Human Herpesvirus 8 Seropositivity in Rural Uganda: Maturation of Sero-epidemiological Studies

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(See the article by Butler et al., on pages 625–34.)

Human herpesvirus 8 (HHV8, also called Kaposi sarcoma [KS]–associated herpesvirus) is a necessary but insufficient cause of KS [1]. KS is a major public health problem in Africa, where it was endemic before the human immunodeficiency virus (HIV) infection epidemic [2], accounting for up to 18% of cancers in adults in some regions, including parts of Uganda, the Congo, and Rwanda [3]. The disease was known to occur in children [4], intuitively suggesting that HHV8 could be transmitted during childhood. Currently, KS is the most common cancer in men and the second most common cancer in women and children in Uganda, highlighting the dramatic impact of the HIV infection epidemic on KS incidence [5]. The discovery of HHV8 in 1994 [1] and subsequent development of antibody assays with reasonable sensitivity and specificity paved the way for sero-epidemiological studies to characterize the distribution of HHV8, the risk factors for infection, and the risk for KS after HHV8 infection. The geographic distribution of HHV8 seropositivity generally parallels that of KS [6, 7]. In sub-Saharan Africa, HHV8 seropositivity is higher (50%–80% in adults) in the eastern and central regions and lower (10%–40% in adults) in western and southern regions [7]. HHV8 infection seroprevalence increases with age in children [8] and is associated with having an HHV8-seropositive mother or family member [9]. HHV8 can be transmitted by transfusion, but the risk is relatively small (2%–3% per transfusion), compared with the risk of community-acquired HHV8 (3% per year) [10, 11]. HHV8 DNA is detected frequently and at high levels in saliva of asymptomatic individuals [12, 13], consistent with the theory that saliva is the dominant conduit of HHV8 spread [14]. Among adults, some studies [15], but not all [16], have shown a modest association of HHV8 seropositivity with age. The association of HHV8 seropositivity with sexual risk factors has been inconsistent [16–20].

The article by Butler et al [21] in this issue of *the Journal* is the largest population-based study to evaluate epidemiological risk factors of HHV8 infection among children and adults in a country where KS is a major public health problem. Thus far, our knowledge of HHV8 sero-epidemiology in Africa has been derived from studies that suffered from many limitations, including relatively small size and especially the reliance on selected populations, such as children attending hospital clinics [10], commercial sex workers[18, 20], patients attending sexually transmitted disease clinics, or selected occupational groups [17, 19]. These limitations may explain, in part, some of the conflicting associations and/or lingering doubts that even consistent findings can be generalized. Butler et al [21] avoided many of the limitations of prior studies. They studied 1383 children (age. 18 months–13 years) and 1477 adults enrolled from their homes in a rural parish in Uganda. They meticulously documented socioeconomic and behavioral risk factors, including saliva sharing practices, which have not been evaluated before, using questionnaires. In addition, they tested for serologic evidence of other infections (cytomegalovirus [CMV], herpes simplex virus-1 [HSV1], hepatitis B virus [HBV]), and HIV) that have established modes of transmission. They detected HHV8 antibodies using an in-house K8.1 immunoassay with which they have accumulated substantial experience in other studies conducted in Uganda [11].

Among the children, they found that HHV8 infection seroprevalence increased with age, doubling from 15.5%

Received 21 October 2010; accepted 19 November 2010.

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Potential conflicts of interest: none reported.

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The Journal of Infectious Diseases 2011;203:575–577
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.
1537-6613/2011/2035-0001$15.00
DOI: 10.1093/infdis/jiq094

to 31.6% among those aged 2–9 years. HHV8 seropositivity was increased when both parents were HHV8 seropositive, when at least 1 other child in the house was HHV8 seropositive and when HSV1 antibodies were detected. HHV8 seropositivity was not related to the sex of the child (27.3% in boys vs 26.6% in girls), nor to HBV, CMV, and EBV seropositivity. Of note, HHV8 seropositivity was not associated with exposure to premasticated food from the mother. Premasticated food also was not associated with CMV, EBV, HBV, or HSV1, which are presumed to be transmitted through contact with saliva. HHV8 seropositivity was increased by 2-fold (95% confidence interval, .99–4.3) with sharing of food and/or sauce plates in the household, which was reported by 91% of the children. Food sharing was also associated with a 3-fold higher prevalence of HBV core antibody (95% confidence interval, 1.2–7.5), but not with CMV, EBV, HBV, or HSV1 seropositivity.

Among the adults, HHV8 seropositivity was higher in men than in women (43% vs 38%; $P = .04$), and it increased slightly with age, in men and women combined, from 42.0% at age 40–49 years to 49.3% after age 50 years. HHV8 seropositivity was unrelated to the number of lifetime sexual partners, history of genital ulcer disease or discharge, or HIV seropositivity. Sexual exposures were associated with HIV infection, providing face validity for the questionnaire data.

The study provides the clearest data thus far that HHV8 in Uganda, and perhaps in much of Africa, is transmitted through nonsexual social interactions, especially in childhood. The clarity can be attributed to their careful population-based epidemiological design, large sample size, detailed interview data, and measurement of biomarkers for related exposures. The study also provides data that low-grade, nonsexual HHV8 transmission probably occurs during adulthood. It is theoretically possible, although unlikely, that the rather small increase in seroprevalence of HHV8 infection with age among adults is attributable to age-related delay in antibody seroconversion following primary infection at a much younger age. Adult seroprevalence of HHV8 infection was different by gender, possibly reflecting different behavioral risk factors that are associated with exposure to HHV8 in men compared with women.

The findings in the current study also highlight the limitations of using a cross-sectional sero-epidemiological study to demonstrate HHV8 transmission. The hypothesis that HHV8 transmission occurs through saliva still has not been confirmed, despite the intuition that exposure would be high with premasticated food. This null result may be explained in part to limited statistical power, because only 8.8% of the mothers reported this practice. However, misclassification of the frequency, load, and timing of salivary exposure to infectious HHV8 is likely. HHV8 is detected frequently in saliva of children (17%; median viral load,10,100 copies /mL; interquartile range [IQR], 320–29,333 copies/mL), their mothers (10 %; median viral load, 7200 copies/mL; IQR, 220–32,000 copies/mL), and in HIV-uninfected adults without KS (22%) in Uganda [12, 13]. Shedding of virus in saliva also varies over time [13], with some individuals shedding virus more consistently and others shedding virus infrequently. Accurate classification of HHV8 exposure through saliva in a cross-sectional sero-epidemiologic study will not be possible. A better approach would be a prospective cohort in a community with a high prevalence of HHV8 infection, then comparing case children who do against control children who do not acquire HHV8 infection. The exposure measure would be receipt of premasticated food but, more informatively, the load of HHV8 shed in frequent, longitudinally collected saliva from mothers and siblings of the case and control children. Determining the relatedness of HHV8 sequences between children, mothers, siblings, and perhaps other close contacts would help confirm the source of HHV8 that is transmitted. Colluzi at al proposed that HHV8 transmission is influenced by use of saliva to soothe blood-sucking arthropod bites [22], another hypothesis that could be confirmed or refuted.

Host vulnerability by genetic variants or immune alteration may also affect the likelihood of HHV8 transmission. A statistical genetics analysis pointed to the possibility of a major recessive gene effect on HHV8 seropositivity [23], and another study suggested that HLA polymorphisms may affect HHV8 shedding [24]. In addition, shedding or vulnerability may be increased, even at low levels of exposure, by helminthic parasites [6, 25].

Finally, to reduce the heavy burden of KS in Africa, especially in the context of the HIV infection epidemic, strategies will be needed to prevent HHV8 transmission. Such prevention strategies will only be effective if the mechanisms of HHV8 transmission are well characterized. Progress has been made, but much more, multidisciplinary, carefully designed and executed research is needed.

Funding

The work was supported by the Intramural Research Program, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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