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Research article

Negative epidemiological association between HSV-1 and HSV-2 infections

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ABSTRACT

Objectives: Existing evidence on an epidemiological association between herpes simplex virus (HSV) type 1 and type 2 infections remains conflicting and inconclusive. Using a multi-national database of HSV-1/2 serological testing, we aimed to assess the existence of an association between both infections.

Design, Setting, and Participants: An HSV-1/2 cross-sectional serological testing database was assembled by merging databases of seroprevalence studies on men blood donors residing currently in Qatar, but from different countries. Specimens were tested for anti-HSV-1 IgG antibodies using HerpeSelect® 1 ELISA, and for anti-HSV-2 IgG antibodies following a two-test algorithm: HerpeSelect® 2 ELISA to test the sera, and Euroline-WB to confirm positive and equivocal specimens. Logistic regressions were conducted to estimate unadjusted and adjusted infection odds ratios.

Results: Serological testing for HSV-1/2 was performed on 2522 specimens. Sero-positivity for HSV-1 and HSV-2 was identified in 2053 (81.5%) and 87 (3.5%) specimens, respectively. Univariable analyses estimated higher odds of HSV-2 infection with increasing age and increasing country income level, and an unadjusted odds ratio with HSV-1 sero-positivity of 0.71 (95% CI 0.43–1.17; p-value 0.172). Adjusting for age and country income level, the adjusted odds ratio of HSV-2 infection with HSV-1 sero-positivity was 0.51 (95% CI 0.30–0.87; p-value 0.013). Sensitivity analyses confirmed this association.

Conclusions: There is a negative association between HSV-1 and HSV-2 infections, suggestive of a protective effect for HSV-1 sero-positivity against HSV-2 acquisition. This finding supports earlier pooled but inconclusive evidence from prospective studies, yet contrasts with pooled findings of earlier cross-sectional studies.

1. Introduction

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infections are common worldwide (Looker et al., 2015), but their epidemiologies vary globally (Khadr et al., 2018; Smith and Robinson, 2002; Weiss, 2004). HSV-1 is usually acquired orally, though evidence from Europe, North America, and Asia suggests increasing sexual transmission via oral sex (Bernstein et al., 2013; Khadr et al., 2018; Lowhagen et al., 2000; Whitley, 2013). Meanwhile, HSV-2 is predominantly acquired sexually, drawing an intriguing epidemiology that shows strong overlap with HIV epidemiology (Abu-Raddad et al., 2008; Kouyoumjian et al., 2018; Looker et al., 2017; Omori and Abu-Raddad, 2017; Omori et al., 2018).

The viruses are closely-related antigenically posing a question about the possibility of a biological or an immunological interaction between the two infections—specifically, whether exposure to HSV-1, normally occurring in childhood (Khadr et al., 2018; Smith and Robinson, 2002), could be protective against HSV-2 infection, normally occurring only after sexual debut (Smith and Robinson, 2002; Weiss, 2004). Nonetheless, the viruses generally infect two different sites, oral versus genital (Bernstein et al., 2013; Gupta et al., 2007), and thus, have different biological niches, with possibly varying immune responses (Stanberry et al., 2000). Such compartmentalization may reduce the potential for an interaction (Looker and Garnett, 2005). Evolutionarily too, the viruses may have evolved to escape any cross protection to survive in human circulation, more so for HSV-2, as it is typically acquired in adulthood, after HSV-1 acquisition (Looker and Garnett, 2005).

Existing evidence on the HSV-1/2 association remains inconclusive (Looker and Garnett, 2005). Pooled results of prospective studies suggest

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a trend of lower risk of HSV-2 infection with prior exposure to HSV-1, however, not statistically significant (Looker and Garnett, 2005). Meanwhile, pooled results of cross-sectional studies suggest a higher risk of HSV-2 infection with prior exposure to HSV-1 in low sexual risk populations and in Europe, but no association in high sexual risk populations and in the United States (Looker and Garnett, 2005). Difficulty of adjusting for confounding factors, such as different risk behaviors and demographic and socio-economic factors; and the fact that some factors could be effect-modifiers as opposed to simple confounders, may explain, in part, the conflicting evidence (Looker and Garnett, 2005). Regardless, it remains unclear whether such an association exists between the two infections (Looker and Garnett, 2005).

Against this background, and thanks to the opportune availability of an existing multi-national cross-sectional individual-level database (Dargham et al., 2018; Nasrallah et al., 2018a, 2018b), we assessed the epidemiological evidence for an HSV-1/2 association.

2. Methods

A database of HSV-1/2 serological testing results was assembled by merging databases of a series of seroprevalence studies (Dargham et al., 2018; Nasrallah et al., 2018a, 2018b). These studies were conducted on samples of men blood donors ≥18 years of age and residing in Qatar, but from different origin countries including: Egypt (N = 358), India (N = 325), Iran (N = 113), Iraq (N = 11), Jordan (N = 200), Lebanon (N = 118), Pakistan (N = 200), Palestine (N = 200), Philippines (N = 120), Qatar (N = 400), Sudan (N = 129), Syria (N = 200), and Yemen (N = 148). The original data was collected from a blood donor center that catered to men, thus the blood specimens and the data originated from men. The non-Qatari expatriates are primarily recent arrivals and short-term residents in Qatar, having spent the majority of their lifetime in their origin countries—their HSV-1/2 seroprevalence should more represent the exposure risk in their home countries, rather than in Qatar (Dargham et al., 2018; Nasrallah et al., 2018b). The total sample size of the merged database was 2522. Besides serological results, the database included very basic socio-demographic variables, only age and nationality.

All HSV serological testing was conducted on existing anonymized blood specimens that were drawn (formerly for other studies (AbuOdeh et al., 2015a; AbuOdeh et al., 2015b; Al-Qahtani et al., 2016; Nasrallah et al., 2017) at Hamad Medical Corporation, Doha, Qatar, between June 2013 and June 2016. Approval for the research was obtained by the appropriate ethic boards at Hamad Medical Corporation (#13204/13), Qatar University (#QUST–CHS–SPR-2017-12), and Weill Cornell Medicine-Qatar (#16-00012).

HSV-1 serology testing was implemented using the HerpeSelect® 1 enzyme linked immunosorbent assay (ELISA) kit (Cat. No. EL0910G-5, Focus Diagnostics, USA) (Focus Diagnostics, 2011a). For HSV-2 serology, and in consideration of published limitations of false sero-positivity in ELISA tests (Ashley-Morrow et al., 2004), a two-test algorithm was incorporated by first using the HerpeSelect® 2 ELISA kit (Cat. No. EL0910G-5, Focus Diagnostics, USA) (Focus Diagnostics, 2011b) to test the sera, and then confirming all positive or equivocal results using the Euroline-Western Blot assay (Cat. No. DY 2531-2401-1 G, Euroimmun Laboratory, Germany) (Euroimmun., 2011). All testing results were analyzed following manufacturers' instructions (Euroimmun., 2011; Focus Diagnostics, 2011a, b).

Further details on these seroprevalence studies and laboratory methods are found in previous publications (Aldisi et al., 2018; Dargham et al., 2018; Nasrallah et al., 2018a, 2018b, 2019).

The main analysis in this study assessed the HSV-1/2 association accounting for age and income level of country of origin. Country income was included as a covariate in view of existing evidence for an association between HSV-1 infection and socio-economic status (Bradley et al., 2014; Smith and Robinson, 2002)—please note the high heterogeneity in the income level between the 13 origin countries represented in this study. For confirmation of results, sensitivity analyses were also conducted to assess the association between these herpes viruses adjusting for age and either country of origin or immigrant status (Qatari national vs. expatriate).

For statistical analysis, age was stratified into eight groups: ≤24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, ≥55. Country of origin was stratified into four gross domestic product (GDP) categories per the World Bank classification (World Bank, 2017): low income, lower-middle income, upper-middle income, and high income countries. Sample characteristics were summarized using frequency distributions. Univariable and multivariable logistic regressions were conducted to assess the HSV-1/2 association. Unadjusted and adjusted odds ratios (OR), along with their respective 95% confidence intervals (CI), were reported. Significance was defined at $\alpha = 0.05$. All analyses were performed using IBM-SPSS version 24.0.

3. Results

Serological testing for HSV-1/2 was performed on 2522 specimens. Sample characteristics are summarized in Table 1. Sero-positivity for HSV-1 and HSV-2 was identified in 2053 (81.5%) and 87 (3.5%) specimens, respectively. Median age of the individuals in this sample was 37 years (ranging between 18 and 88 years). Majority of the sample originated from lower-middle income countries (52.8%; from Egypt, India, Pakistan, Palestine, Philippines, and Sudan), followed by upper-middle income countries (17.5%; from Iran, Iraq, Jordan, and Lebanon), then by a high income country (15.9%; from Qatar), and lastly by low income countries (13.8%; Syria and Yemen).

Results from the univariable and multivariable logistic regressions assessing the HSV-1/2 association are reported in Table 1. Univariable analysis indicated no statistically significant association, and estimated an unadjusted OR of HSV-2 infection of 0.71 (95% CI 0.43–1.17; p-value 0.172). Higher odds of HSV-2 infection were estimated with increasing age and increasing country income level. Adjusting for age and country income level, a significant negative HSV-1/2 association was observed, with an adjusted OR of HSV-2 infection of 0.51 (95% CI 0.30–0.87; p-value 0.013).

A significant negative HSV-1/2 association remained in both sensitivity analyses. An adjusted OR was estimated at 0.53 (95% CI 0.30–0.94; p-value 0.030), when adjusting for age and country of origin, and at 0.49 (95% CI 0.20–0.83; p-value 0.008), when adjusting for age and immigrant status.

4. Discussion

Using a large multi-national database of HSV-1/2 serological testing, we investigated the existence of an association between the two infections. Results indicated lower odds of HSV-2 infection with HSV-1 sero-positivity. This finding, based on cross-sectional data, contrasts with the pooled results of earlier cross-sectional studies that identified a higher odds of HSV-2 infection (in low sexual risk populations and in Europe), or no association (in high sexual risk populations and in the United States) (Looker and Garnett, 2005). However, this finding agrees with the pooled result of prospective studies (Looker and Garnett, 2005), lends credence to the conclusion that the positive HSV-1/2 association found in cross-sectional studies could be erroneous due to confounding (Looker and Garnett, 2005), and supports the higher quality prospective evidence suggesting a protective effect for HSV-1 exposure against HSV-2 acquisition (Looker and Garnett, 2005). This finding indicates the need to investigate and elucidate the immunological mechanism(s) that may explain such an interaction.

Although an HSV-1/2 interaction could possibly be bidirectional (Looker and Garnett, 2005), the cross-sectional design of our study cannot distinguish the direction of the interaction. Although the timing of HSV-1 or HSV-2 infection is unknown in our study, it is unlikely that the observed protective effect could be reversed, meaning HSV-2

Table 1

Sample characteristics of the merged database of the series of seroprevalence studies (Dargham et al., 2018; Nasrallah et al., 2018a, 2018b). Univariable and multivariable logistic regressions assessing the epidemiological association between HSV-1 and HSV-2 infections. Unadjusted and adjusted odds ratios (OR and aOR, respectively) of HSV-2 infection, along with the respective 95% confidence intervals (CI), were reported.

	Sample Characteristics	Univariable Analysis		Multivariable Analysis	
	N (%)	OR (95% CI)	P-value	aOR (95% CI)	P-value
HSV-2[@]					
No	2427 (96.2)				
Yes	87 (3.5)				
Missing	8[@]				
HSV-1[#]					
No	465 (18.5)	Ref			
Yes	2053 (81.5)	0.71 (0.43–1.17)	0.172	0.51 (0.30–0.87)	0.013
Missing	4[#]				
Age					
$\leq$ 24	272 (10.8)	Ref			
25–29	351 (13.9)	1.94 (0.37–10.06)	0.432	2.09 (0.40–10.86)	0.383
30–34	427 (16.9)	4.56 (1.03–20.24)	0.046	5.50 (1.23–24.52)	0.025
35–39	416 (16.5)	4.00 (0.89–18.01)	0.071	4.85 (1.07–21.99)	0.041
40–44	373 (14.8)	5.24 (1.18–23.25)	0.029	6.38 (1.43–28.52)	0.015
45–49	298 (11.8)	4.67 (1.01–21.5)	0.048	5.52 (1.19–25.70)	0.029
50–54	203 (8.1)	6.94 (1.5–32.05)	0.013	7.97 (1.70–37.30)	0.008
$\geq$ 55	180 (7.1)	16.75 (3.86–72.61)	<0.001	19.28 (4.37–85.11)	<0.001
Missing	2				
Gross Domestic Product[*]					
Low income countries	348 (13.8)	Ref		Ref	
Lower-middle income countries	1332 (52.8)	1.81 (0.76–4.30)	0.179	1.61 (0.67–3.86)	0.288
Upper-middle income countries	442 (17.5)	1.59 (0.59–4.29)	0.356	1.28 (0.47–3.48)	0.627
High income countries	400 (15.9)	4.30 (1.76–10.51)	0.001	3.39 (1.36–8.41)	0.009

[#] All four specimens were equivocal.

[@] Five specimens were equivocal and three specimens had insufficient sera for confirmatory testing.

[*] As Per the World Bank classification (World Bank, 2017): low income countries include Syria and Yemen; lower-middle income countries include Egypt, India, Pakistan, Palestine, Philippines, and Sudan; upper-middle income countries include Iran, Iraq, Jordan, and Lebanon; high-income countries include Qatar.

infection protecting against HSV-1 infection. While in Western countries there is considerable HSV-1 incidence beyond childhood (Ayoub et al., 2019; Bernstein et al., 2013; Gilbert et al., 2011; Lowhagen et al., 2000; Nilsen and Myrmel, 2000; Roberts et al., 2003; Samra et al., 2003), in the Middle East and North Africa the vast majority of HSV-1 incidence occurs during childhood (Chaabane et al., 2019; Nasrallah et al., 2018b)—it will be rare for HSV-2 infection to precede HSV-1 infection in the Middle East and North Africa.

This study has limitations. The evidence for a protective effect cannot be regarded as definitive epidemiological evidence. The analyzed database is cross-sectional in nature, and thus cannot capture the temporal trend in exposure. The negative HSV-1/2 association was statistically significant only after adjustment for confounders, but not prior to adjustment. The adjustment was further implemented only for limited number of potential confounders, as available in the database—it was not possible to control for other potential confounders such as sexual risk behavior.

The database included only men donors and of specific age range between 18 and 88 years and median of 37 years—the identified association may not be generalizable to women or other age groups. The reported HSV-1/2 association among blood donors may not reflect the wider and general population. The observed association may not also be generalizable to individuals not eligible as blood donors, such as those HIV seropositive. Demographic information collected from the blood donors were recorded anonymously, and thus over time some of the participants may have contributed more than once.

Though the sample size was large, HSV-1 seroprevalence was high (>80%) and HSV-2 seroprevalence was low (<5%), affecting the statistical power of the study, as evident in the broad confidence intervals. Quality and validated commercial assays were used for HSV-1/2 serological testing, but existing evidence suggests potential variation in assay performance by global population (Ashley-Morrow et al., 2004), thereby potentially affecting our results.

Concluding, HSV-1/2 infections are of growing interest with ongoing efforts to develop vaccines to control their transmission (Gottlieb et al., 2017). This study identified a negative association between these herpes infections, suggestive of a protective effect for HSV-1 sero-positivity against HSV-2 acquisition. This finding supports earlier pooled but inconclusive evidence from prospective studies, yet contrasts with pooled findings of cross-sectional studies. This finding also attests to a possibly strong antigenic link between both infections, thereby supporting the concept of developing a dually-effective vaccine against both viruses.

Ethical consideration

The research work was approved by the ethics boards and research committees at Qatar University, Hamad Medical Corporation, and Weill Cornell Medicine-Qatar.

Declarations

Author contribution statement

Laith Abu-Raddad: conceived and designed the experiments; contributed reagents, materials, analysis tools or data; wrote the paper.

Gheyath Nasrallah: conceived and designed the experiments; performed the experiments.

Soha Dargham: conceived and designed the experiments; analyzed and interpreted the data; wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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