High Titers of Anti-Human Herpesvirus 8 Antibodies in Elderly Males in an Endemic Population

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Human herpesvirus 8 (HHV8) is the etiologic agent of Kaposi’s sarcoma (KS), a tumor occurring mainly among elderly men in its endemic and classical forms. The male-to-female ratio of KS in different endemic populations ranges from 3:1 to 15:1. We investigated the influence of age and gender on anti-HHV8 antibody titers among HHV8-seropositive subjects of an endemic population (1819 villagers with 874 men and 945 women) of African origin living in French Guiana. By using a specific immunofluorescence assay, we found that the overall HHV8 seroprevalence of antibodies against lytic antigens was 11.8%. There was no difference between seroprevalence in males (11.7%) and females (11.8%). Among the 214 HHV8-seropositive subjects, anti-HHV8 antibody titers were found to increase with age (P<.001) and were higher in males than in females (P = .003). The geometric mean of HHV8 antibody titers was 1:105 (95% confidence interval [CI] = 1:77 to 1:144) for males versus 1:62 (95% CI = 1:47 to 1:81) for females. The titers increased from 1:59 (95% CI = 1:43 to 1:80) in males younger than 40 years to 1:452 (95% CI = 1:244 to 1:839) in the oldest male group (aged 50 years and older). Such high antibody titers directed against lytic antigens in males aged 40 years and older parallel the increase of endemic KS incidence in older African men. Our results suggest that the role of gender should also be considered in evaluating the association between anti-HHV8 antibody titers in people aged 40 years and older and the risk of developing KS. [J Natl Cancer Inst 2002; 94:1333–5]

There is now strong epidemiologic evidence and laboratory data indicating that the human herpesvirus 8 (HHV8; also known as Kaposi’s sarcoma [KS]-associated herpesvirus) is the etiologic agent of all forms of KS. KS is a tumor of mixed cellularity occurring mainly among elderly men in its endemic and classical forms (1,2). In endemic populations for KS (incidence ranging from 1 to 5 per 100,000 inhabitants), as in some regions of the Mediterranean basin and of East and Central Africa, the male-to-female ratio for KS ranges from 3:1 to 15:1. In Italy, the median age at diagnosis of classical KS is 64 years (male-to-female ratio of 3:1) (3). In Central African populations, the median age at diagnosis is younger, around 45 years, but nearly 70% of the KS patients are aged 35 and older, and the male-to-female ratio is around 15:1 (2). However, in HHV8 endemic populations, which are superimposed on those endemic for KS, viral seroprevalence increases with age, but no difference according to gender is reported.

We have recently performed a large epidemiologic survey in an HHV8 endemic population of African origin (Noir-Marron) living in two neighboring villages of French Guiana—Maripasoula and Papaïchton—to determine the modes of virus transmission (4). Informed consent was obtained from adults or from parents of minors, and the study was conducted following human experimentation guidelines from Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (CCPPRB) of Necker Hospital, Paris, France, and Commission Nationale de l’Informatique et des Libertés (CNIL). In this population, the overall HHV8 seroprevalence was found to increase with age, but no difference between males and females was observed (4). Human immunodeficiency virus-1 (HIV-1) is very unlikely to influence HHV8 seroprevalence in the Noir-Marron population from these villages since none of the 300 people aged 18–34 years were HIV-1 seropositive (4). The entire Noir-Marron population consists of only about 5000 inhabitants in French Guiana, from which we studied an important representative sample (1819 persons). There are no available data on the KS incidence in such a small group of inhabitants. On the basis of other observations, we believe that the KS incidence in this population is likely to be very low, even over a 10-year period.

The aim of the present study was to investigate the influence of age and gender on anti-HHV8 antibody titers among HHV8-seropositive subjects in this endemic population. All plasma samples were tested at a 1:20 dilution by an immunofluorescence assay (HHV8 IFA; ABI, Columbia, MD) that detected antibodies directed mainly against lytic antigens (4). Anti-HHV8 antibody titers were determined through successive twofold dilutions. Statistical analyses were performed by using a distribution-free analysis of variance based on ranks (PROC RANK and PROC ANOVA procedures of the SAS program, version 6.12; SAS Institute, Cary, NC). Age was considered as a categorical variable with the following six age groups: 2–9, 10–19, 20–29, 30–39, 40–49 and ≥50 years old, as shown in Fig. 1.

The present study included 1819 Noir-Marron individuals (874 men, 945 women) with an overall HHV8-seroprevalence of antibodies against lytic antigens of 11.8% and no statistically significant difference (P = .90) between males (11.7%) and females (11.8%). Among the 214 HHV8 seropositive subjects, anti-HHV8 antibody titers were found to strongly increase with age (P<.001) and were statistically significantly higher in males than in females (P = .003). Overall, the geometric mean of HHV8 antibody titers was 1:105 (95% CI = 1:77 to 1:144) for males versus 1:62 (95% CI = 1:47 to 1:81) for females. With respect to the results shown in Fig. 1, the analysis was also performed using an age cutoff of 40 years. Below age 40, there was no difference in anti-HHV8 antibody levels with age (P = .26) and gender (P = .07). In contrast, in subjects aged 40 years and older, anti-HHV8 antibody titers statistically significantly increased with age (P<.001) and were strongly higher.
in males (1 : 400, 95% CI 1 : 246 to 1 : 650) than in females (1 : 126, 95% CI 1 : 76 to 1 : 211). As an example, the geometric mean of anti-HHV8 antibody titers increased from 1 : 59 (95% CI 1 : 43 to 1 : 80) in males less than 40 years old to 1 : 452 (95% CI 1 : 244 to 1 : 839) in the oldest male group (aged 50 years and older).

To further investigate such findings, we also searched for antibodies directed against the HHV8 latency-associated nuclear antigen (LANA) by IFA with the use of BC3 cells. A positive anti-LANA serology was found in only 68 (31.8%) of the 214 individuals having anti-lytic antibodies. Such a difference, also reported in other studies (5,6), is probably due to the lower sensitivity of the anti-LANA assay and may be related to the fact that the lytic antibody IFA method detects a wider array of antigens than the anti-LANA assay. However, individuals with high anti-lytic antigen titers were more likely to have anti-LANA antibodies than were those with lower anti-lytic antigen titers. The proportion of subjects with anti-LANA antibodies was 7.5% (10 of 132), 59.5% (28 of 47), and 85.7% (30 of 35) among subjects with low (<1 : 80), intermediate (1 : 80–1 : 320), and high (>1 : 320) anti-lytic titers, respectively. Most of the anti-LANA seropositive individuals were older than 40 years (41 of 68) and displayed higher anti-LANA titers (1 : 372, 95% CI 1 : 223 to 1 : 623) than did the 27 subjects younger than 40 years (1 : 191, 95% CI 1 : 121 to 1 : 302), although this difference did not quite reach statistical significance (P = .054). In contrast, there was clearly no difference in anti-LANA antibody levels according to gender (P = .6).

Few studies have investigated the anti-HHV8 antibody titers in endemic populations. One study (7) showed that anti-HHV8 antibody titers in blood donors from different regions of Italy mirror the incidence of KS in those regions. Another study (8) found that, among black South African patients with cancer, the highest anti-HHV8 antibody titers were observed in KS patients. However, both studies analyzed only anti-LANA antibodies and did not investigate the association between gender and the antibody titers.

The present study was performed in an endemic population of African origin. We found that anti-HHV8 antibody titers directed against lytic antigens increased in elderly males. This pattern of variation parallels the increase of endemic KS incidence in elderly African men (2). It is interesting that the association between high titers of antibodies directed against lytic antigens of an oncogenic virus and cancer development has already been established for Epstein-Barr virus (EBV, another human gamma herpesvirus) and Burkitt’s lymphoma or nasopharyngeal carcinoma (9). It is important to note that, whereas there is no gender difference in the EBV seropositive/seronegative status in adults, females have higher antibody titers to EBV lytic antigens (10–12), indicating that the increase of anti-HHV8 antibody titers observed in males is not a common age and gender pattern for human antibodies directed against herpesviruses. Overall, our results suggest that high anti-HHV8 antibody titers directed against lytic antigens could potentially...
be an important risk factor for KS development in HHV8 endemic populations. Epidemiologic confirmation of this result would require large prospective studies in HHV8 endemic populations. Such studies are difficult to conduct. However, it is worthwhile to note that in the specific population of patients co-infected by HHV8 and HIV (mostly homosexual men), a recent epidemiologic study found that increasing anti-HHV8 lytic antibody titers were associated with an increased risk of developing KS (13,14).

REFERENCES


NOTE
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