

BRIEF COMMUNICATION

Prevalence of Human Herpesvirus 8 Antibodies in Young Adults in Denmark (1976–1977)

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Serologic studies (1–5) indicate that an epidemic of human herpesvirus 8 (HHV8) or Kaposi's sarcoma (KS)-associated herpesvirus, the viral etiologic agent of KS, occurred among homosexual men in the United States and in Europe concurrently with the human immunodeficiency virus-1 (HIV) epidemic in the early 1980s. However, studies from the United States (1,6) suggest that HHV8 possibly had become prevalent in some gay communities before the HIV epidemic. Thus, in the first decade of the U.S. HIV epidemic, the risk of acquired immunodeficiency syndrome (AIDS)-related KS in homosexual men was higher in HIV epicenters, such as New York, than elsewhere (6). Accordingly, the risk among homosexual men of being or becoming HHV8 infected from 1982 through 1990 was higher in New York than in Washington, DC (1).

Little is known about the epidemiology of HHV8 in Europe before the HIV epidemic. Although studies (4,7) indicate that HHV8 was disseminated to the European gay communities from the United States or from KS-endemic regions, such as Africa, in conjunction with the introduction of HIV, it is not known whether HHV8 was already prevalent in the gay communities before the HIV epidemic. To study the prevalence of HHV8 infection before the HIV epidemic, we examined sera for HHV8 antibodies in individuals attending an outpatient clinic for a sexually transmitted disease (STD) in Copenhagen, Den-

mark, from March 1976 through February 1977.

This study was approved by the Scientific Ethics Committees for Copenhagen and Frederiksberg Municipalities and by the Danish Data Protection Agency. The study population has been described in detail elsewhere (8). Briefly, from March 1976–February 1977, individuals attending the largest STD outpatient clinic in Copenhagen were invited to participate in a serologic study of gonorrhea. For all participants, information was recorded on age, sex, place of birth, and history of gonorrhea, including the outcome of actual clinical and microbiologic examinations. All participants had blood drawn, and since the original study, the sera have been stored at -20°C . For the present study, we analyzed the sera from 641 anonymous individuals. The sera were analyzed for antibodies against HHV8 as described previously (9). Specifically, antibodies against the lytic phase glycoprotein K8.1 were detected with the use of a recombinant protein enzyme-linked immunosorbent assay (ELISA) (9). The samples that had an optical density of greater than 0.5 were further analyzed for antibodies against the HHV8 latency-associated nuclear antigen by an indirect immunofluorescence assay that used the latently HHV8-infected BCP-1 cell line (9). Sera were classified as HHV8 positive if the optical density reading in the ELISA was greater than 1.0 or for samples with optical density readings between 0.5 and 1.0 if they were also positive by the indirect immunofluorescence assay (9). This testing algorithm is estimated to detect antibodies for HHV8, with a sensitivity of approximately 85% and a specificity of approximately 97% (9).

We assessed age- and sex-specific HHV8 antibody prevalence and also evaluated the relevance of a diagnosis of gonorrhea (ever versus never) and country of origin (participants from classic KS-endemic areas [defined here as African countries, Italy, Israel, and Greece] versus all other countries). The relative risk of having HHV8 antibodies was estimated as the odds ratio (OR) ascertained by logistic regression analyses (SAS version 6.12; SAS Institute Inc., Cary, NC), with likelihood ratio-based 95% confidence intervals (CIs). All statistical tests were two-sided.

Overall, 27 (4.2%) of 641 individuals had HHV8 antibodies. The distribution by age, sex, country of origin, and history of gonorrhea is provided in Table 1. The prevalence was 5.1% (20 of 391) in men (4.1% [13 of 314] among Danish men only) and 2.8% (seven of 250) in women (3.2% [seven of 216] among Danish women only), a statistically nonsignificant difference ($P = .14$) (Table 1). Overall, the prevalence of HHV8 antibodies increased with age (Table 1). Originating from a classic KS-endemic area was associated with a 15.7-fold (95% CI = 5.0 to 45.5) increased likelihood of having HHV8 antibodies (Table 1). Because of the small number of women from KS-endemic areas, however, the increased risk associated with origin could be demonstrated only in men (OR = 15.5; 95% CI = 4.7 to 48.2) (Table 1). Overall, history of gonorrhea was associated with a 3.4-fold (95% CI = 1.4 to 10.4) increased likelihood of having HHV8 antibodies (Table 1). The increased risk of having HHV8 antibodies was associated more strongly with a history of gonorrhea in men (crude OR = 4.5 [95% CI = 1.3 to 15.8]; adjusting for country of origin, OR = 3.8 [95% CI = 1.2 to 16.6]) than in women (OR = 1.9; 95% CI = 0.4 to 13.2). However, after adjusting for country of origin, the difference in risk estimates between men and women was not statistically significant ($P = .24$).

The application of different serologic assays makes it difficult to compare directly the prevalence of HHV8 antibodies in different populations (10). Still, the prevalence of HHV8 antibodies in this study of STD clinic attendees from 1976 through 1977, ranging from 3.2% in women to 4.1% in men, is of a similar order of magnitude to that reported in recent blood donor surveys in other

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Table 1. Human herpesvirus 8 (HHV8) status for 641 patients attending an outpatient clinic for the treatment of sexually transmitted diseases in Copenhagen, Denmark, from March 1976 through February 1977, by age, country of origin, and history of gonorrhea, with risk estimates and 95% confidence intervals*

	Men	Women	All
	HHV8 positive/total No. (% positive)	HHV8 positive/total No. (% positive)	HHV8 positive/total No. (% positive)
Age, y			
<20	0/32 (0)	1/47 (2.1)	1/79 (1.3)
20-24	5/106 (4.7)	2/81 (2.5)	7/187 (3.7)
25-29	4/99 (4.0)	1/58 (1.7)	5/157 (3.2)
30-34	4/76 (5.3)	2/30 (6.7)	6/106 (5.7)
35-39	4/29 (13.8)	1/17 (5.9)	5/46 (10.9)
≥40	3/49 (6.1)	0/17 (0.0)	3/66 (4.5)
OR (per 1-y increase)	1.1 (95% CI = 1.0 to 1.1)	1.0 (95% CI = 0.9 to 1.1)	1.1 (95% CI = 1.0 to 1.1)
P for linear trend†	P = .05	P = .72	P = .04
Country of origin			
Africa/Greece/Italy/Israel	6/16 (37.5)	0/1 (0.0)	6/17 (35.3)
Other countries	14/375 (3.7)	7/249 (2.8)	21/624 (3.4)
OR (endemic origin)	15.5 (95% CI = 4.7 to 48.2)	Not analyzed	15.7 (95% CI = 5.0 to 45.5)
History of gonorrhea			
Yes	17/223 (7.6)	5/144 (3.5)	22/367 (6.0)
No	3/168 (1.8)	2/106 (1.9)	5/274 (1.8)
OR (gonorrhea history)	4.5 (95% CI = 1.3 to 5.8)	1.9 (95% CI = 0.4 to 13.2)	3.4 (95% CI = 1.4 to 10.4)
Total	20/391 (5.1)	7/250 (2.8)	27/641 (4.2)

*CI = confidence interval; OR = odds ratio.

†Tests for departure from linear trend were not statistically significant in men ($P = .24$), in women ($P = .56$), or in all individuals combined ($P = .60$). All statistical tests were two-sided.

countries outside the HHV8-endemic areas [reviewed in (11)].

We have observed previously an increased incidence of non-AIDS-related KS among male immigrants from KS-endemic areas in Denmark during the period from 1970 through 1989 (12). In accordance with this observation and compatible with studies of more recently collected materials (11,13,14), we now find that originating from such geographic regions was a strong determinant for HHV8 infection before the HIV epidemic. Together, our observations indicate that, before the HIV epidemic, individuals from KS-endemic areas may have constituted an important reservoir for HHV8 infection in countries with a low incidence of classic KS.

A history of gonorrhea was also associated with an increased risk of having HHV8 antibodies. Of interest, the association with gonorrhea was most pronounced in men. Although we cannot rule out that this is a chance finding, it is noteworthy that various measures of promiscuity, including STD history, have been associated with a risk of HHV8 infection in homosexual men (2,4,14), whereas evidence for the sexual transmission of HHV8 has been less consistent in women and heterosexual men (13-18). Systematically recorded information on homosexuality or on STDs other than gonorrhea was not

available in our study. However, another study that was performed in 1983 (19) found that homosexual men were excessively represented among male STD patients, constituting approximately 30% of all men with gonorrhea, compared with an estimated 3% of the general male population of the same age (20). Therefore, the observed strong association between a history of gonorrhea and HHV8 seropositivity in men could reflect a high prevalence of HHV8 antibodies in the homosexual population before the onset of the HIV epidemic. This speculation finds indirect support from other studies. For example, in 1981, the prevalence of HHV8 antibodies was 20% in HIV-seronegative homosexual men in Denmark (4). Also, never-married men, a crude epidemiologic surrogate measure for homosexual men, were at increased risk of developing classic KS in Denmark from 1970 through 1989 (12). Moreover, albeit not conspicuous in Denmark, KS incidence started to increase in the other Nordic countries several years before the HIV epidemic, particularly, although not exclusively, among younger men (21). The concept of a pre-HIV epidemic increase in HHV8 antibody prevalence need not conflict with evidence suggesting that the HHV8 epidemic in Denmark (4), similar to that in the U.K. (7), may have been accelerated by sexual contacts with

men from the U.S. epicenters of HIV and HHV8 epidemics, e.g., if, at the onset of the HIV epidemic, the prevalence of HHV8 was markedly higher in these U.S. communities than in the Danish gay community in general.

Our study was based on only 641 anonymous samples from a population at high risk of STDs, accompanied by limited information on demographic and behavioral exposures. The small number of HHV8 antibody-positive individuals produced risk estimates with wide CIs; therefore, our results should be interpreted with caution. Nevertheless, our study suggests that HHV8 infection was prevalent in young adults in Denmark from 1976 to 1977 and that the risk of being infected with HHV8 was associated with originating from an area endemic for classic KS and a history of gonorrhea. Together with other lines of evidence, the latter observation is compatible with the suggestion that the prevalence of HHV8 antibodies may have been elevated in Danish homosexual men before the onset of the HIV epidemic.

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NOTES

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