

Water, Socioeconomic Factors, and Human Herpesvirus 8 Infection in Ugandan Children and Their Mothers

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Background: Human herpesvirus 8 (HHV-8) infection is common in sub-Saharan Africa, but its distribution is uneven. Transmission occurs during childhood within families by unclear routes.

Methods: We evaluated 600 Ugandan children with sickle cell disease and their mothers for factors associated with HHV-8 seropositivity in a cross-sectional study. HHV-8 serostatus was determined using an HHV-8 K8.1 glycoprotein enzyme immunoassay. Odds ratios for seropositivity were estimated using logistic regression, and factor analysis was used to identify clustering among socioeconomic variables.

Results: One hundred seventeen (21%) of 561 children and 166 (34%) of 485 mothers with definite HHV-8 serostatus were seropositive. For children, seropositivity was associated with age, mother's HHV-8 serostatus (especially for children aged 6 years or younger), lower maternal education level, mother's income, and low-status father's occupation ($P < 0.05$ for all). Using communal standpipe or using surface water sources were both associated with seropositivity (OR 2.70, 95% CI 0.80–9.06 and 4.02, 95% CI 1.18–13.7, respectively) as compared to using private tap water. These associations remained, albeit attenuated, after adjusting for maternal education and child's age ($P = 0.08$). In factor analysis, low scores on environmental and family factors, which captured household and parental characteristics, respectively, were positively associated with seropositivity ($P_{\text{trend}} < 0.05$ for both). For mothers, HHV-8 seropositivity was significantly associated with water source and maternal income.

Conclusions: HHV-8 infection in Ugandan children was associated with lower socioeconomic status and using surface water. Households with limited access to water may have less hygienic practices that increase risk for HHV-8 infection.

Key Words: Kaposi sarcoma, Africa, human herpesvirus 8, transmission, water source, environmental factors, socioeconomic factors, epidemiology

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Human herpesvirus 8 (HHV-8, also called Kaposi sarcoma [KS]-associated herpesvirus) is the etiologic agent of KS.¹ HHV-8 infection is highly prevalent in sub-Saharan Africa,^{2,3} contributing to the high incidence of KS in this region.^{4–7} Nonetheless, HHV-8 seroprevalence in Africa is uneven (20%–80% among adults), varying widely by geography and population even across relatively small areas.^{2,5,8–11} This heterogeneity of HHV-8 seroprevalence across Africa could be artifactual (due to interlaboratory variability in assay characteristics^{12,13}) or due to variation in the age or socioeconomic characteristics of the populations studied. In the present study, we examined the associations between HHV-8 seropositivity in Ugandan children and their mothers and socioeconomic and environmental characteristics.

METHODS

Study Subjects and Laboratory Procedures

We evaluated 600 children with sickle cell disease (aged 1–16 years) who were enrolled from the Sickle Cell Clinic at Mulago Hospital, Kampala, Uganda, from November 2001 through April 2002.⁷ Mothers were enrolled when available. The institutional review boards in the United States and Uganda approved the study. Interviewers administered questionnaires eliciting information on education and occupation of both parents, mother's personal income, household density (number of persons per room), number of siblings, availability of electricity in the house, use of mosquito bed nets by children, and household location (urban, periurban, or rural). Source of drinking water was categorized as follows: private tap (piped water in the house); communal standpipe, including underground water pumped to the surface using boreholes, water from protected springs, or wells fitted with a pipe; or surface water, including water from unprotected springs or wells, swamps, ponds, streams, rivers, or lakes.

HHV-8 serostatus was determined using an enzyme-linked immunoassay to detect antibodies to HHV-8 K8.1

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(a structural glycoprotein) in plasma diluted 1:20 as previously described.^{5,7} Subjects with intermediate assay results (39 children and 32 mothers) were considered to have indeterminate HHV-8 serostatus and were excluded from the study.⁷

Statistical Methods

Odds ratios (ORs) and 95% confidence intervals (CIs) for association of individual variables with HHV-8 seropositivity for children and mothers were calculated using logistic regression. Multivariate logistic regression models were fitted using stepwise regression specifying $P < 0.10$ as the entry or stay criterion. The independent contribution of individual variables to the model was determined using the likelihood ratio test, with $P < 0.05$ considered statistically significant.

Because we expected many of the measured socioeconomic and environmental variables to be highly correlated with each other, we also used factor analysis (PROC FACTOR, SAS version 8.0; SAS Institute, Cary, NC) to study the dependence structure between these variables. Factor analysis is a dimension reduction technique that explains covariance relationships among multiple observed variables in terms of a few underlying, but unobservable, quantities called factors.¹⁴ To extract the factors, we repartitioned the common (ie, shared) variance and the unique variance for each observed variable into linear combinations (principle components) and used Kaiser's rule¹⁵ to decide how many factors to retain in the model. For ease of interpretation, we derived orthogonal (ie, uncorrelated) factors through a rotation method (VARIMAX, SAS Institute, Cary, NC) and labeled the factors descriptively according to the contribution of the individual variables to each factor. Factor scores were calculated for each child and used in logistic regression to estimate the association between the factor and children's HHV-8 serostatus and the trend across quartiles of the factors. In additional analyses, we adjusted for child's age and mother's HHV-8 serostatus or included the number of blood transfusions, a variable previously shown to be associated with HHV-8 seropositivity.⁷

RESULTS

HHV-8 Serostatus in Children

Of 561 children with definite HHV-8 serology results, 117 (21%) were seropositive. HHV-8 seropositivity was similar among males and females (23% vs. 19%, respectively; $P = 0.27$) and increased with age from 7% among children aged 1–2 years to 32% among children aged 13–16 years ($P_{\text{trend}} < 0.001$). In unadjusted analysis, HHV-8 seropositivity among children was inversely associated with mother's education but not with her occupation and with low-status father's occupation but not his education (Table 1).

HHV-8 serostatus of children was marginally associated with the mother's HHV-8 status (OR, 1.57; 95% CI, 0.98–2.49), but the strength of association was more pronounced for children aged 6 years or younger. ORs (95% CIs) for seropositivity among children aged 1–2, 3–4, and 5–6 years

were 3.07 (0.48–19.6), 6.09 (1.42–26.2), and 2.63 (0.75–9.17), respectively, while those for children aged 7–9, 10–12, and 13–16 years were 0.88 (0.33–2.32), 0.60 (0.21–1.66), and 3.01 (0.88–10.3), respectively.

In unadjusted analysis, HHV-8 seropositivity was strongly associated with drinking water collected from a communal standpipe or a surface source (Table 1) and weakly associated with not using a mosquito bed net. Seropositivity was unrelated to availability of household electricity, number of siblings, household density, or household location (Table 1). Using either forward and backward stepwise logistic regression, increases in child's age, lower mother's education, and use of surface water sources were associated (at $P < 0.10$) with the child's HHV-8 serostatus. The associations with mother's education and water source remained after further including the mother's serostatus and an interaction between child's age group and mother's serostatus (Table 1). Additional adjustment for household location did not change the results (data not shown).

Using factor analysis, 3 independent factors were identified, which we labeled descriptively as follows: the "family" factor, in which major contributing variables were father's education, father's occupation, household density, and mosquito bed net use; the "maternal" factor, with the strongest contributions from mother's income, occupation, and education; and the "environmental" factor, with the strongest contributions from household location, water source, household electricity, and household density. Water source did not contribute significantly to the family and maternal factors, but it was the second strongest contributing variable, after household location, to the environmental factor. These factors each explained ~33% of the variance in the final communality estimate.

HHV-8 seropositivity was significantly associated with the environmental and family factors but not with the maternal factor (Table 2). The trend of association of the environmental and family factors with seropositivity remained when we controlled for child's age group, mother's serostatus, and the interaction between child's age group and mother's serostatus ($P_{\text{trend}} < 0.05$ for both).

HHV-8 Serostatus in Mothers

Of 485 mothers with definite HHV-8 serology results, 166 (34%) were seropositive. In unadjusted analysis, HHV-8 seropositivity among mothers was associated with her education and income but not her occupation and with her husband's education but not his occupation (Table 3). HHV-8 seropositivity did not vary within the limited age range of the mothers and was unrelated to household electricity and household location. As was observed among children, mother's HHV-8 seropositivity was associated with source of drinking water (Table 3). Using stepwise logistic regression, mother's income and water source were identified as independently associated with her serostatus (Table 3). In factor analysis, HHV-8 seropositivity among mothers was related to the maternal factor but not to the family or environmental factors (Table 2).

TABLE 1. Association Between HHV-8 Seropositivity and Socioeconomic and Environmental Characteristics in Ugandan Children

Characteristic	No.* (% seropositive)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)‡
Mother's occupation			
Professional	69 (20)	Ref	—
Semiskilled	50 (26)	1.38 (0.58–3.27)	
Trader/sales	173 (21)	1.03 (0.52–2.06)	
Housewife	212 (19)	0.91 (0.46–1.80)	
Peasant	52 (25)	1.30 (0.55–3.09)	
<i>P</i> for heterogeneity		0.77	
Father's occupation			
Professional	136 (15)	Ref	—
Semiskilled	189 (18)	1.15 (0.64–2.11)	
Trader/sales	123 (23)	1.61 (0.86–3.02)	
Peasant	61 (33)	2.67 (1.31–5.43)	
<i>P</i> for heterogeneity		0.03	
Mother's education			
Tertiary institution	58 (5)	Ref	Ref
Secondary/high school	256 (21)	4.78 (1.17–15.9)	2.89 (0.82–10.1)
None/primary school	244 (25)	5.98 (1.80–19.8)	3.56 (1.01–12.5)
<i>P</i> for trend		0.001	0.06
Father's education			
Tertiary institution	113 (15)	Ref	—
Secondary/high school	280 (21)	1.54 (0.85–2.78)	
None/primary school	104 (20)	1.43 (0.71–2.89)	
<i>P</i> for trend		0.33	
Mother's income/month, Ugandan shillings			
>150,000	57 (9)	Ref	—
75,000–149,999	103 (23)	3.16 (1.13–8.81)	
35,000–74,999	80 (29)	4.20 (1.49–11.8)	
1–34,999	75 (28)	4.04 (1.42–11.5)	
None	196 (18)	2.26 (0.86–6.07)	
<i>P</i> for heterogeneity		0.01	
Household electricity			
Yes	310 (19)	Ref	—
No	251 (23)	1.22 (0.81–1.84)	
<i>P</i>		0.33	
Child's use of a mosquito bed net			
Yes	260 (17)	Ref	—
No	300 (24)	1.42 (0.98–2.25)	
<i>P</i>		0.06	
No. siblings			
0	35 (14)	Ref	—
1	82 (17)	1.24 (0.41–3.74)	
2	104 (21)	1.52 (0.53–4.39)	
3	114 (20)	1.52 (0.53–4.34)	
≥4	226 (24)	1.88 (0.70–5.09)	
<i>P</i> for trend		0.55	
Household density†			
Low	98 (26)	Ref	—
Medium	178 (19)	0.66 (0.37–1.20)	
High	81 (20)	0.72 (0.35–1.46)	
Very high	203 (21)	0.78 (0.45–1.38)	
<i>P</i> for trend		0.60	
Household drinking water source			
Private tap	37 (8)	Ref	Ref
Communal standpipe	333 (19)	2.70 (0.80–9.06)	1.93 (0.53–6.99)

TABLE 1. (continued) Association Between HHV-8 Seropositivity and Socioeconomic and Environmental Characteristics in Ugandan Children

Characteristic	No.* (% seropositive)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)‡
Surface water	191 (26)	4.02 (1.18–13.7)	3.05 (0.82–11.4)
<i>P</i> for heterogeneity		0.02	0.08
House location			
Urban	37 (17)	Ref	—
Periurban	46 (24)	1.53 (0.94–2.48)	
Rural	31 (22)	1.32 (2.26)	
<i>P</i> for heterogeneity		0.22	

*Totals do not always add up to 561 because of missing data.

†Household density was calculated as persons per room as follows: low ≤1.50; medium, 1.50–2.24; high, 2.25–2.99; very high, ≥3.00.

‡Adjusted OR were derived from a logistic regression model that included mother’s serostatus, child’s age, interaction between mother’s serostatus and child’s age, mother’s education, and water source. The model was fitted to data for children with complete data on mother’s HHV-8 serostatus and age of children (n = 452).

Ref indicates reference level; —, not included in the final model.

DISCUSSION

The novel finding of our study is the association between HHV-8 seropositivity and source of drinking water, demonstrated for both children and their mothers. We also found a strong association between the mother’s HHV-8 serostatus and the serostatus of her child, agreeing with findings of previous studies.^{2,16,17} These associations remained after adjustment for potential confounders, including individual mea-

asures of socioeconomic status and household location. We attribute the association between HHV-8 status and water source to an increased risk for HHV-8 infection among persons with limited access to clean water and the mother–child association to HHV-8 transmission from the mother to younger children.

Two studies, both also conducted in Uganda, previously reported that persons with endemic or AIDS-associated KS were more likely to report drinking, working, or wading in surface water.^{18,19} However, these findings were not replicated in another study of endemic KS in Uganda.²⁰ No association was found between HHV-8 seropositivity and prolonged contact with water for adults with cancer⁹ or with water source in another study of children attending an urban hospital in Kampala with a variety of diagnoses.²¹

Although water source may be a marker for socioeconomic status or house location (rural households are more likely to use surface water sources), the associations with water source remained when we adjusted for empirical measures of socioeconomic status and household location. One explanation could be that HHV-8 is a waterborne agent. However, herpesviruses are not known to be transmitted by water, and HHV-8 is not readily detected in urine or stool.²² Instead, we speculate that the water associations that we found are a marker for poor personal hygiene habits practiced by people with limited access to water. Persons who need to fetch water from distant communal sources are likely to use less water at home, given the effort it takes to obtain water for their house.²³ A lower mean daily water consumption was reported by East African households without private taps compared with those with piped water (20.5 vs. 57.8 L/d, respectively).²⁴ Plausibly, unhygienic water-saving practices, such as less frequent bathing and hand washing or the use of saliva to clean children’s faces,² are likely to be more prevalent in households with water shortage than in households with easy access to water. Such practices could facilitate saliva-mediated HHV-8 transmission from mother to child or from sibling to sibling.

The associations between HHV-8 seropositivity and measures of lower socioeconomic status were not uniformly consistent. For example, children’s HHV-8 serostatus was associated with mother’s education but not her occupation. Such inconsistencies indicate that the relationships among the

TABLE 2. HHV-8 Seroprevalence Among Ugandan Children and Mothers by Quartiles of Factors Related to Socioeconomic Status and Environment

	Maternal Factor*	Family Factor*	Environmental Factor*
Children			
1st quartile	23 (20)	16 (14)	17 (15)
2nd quartile	25 (23)	19 (17)	20 (18)
3rd quartile	19 (17)	27 (25)	19 (17)
4th quartile	21 (19)	26 (24)	32 (30)
<i>P</i> for trend	0.62	0.02	0.009
Adjusted <i>P</i> for trend†	0.76	0.05	0.03
Mothers			
1st quartile	22 (22)	26 (27)	32 (31)
2nd quartile	35 (33)	31 (32)	35 (34)
3rd quartile	35 (36)	36 (37)	27 (28)
4th quartile	35 (38)	34 (33)	33 (35)
<i>P</i> for trend	0.02	0.28	0.80

Values are no. (% seropositive) of subjects. Factors were derived separately for children and mothers.

*See Methods for derivation of factors. Each factor was a linear combination of 11 socioeconomic and environmental variables. Higher factor values corresponded to lower socioeconomic status or poorer environment. Factors were labeled according to the variables that contributed most to the factor, as measured by a standardized scoring coefficient of ≥0.2. The most important variables for each factor were (standardized scoring coefficient in parentheses) as follows: family factor, father’s education (0.41), father’s occupation (0.37), household density (0.40), and child’s use of a mosquito bed net (0.24); maternal factor, mother’s income (0.54), mother’s education (0.22), and mother’s occupation (0.49); and environmental factor, household location (0.51), household electricity (–0.31), household density (–0.33), and water source (0.40).

†Adjusted *P* for trend was derived in a logistic regression model that included the factor, child’s age, mother’s serostatus, and interaction between child’s age and mother’s serostatus.

TABLE 3. Association Between HHV-8 Serostatus and Socioeconomic and Environmental Characteristics in Ugandan Women

Characteristic	No.* (% seropositive)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
Woman's occupation			
Professional	58 (24)	Ref	—
Semiskilled	42 (33)	1.57 (0.65–3.79)	
Trader/sales	165 (33)	1.53 (0.77–3.03)	
Housewife	171 (37)	1.83 (0.93–3.61)	
Peasant	49 (43)	2.36 (1.03–5.38)	
<i>P</i> for heterogeneity		0.28	
Husband's occupation			
Professional	114 (29)	Ref	—
Semiskilled	165 (32)	1.16 (0.69–1.95)	
Trader/sales	112 (32)	1.16 (0.66–2.05)	
Peasant	51 (45)	2.02 (1.02–4.0)	
<i>P</i> for heterogeneity		0.24	
Woman's education			
Tertiary institution	44 (27)	Ref	—
Secondary/high school	223 (31)	1.17 (0.57–2.41)	
None/primary school	218 (40)	1.74 (0.85–5.56)	
<i>P</i> for trend		0.03	
Husband's education			
Tertiary	97 (27)	Ref	—
Secondary/high school	240 (30)	1.16 (0.68–1.97)	
None/primary	98 (46)	2.25 (1.23–4.11)	
<i>P</i> for trend		0.006	
Woman's income/month, Ugandan shillings			
>150,000	48 (25)	Ref	Ref
75–159,999	97 (22)	0.83 (0.38–1.87)	0.72 (0.32–1.64)
<35,000–74,999	72 (42)	2.14 (0.96–4.79)	1.86 (0.82–4.22)
>1–34,999	70 (44)	2.38 (1.07–5.34)	1.97 (0.87–4.51)
None	159 (35)	1.59 (0.76–3.29)	1.34 (0.63–2.83)
<i>P</i> for heterogeneity		0.008	0.02
Household electricity			
Yes	271 (31)	Ref	—
No	214 (38)	1.33 (0.91–1.94)	
<i>P</i>		0.14	
Household drinking water source			
Private tap	30 (13)	Ref	Ref
Communal standpipe	292 (34)	3.39 (1.15–9.97)	3.55 (1.02–12.4)
Surface water	163 (38)	4.00 (1.33–12.0)	3.70 (1.04–13.2)
<i>P</i> for heterogeneity		0.02	0.07
House location			
Urban	73 (38)	Ref	
Periurban	51 (31)	0.73 (0.47–1.14)	
Rural	41 (32)	0.78 (0.49–1.25)	
<i>P</i> for heterogeneity		0.33	

*Totals do not always add up to 485 because of missing data.

†Adjusted ORs were derived from a logistic regression model that included woman's income and water source.

Ref indicates reference level; —, not included in the final model.

questionnaire variables, the aspects of underlying socioeconomic status or hygiene for which they are markers of, and HHV-8 infection are complex. Using factor analyses, we observed that HHV-8 serostatus of children was associated with components of socioeconomic status related to mother's and father's education and occupation, as well as measures specific to the mother. For mothers, the maternal factor was

important. Current household density and location were unrelated to HHV-8 seropositivity, perhaps because most mothers would have been infected as children. Thus, the maternal factor may reflect the mother's childhood socioeconomic status.

HHV-8 seroprevalence varies considerably within Africa and elsewhere. HHV-8 seroprevalence ranges from 2%–29%

in Europe and the United States^{25,26} to 20%–80% in sub-Saharan Africa and 50% among Amerindians in Brazil,²⁷ suggesting a pattern of high prevalence in less-developed poor societies. Within Africa, seroprevalence among children is lower in studies of mainly urban children (eg, 28% in Cameroon,²⁸ 8% in South Africa,¹⁷ and 21% in Kampala, Uganda⁷) and somewhat higher in studies of mainly rural children (eg, 57% in northern Tanzania² and 39% in the West Nile region of Uganda¹⁰). Although HHV-8 seroprevalence cannot be easily compared across studies because of interlaboratory variation in the HHV-8 assays used,^{12,13} some variation could be due to socioeconomic or environmental factors related to water access or to compensating habits adopted in households with severe water shortage. Even so, in Asia, HHV-8 seroprevalence is low and KS is quite rare²⁵ despite poverty and inadequate access to water in many areas.

Advantages of our study include having a large, well-characterized population of children and their mothers. An additional strength of our study was our use of factor analysis to better elucidate the relationships of socioeconomic and environmental characteristics with HHV-8 infection. Nonetheless, we enrolled subjects only from a fairly well-developed region encompassing a major city (Kampala) and its environs. Some subjects classified as rural had access to indoor tap water, electricity, and other amenities commonly found only in urban areas, which may limit the generalizability of our findings. Furthermore, all children had sickle cell disease, which is associated with humoral immune deficits and anemia. Nevertheless, the findings for their mothers, who did not have sickle cell disease, were consistent with an increased risk for HHV-8 infection in persons of a lower socioeconomic status and those consuming surface water.

In conclusion, HHV-8 seropositivity among Ugandan children was associated with the mother's HHV-8 status, lower socioeconomic characteristics, and use of surface water sources. We posit that use of surface water sources is associated with poor hygienic practices, which increase HHV-8 transmission in affected households.

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