood specimen taken for the purpose of unrelated routine antenatal testing.

Vials were numbered and accompanied by an anonymous form which carried the number and also information on age in 5 year intervals, ethnic origin, place of birth and, where applicable, date of immigration in 5 year intervals. To define the ethnic origin, the following conventions were employed. *Asia* denotes India, Bangladesh, Pakistan, *SE Asia* refers to Hong Kong, Singapore, Malaysia, Vietnam, Korea, China, the *West Indies* comprise the American New Commonwealth countries. The terms Asian, SE Asian, African and West Indian refer to ethnic origin rather than to country of birth, residence or nationality. The designation *white Caucasian* is used to distinguish people of European ancestry from the other groups [28].

The blood specimens and forms were sent to the Regional Virus Laboratory (RVL) at East Birmingham Hospital. This procedure and study had the approval of the local Ethical Committee.

Test procedures

Sera were screened by a passive particle agglutination test (PPAT, Serodia), and confirmatory tests were carried out by ELISA (Dupont) and an in house immunofluorescence test [14].

Table 1. Place of birth and ethnic origin of subpopulation in an unlinked anonymized screen for HTLV-1 infection in an antenatal clinic, Birmingham, Feb. 1990–Jan. 1991

Ethnic origin	Number of women with place of birth in							Total no. of women by ethnic origin (%)
	UK	Asia	West Indies	Africa	SE Asia	Europe (non-UK)	Other	
White Caucasian	1548	4		1		46	5	1604 (45.5)
Asian	328	886	1	51	6		2	1274 (36.2)
West Indian	423	2	78				1	504 (14.3)
African	3			12				15 (0.4)
SE Asian					40	1		41 (1.2)
Other	70		1	1			12	84 (2.4)
Total no. of women by place of birth (%)	2372 (67.3)	892 (25.3)	80 (2.3)	65 (1.8)	46 (1.3)	47 (1.3)	20 (0.6)	3522 (100.0)

Sera positive by these three tests at the RVL were referred to the Virus Reference Laboratory (VRL) of the Public Health Laboratory Service (PHLS), London, where they were retested by PPAT and ELISA (Abbott) and in addition by a competitive radioimmunoassay (Compria [29]), an IgG antigen capture RIA (Gacria [29, 30], Western blot (Dupont [29, 31]), and radioimmunoprecipitation assays (RIPA [31]). One indeterminate serum was retested by Western blot using reagents of Cambridge Biotech. Seropositivity by Western blot was determined according to the WHO criteria of 1990 (32): only sera reacting with the *gag* encoded proteins p19 and p24 (or the precursor p53) and the *env* encoded proteins gp46 and/or gp68 were regarded as HTLV-1 antibody positive.

RESULTS AND DISCUSSION

The ethnic origin and place of birth of the 3522 pregnant women tested are shown in Table 1. Almost half (45%) were white Caucasians of whom 96% were born in the United Kingdom. One third were Asian, of whom about 70% were born in Asia and the rest mostly in the United Kingdom. Fifteen percent were West Indian, but of them only about 15% were immigrants; the rest were born in the United Kingdom. Only 15 African women were tested, 12 of whom were born in African countries.

The mean age in the major subpopulations of the antenatal survey was 24–31 years ranging from 18 to 48 years. The mean age of all women was 26 ± 6 years (range 18–48 years). There was no significant difference in the mean ages of the different ethnic groups.

A total of six HTLV-1 antibody-positive or indeterminate sera were found (Table 2), an overall seroprevalence of 0.17% (95% confidence limits 0.08–0.37). Unequivocal seropositivity was recorded for one African woman born in Africa, one West Indian woman born in the Caribbean and three women of white Caucasian origin born in the United Kingdom. One indeterminate result was recorded for one West Indian woman born in Jamaica. This serum was repeatedly positive by PPAT, one commercial ELISA, the Compria test and by Western blot.

though only with *gag* bands. The *Gacria* was positive in only one specimen (Table 2).

It is difficult to judge what is reactive in the indeterminate serum (Table 2). Weber and colleagues [30] described some false positive sera all of which were negative by a competitive ELISA. According to guidelines of a Working Group of WHO [32] seropositivity is unambiguously proved by the detection of both *gag* and *env* bands on Western blot or RIPA. It is, however, known that *env*-specific antibody is often missed by Western blot when it can be found by RIPA. Furthermore, Hartley and colleagues [31] point out that a majority of sera which were indeterminate by Western blot but showed p19 and p24 bands, were positive by RIPA; therefore they concluded that detection of *env* antibodies was relatively insensitive. Recent experience in our laboratory with sera from different areas of Brazil showed that indeterminate HTLV-1 antibody results can be frequent (Wong, Mawson, Orton, Skidmore and Desselberger, in preparation), and similar observations have been made elsewhere [31, 33, 34]. Therefore, rather than counting this indeterminate result as a false positive, one could consider that it reflects infections with cocirculating viruses which are related, but not identical to HTLV-1, as discussed by others [11, 33–35]. Alternatively, indeterminate sera may have low titres of, or may have lost antibody to, *env* antigen. Our main conclusions (below) would not be significantly altered if the indeterminate result were excluded.

Confirmation of infection by the polymerase chain reaction, PCR [22, 34], was not carried out on the serum specimens because HTLV-1 progeny is mostly cell-bound and because we could not collect cellular specimens from the seropositive individuals due to the nature of sample collection. Clearly, indeterminate serological results should be checked by PCR where possible, but even then the ambiguity may not be solved [34]. Counting both the unambiguously positive and the indeterminate results, annual seroprevalence figures for the relevant subpopulations (Table 1) in the chance sample were calculated (Table 3). The prevalences of 2.56% (2/78; 95% confidence limits: 0.76–9.11%) for the West Indian immigrants and 8.3% (1/12; 95% confidence limits 2.0–38.3%) for the African immigrants are similar to prevalence data for these geographical areas [8, 36]. The annual seroprevalence in white Caucasians born in England, was much lower at 0.19% (3/1548; 95% confidence limits 0.07–0.57%). The low numbers of positive specimens do not allow us to attach formal significance to these differences in prevalence, although the confidence limits for white Caucasians do not overlap with those for West Indian or African immigrants. Seropositive cases were not found among the 1274 Asians nor among the 423 West Indians born in the United Kingdom (Table 1). The absence of seropositivity in UK-born West Indians confirms earlier reports although infection has been found in some UK-born children of patients with TSP [13, 14].

In our study neither the ethnic origin or birthplace of the womens' husbands or partners nor a history of blood transfusion were recorded. Therefore, no statement can be made as to whether the seropositivity in the three white Caucasian women is epidemiologically linked to the higher levels of seropositivity in the West Indian and African subpopulations. However, it seems likely that the white Caucasian women born in the UK acquired their infection by sexual or blood contact with

Table 2. Details of epidemiological data and test results of six cases reacting positive (5) or indeterminate (1) for antibody against HTLV-1

Patient no	Age (yr)	Ethnic origin	Country of birth	Age at time of immigration (yr)	Test reactivities*							Result
					IIFT	ELISA	COMPRIA	GACRIA	Western blot†	RIPA		
1	38	West Indian	Jamaica	33	(+)	-	+	-	-	p19, 24	No bands	Indeterminate
2	33	Caucasian (UK)	England	-	+	+	+	-	-	p19, 24	p24, gp68	Positive
3	18	Caucasian (UK)	England	-	+	+	+	-	-	p19, 24	ND‡	Positive
4	33	West Indian	St Kitts	8	+	+	+	-	-	p19, 24, 53 gp46	ND	Positive
5	27	African	Gambia	23	+	+	+	+	+	p19, 24, 53 gp46	ND	Positive
6	23	Caucasian (UK)	England	-	+	+	-	-	-	p19, 24, 53 gp46	ND	Positive

* All sera reacted positive by PPAT (at both RVL and VRL) and ELISA (Dupont, at RVL).

† Bands p19, 24 and 53 are gag derived, gp46 and gp68 env derived.

‡ This specimen was retested by Western blot (using reagents of Cambridge Biotech) and found to be positive by additional reaction with an env derived protein.

Table 3. *Annual prevalence of infection with HTLV-1 or related viruses in pregnant women of different ethnic origin and country of birth, Birmingham, Feb. 1990–Jan. 1991*

Ethnic origin	Country of birth	No screened	Infected with HTLV-1 or related virus	
			No	% (95% confidence limits)*
West Indian	West Indies	78	2†	2.56 (0.76–0.11)
African	Africa	12	1	8.3 (2.0–38.3)
White Caucasian	UK	1548	3	0.19 (0.07–0.57)
(Total)		(1639)	(6)	(0.4)
Total screened		3522	6	0.17 (0.08–0.37)

* The confidence limits were obtained by assuming the observed number to be a variable with a Poisson distribution. (For the upper confidence limit of the ratio 1/12 the binomial distribution was used.)

† 1 positive, 1 indeterminate.

a member of one of the higher seroprevalence groups. The seroprevalence figure of 0.2% among white Caucasian women might be higher in Birmingham than elsewhere in the UK, as Birmingham has a multiracial population.

Previous studies have reported confirmed HTLV-1 seroprevalence rates among pregnant women in London antenatal care of 1/135 cases (0.7%) for women from Africa and 5/260 cases (1.9%) for women immigrants from Caribbean countries [29]. A retrospective study in a London antenatal clinic reported that 10/3760 sera (0.3%) were positive for HTLV-1 antibody; of those, 6 were from West Indian and 2 from West African immigrant women [37]. By comparison 0.02% of unselected blood donors were found to be positive in the UK (J. Barbara, personal communication and [29]); even lower estimates were made for the UK as a whole [38]. Further prevalence testing for HTLV-1 infections in large numbers of normal blood donors is continuing in the London area at present (J. Barbara, personal communication and Note added in proof).

In conclusion it can be stated that HTLV-1 infection in antenatal sera in an urban environment in England was found mainly where it was expected [13, 14], namely in West Indian and African immigrants. The seroprevalence in white Caucasian women born in England is low (0.2%). It is, however, similar in size to the prevalence of HBsAg carriers in the healthy blood donor population in the United Kingdom, and the comparatively low HBsAg carrier rate has led to routine screening of all antenatal sera in various parts of the country so that immediate postnatal vaccination against HBV infection can be offered. This has been shown to be a highly successful public health measure [39–40].

As most infantile HTLV-1 infections occur postnatally [15, 22], and as there is good evidence that this can be prevented by abstaining from breast feeding [21, 25] or by physical treatment of breast milk [26, 27], routine antenatal screening for HTLV-1 infection should now be considered, at least in multiracial areas. The implications and costs of such a programme are enormous, and Cruickshank and colleagues [41] have regarded policies of preventing HTLV-1 carrier mothers from breast-feeding as a premature measure in low prevalence

areas. The observation that the lifelong risk of developing TSP after infection early in life is approximately 1/400 [42] must also enter the cost-benefit analysis. More data from a larger sample size are desirable in order to improve the precision of estimates in the different subpopulations. There is a need to improve confirmatory testing which is critical for epidemiological studies of HTLV-1 infections.

Future investigations of HTLV-1 infections in white Caucasians should ideally include collection of data on previous blood transfusions and on the ethnicity of husbands/partners. The latter data may be difficult to obtain. Together with HTLV-1 prevalence data in blood donors [38] such investigations will help to further unravel the epidemiology of infection with these retroviruses in the UK and to decide properly the need for HTLV-1 antibody testing during pregnancy and in blood donors [43, 44].

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Note added in proof

Only five out of 105760 consecutive blood donations (= 0.005%) obtained in North London in 1991 were confirmed to be HTLV-1 antibody positive, but four of them were Caucasian women whose risk factor for infection were sexual contacts with men from HTLV-1 endemic regions (Brennan MT, Runganga J, Barbara JAJ, Contreras M. The prevalence of anti-HTLV-1 in North London blood donors. Abstract, Symposium HTLV-1, Montpellier, France, 1992).

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