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Đaković Rode, Oktavija; Židovec Lepej, Snježana; Begovac, Josip

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Seroprevalence of Herpes Simplex Virus Type 2 in Adult HIV-Infected Patients and Blood Donors in Croatia

Oktavija Đaković Rode, Snježana Židovec Lepej and Josip Begovac

University Hospital for Infectious Diseases »Dr. Fran Mihaljević«, Zagreb, Croatia

A B S T R A C T

The present study estimates herpes simplex virus type 2 (HSV-2) seroprevalence and evaluates its association with age, sex, human herpesvirus type 8 (HHV-8) and human immunodeficiency virus (HIV) among adults in Croatia. A cross-sectional survey included 166 HIV-infected patients and 219 blood donors. Antibodies against HSV-2 were determined by enzyme immunoassays based on gG2 recombinant glycoprotein. HSV-2 seroprevalence was 45.8% in HIV-infected patients and 8.7% in blood donors ($p<0.0001$; OR 8.8; 95% CI 5.05–15.49). Independent predictors of HSV-2 seropositivity were HIV infection (OR 11.0; 95% CI 5.93–20.41), female gender (OR 2.28; 95% CI 1.22–4.26), older age (OR 3.93; 95% CI 2.74–7.11), and HHV-8 seropositivity (OR 2.72; 95% CI 1.09–6.75). Understanding the epidemiology of HSV-2 is a critical first step in designing interventions to decrease HSV-2 and HIV transmission. The association of HSV-2 with HIV infection and HHV-8 antibodies suggests a similar transmission route.

Key words: *HSV-2, Croatia, HIV, blood donors, HHV-8, seroprevalence*

Introduction

Herpes simplex virus type 2 (HSV-2) is one of the most common causes of genital ulceration[1–3]. Genital herpes is a lifelong incurable infection that causes medical, psychological and social concerns. There is a synergistic interaction between HSV-2 and HIV[1–4]. HSV-2 increases risk of HIV acquisition and transmission while HIV increases clinical and subclinical HSV-2 reactivation[4]. Further, HSV-2 reactivation increases HIV viral load in secretions obtained from genital herpes lesions as well as in plasma[1–4]. Accurate type specific HSV serological methods facilitate HSV diagnostics, and allow a better understanding of the burden of infection[3,4]. The prevalence of HSV-2 varies in different populations[5–10]. HSV-2 antibodies are found more frequently at older age, in females, in populations with risky sexual behaviour and in HIV-infected patients[1–10].

Human herpesvirus type 8 (HHV-8) seems to share similar transmission routes as HSV-2, and shows various prevalences in different populations[11,12]. Low prevalence of HIV infection in Croatia has been reported so far[13,14].

The seroprevalence of herpes simplex virus type 2 (HSV-2) antibodies in adults in Croatia has as yet not been described. The aim of the present study is to report the HSV-2 antibody prevalence in adult HIV-infected patients compared to blood donors.

Methods

Study population

A cross-sectional study was conducted at the University Hospital for Infectious Diseases, Zagreb, Croatia between May 1999 and August 2001. The study included 385 participants: 166 HIV-infected patients and 219 blood donors. Age and gender was reported in all subjects as well as the risk groups in HIV-infected patients.

Serological testing

We analyzed serum samples for antibodies against HSV-2 and HHV-8. All sera were frozen and stored at

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–20 °C till testing. Antibodies to HSV-2 were determined by enzyme-linked immunosorbent assays (ELISA) based on gG2 recombinant HSV-2 specific glycoprotein (ETI--HSVK-G 2, DiaSorin, Italy). Equivocal HSV-2 EIA results led to confirmatory immunoblot (HerpesSelect 1 and 2 Immunoblot IgG, Focus, USA). HHV-8 antibodies were analyzed with commercially available ELISA (HHV--8 IgG Antibody, ABI, Columbia, USA). All tests were performed and interpreted according to the manufacturer's guidelines.

Statistical analysis

Bivariate associations were evaluated by odds ratio (OR) and corresponding 95% confidence intervals (CI). The association of gender, age (dichotomized at 40 years), and HIV and HHV-8 status with HSV-2 seropositivity was examined in a multivariable logistic regression model. Statistical analysis was performed with STATA software version 8.0.

Results

HSV-2 antibodies were analyzed in 166 HIV-infected patients (males, 74.1%) and 219 blood donors (males, 79.0%). The median age for both study groups was 39 years (ranges 19–74 for HIV-infected patients and 18–64 for blood donors). Seventy-three (44.0%) HIV-infected patients and 116 (53.0%) blood donors were older than 40 years.

The seroprevalence of HSV-2 was 45.8% in HIV-infected patients and 8.7% in blood donors ($p<0.0001$; OR 8.84; 95% CI 5.05–15.49). Among HIV-infected patients and blood donors older than 40 years HSV-2 seroprevalence was 61.6% and 13.9% respectively ($p<0.001$; OR 9.94; 95% CI 4.89–20.18). Among subjects younger than 40 years 33.3% HIV-infected patients and 2.9% blood donors had HSV-2 antibodies ($p<0.001$; OR 16.67; 95% CI 4.89–56.83). We found HSV-2 antibodies in 43.9% male and 51.2% female HIV-infected patients ($p=0.48$), and 7.5% male and 13.0% female blood donors ($p=0.25$). Among HIV-infected men who had sex with men (MSM) HSV-2 seroprevalence was similar to other risk groups (52.1% in MSM vs. 43.2% in non-MSM; $p=0.31$). The data on HHV-8 has been previously reported (12). Briefly, the seroprevalence of HHV-8 was 13.3% (22 of 166 subjects) in HIV-infected patients and 4.1% (9 of 219 subjects) in blood donors[12].

In our analysis HSV-2-antibodies were associated with HIV-infection, female gender, older age and HHV-8 seropositivity (Table 1).

Discussion

We found that HSV-2 antibodies were more common in HIV-infected patients than in blood donors. HSV-2 seroprevalence of 45.8% in HIV-infected patients was similar to one found in Germany, but lower than in Coventry, United Kingdom[8,9]. Higher HSV-2 seroprevalence rates in HIV-infected patients have been reported from Africa (up to 90%) or in clinics where many HIV patients of African origin are treated[9,10]. HSV-2 seroprevalence in Croatian blood donors (8.7%) was similar to the 4 to 24% range reported by Peabody et al. in the general population of different European countries[5]. However, direct comparison of seroprevalence studies is difficult because study populations varied and different serological tests were used.

HSV-2 antibody status is stated as a surrogate marker of sexual behaviour. This could explain the higher seroprevalence rate in older age. Women generally had a higher HSV-2 seroprevalence compared to men[1–10]. In our study females were 2.33 more likely to have HSV-2 antibodies than males on multivariable analysis. Peabody et al.[3,5] reported that women were 1.26 to 1.64 more likely to have HSV-2 antibodies than men in different European countries.

There is epidemiological and biological evidence of an interaction between HSV-2 and HIV[1–4]. The HIV infectiousness is increased in persons coinfected with HSV-2. HSV-2 reactivation and shedding are more frequent among those with higher HIV plasma viral load and lower $CD4^+$ T-cells count. HSV-2 increases HIV susceptibility by pro-

TABLE 1
FACTORS ASSOCIATED WITH THE PRESENCE OF HSV-2 ANTIBODIES AMONG 385 CROATIAN ADULTS: 166 HIV-INFECTED PATIENTS AND 219 BLOOD DONORS

	Univariable (OR; 95% CI)	p value	Multivariable* (OR; 95% CI)	p value
HIV infection (yes vs. no)	8.84 (5.05–15.49)	<0.0001	11.00 (6.92–20.41)	<0.0001
HHV-8 antibodies (yes vs. no)	4.28 (2.02–9.07)	<0.0001	2.72 (1.09–6.75)	0.031
Gender (male vs. female)	0.64 (0.38–1.08)	0.09	0.43 (0.23–0.82)	0.01
Age (>40 vs. ≤40 years)	2.29 (1.47–3.70)	0.001	3.93 (2.17–7.11)	<0.0001

OR – odds ratio; CI – confidence interval
* The odds ratio for each variable was adjusted for all other variables in the table

viding a portal of entry, at which more activated $CD4^+$ T-cells as the target for HIV can be found[2–4]. Recognition, diagnostics and treatment of genital herpes might prevent transmission of HIV[1–4].

HSV-2 is a well known sexually transmitted agent that is related with HHV-8, and vice versa[11]. HSV-2 and HHV-8 might share similar acquisition modes, although the exact routes of HHV-8 transmission are still controversial[11,12]. Mediterranean countries such as Croatia were labelled as areas with high HHV-8 prevalence[11], but we found that the seroprevalence of HHV-8 in our country was low (4.1% in blood donors and 13.3% in HIV-infected patients)[12].

Limitations of our study should be noted. We used a convenience sample; however, we studied 166 out of around 300 HIV-infected patients registered in Croatia from 1985 till 2001[13,14]. Our subjects demographically resembled the HIV population in Croatia (13,14). Hence, our results might be generalized for the HIV-infected population in Croatia.

In conclusion, we found a relatively high HSV-2 seroprevalence in HIV-infected patients. HIV infection was the strongest predictor of HSV-2 seropositivity. Other factors associated with HSV-2 seroprevalence were age more than 40 years, female gender and HHV-8 seropositivity.

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O. Đaković Rode

University Hospital for Infectious Diseases »Dr. Fran Mihaljević«, Mirogojska 8, 10000 Zagreb, Croatia
e-mail: orode@bfm.hr

SEROPREVALENCIJA VIRUSA HERPES SIMPLEX TIPA 2 U ODRASLIH OSOBA ZARAŽENIH HIV-OM I DOBROVOLJIH DAROVATELJA KRVI U HRVATSKOJ

SAŽETAK

Prikazani su rezultati istraživanja seroprevalencije virusa herpes simplex tipa 2 (HSV-2) u odraslih osoba u Hrvatskoj te povezanost HSV-2 s dobi, spolom, humanim herpesvirusom tipa 8 (HHV-8) i virusom humane imunodeficijencije (HIV). U presječnu studiju je uključeno 166 HIV-inficiranih pacijenata i 219 dobrovoljnih darovatelja krvi. Protutijela na HSV-2 su određena imunoenzimskim testom koji se temeljio na gG2 rekombinantnim glikoproteinima. Seroprevalencija HSV-2 u HIV-inficiranih pacijenata bila je 45,8%, a u dobrovoljnih darovatelja krvi 8,7% ($p<0.0001$; OR 8,8; 95% CI 5,05–15,49). Nezavisni prediktori za HSV-2 bili su HIV-infekcija (OR 11,0; 95% CI 5,93–20,41), ženski spol (OR 2,28; 95% CI 1,22–4,26), starija dob (OR 3,93; 95% CI 2,74–7,11) i seropozitivnost HHV-8 (OR 2,72; 95% CI 1,09–6,75). Poznavanje epidemiologije HSV-2 je prvi korak u kreiranju mjera za smanjivanje prijenosa HSV-2 i HIV-a. Povezanost HSV-2 s HIV-infekcijom i protutijelima na HHV-8 upućuje na sličan put prijenosa.