

PREVALENCE OF HUMAN HERPESVIRUS 8 ANTIBODIES IN THE POPULATION OF BELÉM, PARÁ, BRAZIL

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SUMMARY

Serum samples from 497 children and adults inhabiting two neighbourhoods (Guamá and Terra Firme) in Belém, Pará, North Brazil were screened for the presence of human herpesvirus 8 (HHV-8) antibody using an enzyme-linked immunosorbent assay. An overall 16.3% prevalence was found for these urban communities. Taken both genders together, prevalence rates of HHV-8 antibody increase gradually, across age-groups, ranging from 12.0% to 33.3%. When seroprevalence is analysed by gender, similar rates are found for female (18.4%) and male (14.0%) individuals. In the former gender group, seroprevalence rates increased from 10.3%, in children ≤ 10 years of age, to 30.0% in adults 41-50 years of age. Conversely, among male subjects, the prevalence of HHV-8 antibodies decreased from 13.3% in children/young adults aged ≤ 10 to 20 years of age to 6.1% in adults aged 21-30 years. From the 31-40 year-old group male onwards, seropositivity rates increased gradually, ranging from 8.3% to 66.7%. A significant difference in seropositivity rates was noted when comparing 21-30 age groups for female and male subjects: 23.3% and 6.1%, respectively ($P = 0.03$). Geometric mean optical densities were found to increase slightly from the lower to the higher age-groups. Our data suggest that transmission of HHV-8 occurs frequently in the general urban population of Belém, and that prevalence of antibody seems to increase with age.

KEYWORDS: Prevalence; Human Herpesvirus 8; Urban population.

INTRODUCTION

Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma herpesvirus (KSHV), was discovered by CHANG *et al.* (1994)¹³ as a KS-specific DNA fragment. HHV-8 that belongs to the *Rhadinovirus*, or gamma-2 herpesvirus, genus within the subfamily *Gammapherpesvirinae*^{12,32}.

HHV-8 DNA sequences have been detected in peripheral blood lymphocytes of HIV-positive individuals with or without KS^{10,21,22,48}, in B-cell body cavity lymphomas^{9,18,37}, in uroepithelial cells of healthy immunocompetent individuals³¹, in HIV-1 negative patients with Bowen's disease²¹, in multicentric Castlemann's disease^{18,21}, in prostate tissue and in human semen^{7,20,31}. HHV-8 has also been associated with other tumors, including angiosarcomas, hemangiomas, malignant squamous cell carcinomas and actinic keratosis²³. This virus was also recently reported to infect healthy blood donors⁵. The presence of HHV-8 DNA in tonsillar swabs and saliva^{11,14,15} suggests that the virus replicates in tonsils and then is shed in saliva, which would contribute to HHV-8 transmission. This was also observed for the others herpesviruses^{15,16}.

Seroepidemiological studies suggest that HHV-8 has two major modes of transmission: sexual and non-sexual. The latter route of

transmission involves body fluids such as nasal secretions, saliva and blood therefore explaining the ample distribution of HHV-8 in many areas of the world^{5,6,24,28,38,43,45}.

HHV-8 is known to have a worldwide occurrence but infection rates vary according to a combination of geographic and behavioural risk factors^{2,37}. HHV-8 antibody titers among infected healthy adults were found to be higher in regions with high HHV-8 seroprevalence rates and where KS disease is common^{17,33}. In African populations with high rates of endemic KS, the prevalence of HHV-8 antibody in adults ranges from 30 to 60%^{1,33,40}. In contrast, seroprevalence rates among healthy heterosexual adults in North American and European populations are reported to be generally low, of 1-2%^{17,39}. Intermediate prevalence rates of HHV-8 antibodies among adults have been reported for Italy and Greece (20-35%)^{9,42,44,46}, whereas HHV-8 prevalence in Central American and Caribbean populations has been reported to range between 10 and 29%^{19,25,41}.

In Brazil, the prevalence of HHV-8 antibodies in the general populations has not yet been established. Indeed, studies carried out to date in Brazil have focussed on population groups that would theoretically be at increased risk of acquiring HHV-8 infection. Two of these studies have focussed on HHV-8 infection among HIV-positive patients with or

without KS^{10,22,49}. In this context, it has been demonstrated that the prevalence of HHV-8 antibody is higher among HIV-1 infected gay men with KS, as compared with other Brazilian groups. Of importance, an epidemiological survey conducted by ZAGO *et al.*⁴⁸, (2000) in Southeastern Brazil yielded HHV-8 antibody rates to latent nuclear antigens of 80% among HIV-positive patients with KS, whereas much lower, but similar seropositivity rates, were found for HIV-positive patients without KS (14.6%) and casualty patients (9.6%).

Recent seroepidemiological studies among remote Amerindian communities living in Northern Brazil - using an immunofluorescence test for latent antibody - showed an unusually high, overall 53% prevalence. In addition to this, a new HHV-8 E subtype was found to be hyperendemic in these Amerindians, although KS has not been reported to occur among them³.

The present investigation dealt with the prevalence of HHV-8 antibody [immunoglobulin G class (IgG)] in normal populations inhabiting two neighbouring, crowded districts of Belém, Northern Brazil.

MATERIALS AND METHODS

The present study involved 81 low-income families - including 497 subjects - living in 2 neighbourhoods ("Guamá" and "Terra Firme") of Belém, Brazil. These families were randomly selected from records of a previous rotavirus vaccine field trial conducted at the same site (LINHARES, *et al.*²⁶, 1996). Blood samples were drawn - by antecubital venepuncture - from all individuals (n = 497) (236 of whom were male) from August to December 1994. Infants aged less than six months were not enrolled to participate in this study. Overall, ages ranged from 7 months to 70 years (mean, 18 years, SD = 15). All sera were stored frozen, at - 20 °C, until (anonymously) processed for the presence of HHV-8 antibody.

Detection of IgG antibodies to HHV-8 was made using a commercial enzyme-linked immunosorbent assay (ELISA) developed by ADVANCED BIOTECHNOLOGIES™ (Columbia, Maryland, USA). This is an assay that includes solid-phase multiple-well strips coated with solubilized HHV-8 whole virus extract isolated from the KS-1 cell line³⁵. The KS-1 cell line is derived from a body cavity lymphoma, as previously described³⁶. Sera were tested at a (single) dilution of 1:100, according to manufacturer's instructions. ELISA results were calculated dividing optical density (O.D.) values of serum samples by the mean absorbance of cut-off. Serum samples yielding O.D. ratios of ≥ 1.00 were ranged as positive.

The data were analyzed using the EPI-INFO software version 6.0 (Atlanta, GA, USA). Rates were compared using the Mantel-Haenszel chi-square test of association or Fisher's exact test, when applicable. Significance was defined as P < 0.05.

RESULTS

Overall, 16.3% (81/497) of tested persons had HHV-8 antibody, with prevalence rates increasing from 12.0% to 33.3% across age groups (Table 1). Taking all age-groups together, similar seroprevalence rates were found for women and men: 18.4% and 14.0%, respectively. Increasing

percentages of HHV-8 antibody were observed in women from the first (10.3%) to the fifth age groups, and a comparatively low prevalence, 20%, was found among individuals over 50 years of age. Among male subjects the prevalence of HHV-8 antibody decreased from 13.3%, in children/young adults aged ≤ 10 to 20 years, to 6.1% in adults aged 21-30 years. In the following age groups, 8.3% positivity was detected in adults aged 31-40 years, rising to 66.7% in the age group > 50 years. A significant difference in prevalences was detected when comparing female and male individuals aged 21-30 years: 23.3% and 6.1%, respectively (P = 0.03). Serum anti-HHV-8 IgG concentrations - as measured by geometric mean optical densities (GMODs) according to age groups, are shown in Table 2. GMOD values increased slightly from the first to the fourth age groups (range, 1.5 to 1.9), decreasing across age-groups of more than 40 years. Overall GMODs for Female tended to be higher than those for Male: 1.8 and 1.5, respectively.

Table 1
Prevalence of antibody to HHV-8 according to age and gender in Belém, Pará, Brazil

Age groups (years)	No. of sera positive/No. tested (%)		
	Total	Female	Male
≤ 10	26/217 (12.0%)	10/97 (10.3%)	16/120 (13.3%)
11- 20	16/92 (17.4%)	10/47 (21.3%)	6/45 (13.3%)
21- 30	16/93 (17.2%)	14/60 (23.3%) ^a	2/33 (6.1%) ^b
31- 40	10/56 (18.0%)	8/32 (25.0%)	2/24 (8.3%)
41- 50	6/18 (33.3%)	3/10 (30.0%)	3/8 (37.5%)
>50	7/21 (33.3%)	3/15 (20.0%)	4/6 (66.7%)
Total	81/497 (16.3%)	48/261 (18.4%)	33/236 (14.0%)

^a vs ^b Significant difference between prevalence rates (P = 0.03)

Table 2
Distribution of geometric mean optical densities of HHV-8 antibody according to age and gender in Belém, Pará, Brazil

Age (years)	Geometric mean optical densities		
	Female	Male	Total
≤10 ^a	1.5 (97)	1.6 (120)	1.5 (217)
11-20	1.8 (47)	1.5 (45)	1.7 (92)
21-30	1.9 (60)	1.3 (33)	1.8 (93)
31-40	1.9 (32)	2.3 (24)	1.9 (56)
41-50	2.0 (10)	1.2 (8)	1.5 (18)
> 50	1.7 (15)	1.9 (6)	1.8 (21)
Total	1.8 (261)	1.5 (236)	1.7 (497)

^a All children in this age-group were older than 6 months.

DISCUSSION

Recent studies^{2,17,35,37} have indicated a great variability in the HHV-8 antibody prevalence in different geographic areas worldwide. Serological and molecular studies suggest that HHV-8 may be largely distributed in the human population and, like other herpesviruses, it has

the potential of infecting latently tissues and body fluids, until reactivation^{4,11,25,27,38}. Worldwide, recent serosurveys indicate that HHV-8 infection rates in various populations vary considerably, according to a combination of geographic and behavioural factors^{2,17,35,37,38}. In Brazil, very few studies have dealt with the epidemiology of HHV-8 infection in the general population. In fact, most of these investigations have focussed on specific, high-risk groups of the population, such as those represented by HIV-seropositive individuals with or without KS^{10,22,48,49}.

The goal of the present study was therefore to determine the prevalence of HHV-8 antibodies in Belém, Brazil, regardless of the target population's HIV serological status. To our knowledge, this seems to be the first approach in Northern Brazil aimed at assessing the immune status of the general, urban population to HHV-8⁴⁹.

The overall HHV-8 seroprevalence (16.3%) in the Belém low-income, urban communities is comparable to those observed for adult populations in Italy and Greece^{18,37,42,46}, where seropositivity rates averaged 19.5%. These similarities suggest that both crowding and poor sanitation, which are prevailing conditions in the resource poor study areas of Belém, do not seem to enhance the potential for HHV-8 transmission, as already demonstrated in previous studies. It should be pointed out, however, that a few investigations propose a direct relationship between poor socioeconomic condition and the potential for HHV-8 transmission²⁹.

Unlike the comparison made above, local seroprevalence rates were much lower than those reported for endemic countries in Africa, as well as for hyperendemic Brazilian Amerindian remote communities^{1,3,33,40}. The high prevalence in African countries might be explained by the fact that HHV-8 infection rates generally parallel KS disease which is known to be endemic in several parts of the continent, particularly East Africa. Among hyperendemic Amerindian tribes, where KS has not been reported, it has been postulated that transmission is probably oral rather than sexual. Moreover, it has been hypothesized that Indians' genetic homogeneity may permit more frequent transmission of HHV-8 than that in heterogeneous populations. Studies conducted in Southeastern Brazil by ZAGO *et al.*⁴⁸ (2000) found a 4.6% seroprevalence among blood donors, a rate which is lower than that yielded for the urban population of Belém, Brazil. Although such a difference may be related to the use of different serological assays between studies under comparison, it seems plausible to postulate that blood donor groups *per se* are at an inherently lower risk of becoming infected by HHV-8 than is the general population taken as a whole.

In this study, the overall prevalence rate of HHV-8 antibodies in children aged ≤ 10 years (12.0%) was found to be lower, as compared with data from several authors^{8,25,39}. In spite of this, however, it can be concluded that, in Belém, Brazil, a significant proportion of HHV-8 infection occurs during childhood, suggesting horizontal transmission, perhaps among siblings, but also from mother to child³⁴. The fact that there are progressively increasing prevalence rates with increasing age suggests endemicity of HHV-8 infection in the Belém urban communities. In this context, it is most likely that transmission through sexual route also play a role during adolescence and adulthood^{8,25,47}. It is noticeable that antibody prevalence rate peaks - 33.3% - among adults aged ≥ 41 years, including the elderly, and this raises the question on whether HHV-8 reactivation may occur in addition to the largely proposed sexual- and- nonsexual routes of transmission, particularly among the oldest

persons^{4,11,22,30}. Of note, in female subjects the pattern of antibody acquisition by age is similar to that of both gender groups taken together; however, among male individuals there was a significant decrease in seroprevalence rates from the group of individuals aged ≤ 10 -20 years to that of 21-40 years. Although this may have occurred by chance, mainly because of the small sample size, it could be hypothesized that sexual route transmission might play a major role in the latter age group, and men would be at lower risk of HHV-8 infection than women⁷.

It was observed that seropositivity rate in female adults aged 21-30 years was significantly higher than that for male individuals clustered in the same age group ($P = 0.02$). Although there is currently no well-founded explanation for this difference, one can postulate that women are at greater risk of HHV-8 infection, since this virus can be shed into semen and might be transmitted during sexual intercourse⁷. Conversely, shedding of HHV-8 into the genital tract of infected women is known to be uncommon, suggesting that female-to-male transmission is probably low⁴⁷.

The progressive increase of geometric mean optical densities (GMODs) across age-groups essentially reflects the pattern of antibody acquisition as indicated by seroprevalence rates.

The results presented herein indicate that HHV-8 infection is endemic in the urban population of Belém, Brazil. It is suggested that a significant proportion of transmission occurs during childhood and that adult women may be at greater risk of HHV-8 infection than men. Further local studies are planned, focussing on the epidemiological features of HHV-8 infection in high-risk groups, for example, HIV-infected persons with KS.

RESUMO

Prevalência de anticorpos para o herpesvírus humano tipo 8 na população de Belém, Pará, Brasil

Amostras de soro de 497 crianças e adultos residentes em 2 bairros (Terra Firme e Guamá) de Belém, Pará, norte do Brasil foram examinadas com o propósito de detectar-se anticorpos para o herpesvírus 8, utilizando-se a técnica imunoenzimática. A soroprevalência total nessas comunidades urbanas foi de 16,3%. As taxas de prevalência de anticorpos para o HHV-8, considerando ambos os sexos, aumentou progressivamente através dos grupos de idade, variando de 12,0% a 33,3%. Quando a soroprevalência é analisada por sexo, taxas similares são encontradas para os indivíduos do sexo feminino (18,4%) e masculino (14,0%). A taxa de prevalência no sexo feminino aumentou de 10,3%, em crianças ≤ 10 anos, para 30,0% nos adultos de 41-50 anos. Já nos indivíduos do sexo masculino, a prevalência de anticorpos para o HHV-8 decresceu de 13,3%, nas crianças/adultos de ≤ 10 a 20 anos de idade, para 6,1% em adultos com 21-30 anos. Do grupo etário de 31-40 anos para frente, as taxas de soropositividade relativas ao sexo masculino aumentaram gradualmente de 8,3% a 66,7%. Diferença significativa foi observada nas taxas de soropositividade relacionadas ao grupo etário de 21-30 anos, se comparados indivíduos dos sexos feminino e masculino: 23,3% e 6,1%, respectivamente ($P = 0,03$). A média geométrica das densidades óticas aumentaram progressivamente do menor para o maior grupo de idade. Nossos dados sugerem que a transmissão do HHV-8 ocorre com frequência na população de Belém e que a prevalência de anticorpos observada aumentou com a idade.

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