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Seroprevalence of human herpesvirus-8 (HHV-8) in countries of Southeast Asia compared to the USA, the Caribbean and Africa

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Summary Seroprevalence of HHV-8 has been studied in Malaysia, India, Sri Lanka, Thailand, Trinidad, Jamaica and the USA, in both healthy individuals and those infected with HIV. Seroprevalence was found to be low in these countries in both the healthy and the HIV-infected populations. This correlates with the fact that hardly any AIDS-related Kaposi's sarcoma has been reported in these countries. In contrast, the African countries of Ghana, Uganda and Zambia showed high seroprevalences in both healthy and HIV-infected populations. This suggests that human herpes virus-8 (HHV-8) may be either a recently introduced virus or one that has extremely low infectivity. Nasopharyngeal and oral carcinoma patients from Malaysia, Hong Kong and Sri Lanka who have very high EBV titres show that only 3/82 (3.7%) have antibody to HHV-8, demonstrating that there is little, if any, cross-reactivity between antibodies to these two gamma viruses. © 1999 Cancer Research Campaign

Human herpesvirus-8 (HHV-8), also known as Kaposi's sarcoma associated herpesvirus (KSHV), is associated with the aetiopathogenesis of Kaposi's sarcoma (KS), body cavity B-cell lymphoma, also called primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD) (Chang et al, 1994; Chang and Moore, 1996; Ganem, 1996; IARC, 1997; Boshoff and Weiss, 1998; Schulz, 1998). Current serological and molecular assays indicate that HHV-8 infection is not widespread, but predominantly restricted to populations at risk of AIDS-associated, endemic, or classic KS (Chang and Moore, 1996; IARC, 1997; Boshoff and Weiss, 1998; Schulz, 1998). The assays employed to measure HHV-8 antibodies include immunofluorescence assays (IFA) for latent and lytic proteins (Gao et al, 1996*a*; Kedes et al, 1996; Miller et al, 1996); ELISA for latent associated nuclear antigen (LANA) (Oskenhendler et al, 1998; Gao et al, 1996*b*), ORF 65 (Simpson et al, 1996), ORF 26 (Davis et al, 1997), and whole virus (Chatlynne et al, 1998); as well as K8.1 (Raab et al, 1998), capsid protein (Lin et al, 1997), and BC-1 cell extract (Schulz, 1998) immunoblots.

There are no serological data available on the prevalence of HHV-8 in Southeast Asia or the Indian subcontinent. Although HIV is now a common problem in this subcontinent (Bhoopat et al, 1994), classic and endemic KS do not occur (Wabinga et al, 1993; Ziegler, 1993; Bhoopat et al, 1994; Sukpanichant et al, 1998), and the incidence of AIDS-associated KS appears very low (Bhoopat et al, 1994; Sukpanichant et al, 1998). We investigated the prevalence in healthy individuals of HHV-8 (Table 1) in Southeast Asia (n = 234 from Malaysia and Thailand), Indian subcontinent (n = 188 from India and Sri Lanka), the West Indies (n = 410 from Jamaica and Trinidad), and three African countries (n = 164 from Uganda, Zambia and Ghana) and compared this with healthy donors' sera from the USA (n = 135). Where available, we also tested a limited number of sera from HIV-1-infected patients (Table 2) for HHV-8 antibody to see if the prevalence differed from the healthy population: India (n = 42), Thailand (n = 196), Zambia (n = 25), Uganda (n = 35), Trinidad (n = 12) and the USA (n = 124).

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MATERIALS AND METHODS

We employed a recently described whole virus enzyme-linked immunosorbent assay (ELISA; Advanced Biotechnologies Inc, Columbia, MD, USA) using sucrose-banded HHV-8 virus lysate as the source of antigen (Chatlynne et al, 1998). A whole virus ELISA has advantages over using individual viral proteins as a source of antigen, since the viral lysate contains a broad spectrum of seroreactivity compared to that detected by a single viral protein in ELISA, IFA, or immunoblots. Since this ELISA detects predominantly proteins to lytic antigens, we also compared this ELISA to a lytic antigen IFA in a subset of KS- and HIV-positive

Table 1 Detection of IgG antibody to HHV-8 (KSHV) lytic proteins by ELISA of populations from the USA, India, Sri Lanka, Thailand, Malaysia, Jamaica, Trinidad, Uganda, Zambia and Ghana

Country	Age (years) range	Male–Female	Group	Number of antibody positive/number tested[a]	Per cent positive
Infected controls	54–92	19–1	A. Classical (HIV-negative)	20/20	100.0
(Kaposi's sarcoma)	33–61	10–0	B. HIV-infected	9/10	90.0
1. *USA*	22–78	87–48	Blood donors	7/135	5.2
2. *Southeast Asia*					
India[b]	20–58	56–52	Healthy individuals	4/108	4.0
Thailand[c]	17–69	39–36	Healthy individuals	3/75	4.0
Malaysia	9–85	113–46	Healthy individuals	7/159	4.4
Sri Lanka[b]	21–78	48–32	Healthy individuals	3/80	3.8
3. *Caribbean*					
Jamaica	18–64	124–123	Blood donors	9/250	3.6
Trinidad[d]	20–>50	89–67	Blood donors	2/160	1.3
4. *Africa*					
Uganda	18–67	44–18	Healthy individuals	24/62	38.7
Zambia	17–68	22–18	Healthy individuals	15/40	37.5
Ghana	13–72	47–15	Healthy individuals	26/62	41.9

[a]All sera were tested for IgG at a dilution of 1:80 or 1:100 using sucrose density gradient purified HHV-8 as source of antigen. Negative: OD ≤ 0.113, equivocal: OD > 0.113 and < 0.128, positive: OD ≥ 0.128. HHV-8 antibody positive sera were rerun for conformation by IFA for lytic antigens at dilutions of 1:40. A few antibody negative sera from each country were run as controls. [b]Sera were collected in order to screen for HHV-6 and EBV. [c]Sera were collected to screen for HIV. Age and sex of three individuals were not traceable. [d]Four individuals' age and sex data were not available.

Table 2 Distribution of HHV-8 IgG antibody in HIV-1-positive individuals who do not have Kaposi's sarcoma[a]

Country	Group	Age (years) range	Male–Female	No. of antibody positive/No. tested	Per cent Positive
USA	HIV + homosexual men	21–55	62–0	27/62	43.5
	HIV + Non-KS (current)[b]	33–52	16–0	8/16	50.0
	HIV + Non-KS (retrospective)[c]	31–58	46–0	13/46	28.3
India	HIV-1 +	20–58	30–12	1/42	2.4
No HIV-associated KS reported					
Thailand	HIV-1+	19–41	100–96	22/196	11.2
No HIV-associated KS reported					
Uganda	HIV-1+	20–62	22–13	16/35	45.7
Zambia	HIV-1+	22–69	18–7	11/25	44.0
Trinidad	HIV-1+	20–50	9–3	0/12	0

[a]Sera were tested by ELISA to purified virus, some LNA (BCP-1 cell antibody), and by IFA to lytic proteins (KS-1 cell substrate). [b]Six of the eight that were antibody positive have since developed KS. [c]Patients either died or did not develop KS in the 10 years following the sample.

patient sera (n = 58). For the ELISA, sera were diluted at least 1:80 and for lytic IFA, sera were tested at a dilution of 1:40. Frozen and coded sera were shipped to the laboratory in Columbia, Maryland, for testing. Serum (obtained from Malaysia, Hong Kong and Sri Lanka) from patients with nasopharyngeal carcinoma, oral carcinoma and other diseases (infectious mononucleosis and African Burkitt's lymphoma) were also titred for Epstein–Barr virus (EBV) to see if patients with high EBV titres also tested positive for HHV-8, and to see if antibodies to EBV might cross-react with HHV-8 (Table 3).

Collection of serological samples

Serum/plasma samples from the USA

The healthy subjects consisted of blood donors and laboratory workers. The samples were obtained from a blood bank and drawn in a clinical laboratory. The HIV+, classical KS, and HIV+ KS sera came from the Department of Dermatology, New York University Medical Center, North Shore University Hospital (kindly provided by Drs A Friedman-Kien and Mark Kaplan), and the Norris Cancer Research Center, University of Southern California, Los Angeles (collected by Dr P Gill).

Samples from India

These were collected from individuals at blood bank facilities in Bombay, Madras and New Delhi for HIV testing. Therefore, the samples consisted of both healthy donors (HIV-negative) and HIV-positive individuals who were antibody-positive by radioimmunoassay and Western blot.

Samples from nasopharyngeal carcinoma, oral carcinoma, infectious mononucleosis, African Burkitt's lymphoma and from healthy donors and HIV+ patients from Africa

Most of the nasopharyngeal carcinoma (NPC) and all of the oral carcinoma (OC) sera were provided by the University of Malaya, Kuala Lumpur. All of the OC sera originally came from Sri Lanka

Table 3 Sera with high EBV antibody titres have no cross-reactivity with HHV-8

Sera type	No. tested	Male–Female	Age (years) range	Range of EBV-VCA antibody titres[a]	Range of EBV-EA antibody titres[b]	EBV IgG (titre) of HHV-8 antibody positive samples	HHV-8 IgG antibody (titre)	
Nasopharyngeal carcinoma patients (Malaysia and Hong Kong)	42	32–10	35–78	IgG 1:640–>1:5120	IgA 1:80–>1:320	1:1280 1:2560	2/42 (4.8)	(%) 1:80 1:160
Oral squamous carcinoma patients (Sri Lanka)	40	30–10	21–82	IgG 1:640–≥1:1280	ND[c]	1:640	1/40 (2.5)	≥1:80
Infectious mononucleosis patients (USA)	7	5–2	17–25	IgM 1:40–≥1:160	ND	–	0/7 (0)	
Burkitt's lymphoma children (Ghana)	12	8–4	6–16	IgG 1:320–≥1:1280	IgG 1:80–1:320	1:640	1/12 (8.3)	(1:160)

[a]The sera for antibody to EBV-VCA were tested by IFA using P3HR-1 Clone 1B cells of which 20% expressed VCA. [b]The antibody to EBV-EA was tested by IFA on Raji cells superinfected with EBV isolated from P3HR-1 cells. At 48 hours post infection, >50% of the Raji cells expressed EA. [c]ND – not done

to the University of Malaya for HHV-6/HHV-7 and other studies. The other NPC, African Burkitt's lymphoma (BL), and infectious mononucleosis (IM) sera were obtained from the Department of Microbiology/Immunology, Georgetown University School of Medicine, Washington, DC. These NPC sera originally came from Hong Kong (kindly supplied by Dr Ng). The BL sera (Table 3) from Ghana were originally part of another study on EBV conducted by Drs Robert Bigger and Paul Levine (National Cancer Institute's (NCI) Burkitt's lymphoma project). These sera were collected in the late 1960s and stored at the NCI Natural Products Repository. Some of the African sera (Uganda and Zambia) were made available by the Georgetown University, Washington, DC, the Cancer Research Institute, London, UK and the Natural Products Repository, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, Maryland. All of the healthy donors' sera from Ghana were also obtained from the Natural Products Repository of NCI and were collected in 1990 and 1991 from the Roforidua region for other NCI studies (ID = Ghana/Africa, ID = ward controls and ID = Kocle hospital).

Serum samples from Malaysia

These were collected from healthy donors by two of the authors, Drs Yadav and Norhanom, at the Institute of Advanced Studies, University of Malaya, as a part of an EBV seroepidemiology study. These sera were obtained from Chinese, Malays and Indians, whereas the NPC sera were from Chinese and Malays. These sera were stored at the University facility at –20°C.

Serum samples from Thailand

Serum samples of HIV-negative donors were collected at the Mahidol University of Thailand. The serum samples from HIV-positive donors were collected from the Remune Trail Center. Among the healthy donors (HIV-negative), three were found to be HHV-8 antibody-positive workers who applied for a permit to seek work in the Middle East. The age and sex of four serum samples were not traceable (Table 1).

Serum samples from Jamaica

Sera samples from normal blood donors were obtained from the National Transfusion Service, Kingston, Jamaica.

Serum samples from Trinidad

All samples from Trinidad were collected (Drs Cleghorn, Jack and Edwards) after informed consent from adult STD clinic attendees as part of a larger NIH-funded study to screen for early HIV-1 infection in the period 1995–1997.

Age and sex of donors

Age and sex of individuals from whom sera were collected varied in each group, whether collected at a clinic (as previously indicated), blood bank, or as part of a study group from healthy adults in the USA, India, Sri Lanka, Malaysia, Thailand, Uganda, Zambia, Ghana, Jamaica and Trinidad, and HIV-infected individuals from the USA, India, Trinidad, Thailand, Uganda, Zambia and Ghana (with and without KS). The age (range) and sex distribution of all sera tested are provided in Table 1, 2 and 3.

RESULTS AND DISCUSSION

Table 1 shows the distribution of HHV-8 IgG antibodies in healthy individuals from the countries tested. We used sera from patients with KS for a positive control, and all of these sera were positive for HHV-8 IgG antibody. The prevalence of HHV-8 in 5.2% of blood donors in the USA correlates with that previously reported using both latent IFA and immunoblot assays (Gao et al, 1996*a*; Kedes et al, 1996; Miller et al, 1996). The higher prevalence of HHV-8 in adults from Uganda (38.7%) and Zambia (37.5%) correlates with the incidence of endemic KS and the high incidence of AIDS-associated KS in these countries (Wabinga et al, 1993). In Ghana, however, the high seroprevalence of HHV-8 (41.9%) does not correlate with an increased incidence of African endemic KS (Ziegler, 1993), indicating that co-factors are probably necessary to precipitate endemic KS (Ziegler, 1993; Bourboulia et al, 1998). The high seroprevalence of HHV-8 antibody to lytic viral antigens further supports another study of pregnant African women and prostitutes from Cameroon (Bestetti et al, 1998) in which 52.6% who were HIV-positive demonstrated IgG antibody to HHV-8, compared to 42.6% who were HIV-negative. This is the first report to document the prevalence of KSHV in the Far East in healthy individuals (Table 1) and in HIV-1-positive individuals from these

countries (Table 2). As in other countries where endemic and classic KS are rare (e.g. Northern America and North Western Europe), HHV-8 infection appears restricted to less than 5% of healthy adults. Similarly, HHV-8 is not a common infection of healthy adults in the two West Indian countries tested: Trinidad (1.3%) and Jamaica (3.6%) (Manns et al, 1998). In HIV-1-infected populations, seroprevalence of HHV-8 is generally elevated above that of the general population in areas where KS is associated with HIV infection (e.g. USA); but in areas (India, Thailand) where HIV infection is on the increase, the lack of evidence of KS does not correlate. In spite of the high prevalency of HIV and AIDS in India and Thailand, the seroprevalency of HHV-8 is much lower in this population than in comparable HIV-positive populations in the USA or Africa (Table 2). The number of HIV-positive samples from Trinidad is too small to draw any conclusions; however, it may be similar to India and Thailand.

Since infection with EBV is widespread in the Far East and Indian subcontinent and is associated with NPC and endemic Burkitt's lymphoma, we tested sera from 40 patients with NPC from Malaysia and Hong Kong, from 40 patients with oral squamous carcinoma (OC) from Sri Lanka, from seven IM patients in the USA, and from 12 children with BL from Ghana to determine whether there is any immunologic cross-reactivity between the two human gamma herpesviruses, i.e. EBV and HHV-8, using this ELISA (Table 3). EBV antibodies were tested by IFA for anti-VCA IgG using a preparation of P3HR-1 cells (Clone 1B), that is about 20% positive for EBV viral capsid antigen (VCA). IgG and IgA antibody to EBV early antigen (EA) was tested by IFA with Raji cells superinfected with the P3HR-1 strain of EBV. After 48 h superinfection, approximately 60% of the cells are positive for EA as determined by monoclonal antibodies to EA-diffuse (EA-D) and EA-restricted (EA-R) (kindly provided by Dr Gary Pearson of the Georgetown University School of Medicine, Washington, DC). To test for EBV IgM, sera were first preabsorbed to remove IgG antibodies and then incubated on fixed P3HR-1 cells for 3 h. Table 3 shows the results of this study. The 42 NPC patients had very high IgG and IgA antibody titres to EBV-VCA and EBV-EA, but only two of these patients demonstrated antibodies to HHV-8. In addition, one serum from 40 patients with OC tested positive for HHV-8 IgG. Out of 12 BL patients with antibody to EBV, one had antibody to HHV-8. Seven IM sera with EBV IgM antibody were all negative for HHV-8 IgG. The titres of HHV-8 IgG-positive sera, i.e. NPC, OC and BL, are given in Table 3, which showed that the titres were not elevated (as observed in KS sera) (Chatlynne et al, 1998) in spite of the high EBV titres antibody (Table 3). This supports a lack of cross-reactivity between HHV-8 and anti-EBV antibodies in this ELISA, and further indicates that the HHV-8 IgG antibody detected in the general populations, HIV-positive individuals, and KS patients of the various countries tested was specific. This data further supports our previous finding where KS sera, after adsorption for EBV antibody, retained the HHV-8 IgG (Chatlynne et al, 1998).

In this study, we show that HHV-8 is not a common human pathogen in Southeast Asia or the Caribbean. Current data indicate that HHV-8 infection is more prevalent in countries where classic and endemic KS occurs (Whitby et al, 1998). In these countries, horizontal transmission and mother-to-child transmission are likely to occur (Bourboulia et al, 1998; Luppi et al, 1998; Gessain et al, 1999). In countries with a low incidence of classic or endemic KS, HHV-8 is predominantly found in homosexual men at risk of developing KS (Luppi et al, 1998; Martin et al, 1998; Verbeek et al, 1998), and is a sexually transmitted agent among these individuals (Martin et al, 1998). In Southeast Asia and the Caribbean, HHV-8 might be a relatively newly introduced pathogen. The restricted distribution of HHV-8 in these populations also correlates with the relatively low incidence of reported cases of classical KS or AIDS KS (Gill, personal communication, 1998; Jensen, personal communication, 1998). Longitudinal follow-up studies of individuals infected with HHV-8 in Southeast Asia and the Caribbean will help to assess the participation of this viral agent in the pathogenesis of KS and other diseases or malignancies. Future studies will attempt to determine the mode(s) of transmission of HHV-8 in the Far East and whether HHV-8 was present in sera collected prior to the AIDS epidemic.

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