Genital Herpes. An underestimated infection in Romania

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Abstract

Objective. *The present study aimed to assess the seroprevalence of herpes simplex type 2 (HSV-2) infections in a representative Romanian population sample and to evaluate clinical and epidemiological features of HSV-2 seropositive patients.* ***Methods.*** *The study was conducted between 2004 and 2007 on a total number of 1058 subjects (761 females, 297 males). Study population was divided in two groups, Group A consisting of 500 pregnant women and Group B consisting of 600 non-pregnant women and men. All the patients were tested for glycoprotein G1 (gpG1)-HSV1-IgG and gpG1-HSV2-IgG antibodies, and randomly retested 7% of the serum sample. We conducted a cross sectional seroprevalence analysis for HSV-2 and a case-control analysis (HSV-2-positive versus HSV-2-negative patients).* ***Results.*** *The overall HSV-2 seroprevalence was 15.2%. Women had a statistically significant higher HSV-2 seroprevalence compared to men (17% versus 10.8%, p<0.05). Strikingly, we found most of a quarter of HSV-2 seropositive patients (23%) having a history of genital herpes.* ***Conclusion.*** *Our study reports a seroprevalence of HSV-2 in Romania of 15.2%, which falls within the range of Eastern European countries. The reservoir of infection was asymptomatic in most cases.*

Keywords: *herpes simplex virus, seroprevalence, antibodies*

Introduction

Worldwide, genital herpes represents an important public health concern, since it is among the most frequent sexually transmitted infections (STI) and the primary cause for genital ulcers[1,2,3].

The prevalence of herpes simplex virus type 2 (HSV-2) infection greatly varies between different world regions, from roughly 16% in Western Europe and United States to almost 70% in Sub-Saharan Africa[4,5]. HSV-2 is the most common cause for genital herpes, although in some areas HSV-1 predominates[6]. It was estimated that 80% of the infected patients are asymptomatic, and therefore undiagnosed[3] roughly 75% of infected individuals being unaware of their state[7,8]. Although until recently it was considered that only the patients presenting with genital ulcers can spread HSV-2, it is now well known the notion of asymptomatic viral shedding, as an important source for subsequent infections.

Therefore, HSV-2 can be vertically transmitted, and generate severe infection in newborns, presenting a higher risk and mortality with associated sequelae[9]. This emphasizes the importance of active screening in pregnant women and of the preventive measures for mother to child transmission[3].

Moreover, there seems to be an epidemiological synergy between HSV-2 and HIV-1 infections. HSV-2 genital lesions are veritable gateways for HIV infection, in respect with HSV infected patients which have 2-4 folds higher risk for acquiring HIV infection[10].

Genital herpes can have multiple clinical forms and may be difficult to diagnose. Primary genital herpes infection tends to last longer and to be more severe than subsequent or recurrent episodes. Severe generalized disease with extensive lesions and involvement of internal organs may be noted in immunocompromised patients and in newborns of infected mothers. Genital herpes may have important psychosocial, psychosexual and psychological morbidity[3].

In the past decades there have been major advances in the laboratory diagnosis of HSV infection, with rapid serological tests to differentiate between HSV-1 and HSV-2. At the present, based on the newest tests, the diagnosis cand be confirmed even during consultation[3].

Considering the large proportion of asymptomatic patients, the true prevalence of HSV-2 infection can only be estimated in seroprevalence studies using type-specific HSV-2-Immunoglobulin (Ig) G tests. Our study aims to estimate the seroprevalence of HSV-2 in a representative sample for Romanian population. To our knowledge, this is the only study performed in Romania.

Methods

The present study is part of an international research grant entitled "*Cross-sectional study of HSV-1 and HSV-2 seroprevalence in Central and South-Eastern Europe*" (EPI40077/6822010), funded by Focus Technologies (USA) and GSK Research & Development Limited (UK). Of nine competing protocols only those from Poland, Romania, Hungary and Greece were selected. Project evaluation was carried out by International Herpes Management

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Forum and World Health Organization experts. Two international experts were appointed for Romania to monitor and validate research results, Dr. J. Smith (University of North Carolina, NC, USA, WHO Epidemiologist) and Dr. JE Malkin (IHMF Board Member, WHO Epidemiologist).

The study was conducted between 2004 and 2007 on 1100 subjects, a statistically representative sample for Romanian population. The local Ethics Committee approval was obtained. Study population was divided in two groups: Group A, 500 pregnant women, who came for prenatal visits at Elias University Emergency Hospital, from Bucharest, and Group B, 600 non-pregnant women and men admitted at The National Institute for Infectious Diseases "Prof. Dr. Matei Bals" from the same city for other infections than STIs. Patients with symptomatic HSV, varicella-zoster virus, STIs, HIV and hepatitis B virus infected were excluded. After signing the informed consent, all patients completed a questionnaire which included age, education level, socio-economic level, age at first sexual contact, number of partners, and use of condoms, STIs history, smoking and alcohol habits. All the patients were tested for glycoprotein G1 (gpG1)-HSV-1-IgG and gpG1-HSV-2-IgG antibodies. We used Focus HerpeSelect ELISA tests (Focus Technologies), with a cut-off value of 1.1 IU/ml. We randomly retested 7% of the serum samples. We conducted a cross sectional seroprevalence analysis for HSV-2 and a case-control analysis (HSV-2-positive *versus* HSV-2-negative patients).

We used SPSS (12.0, SPSS Inc., Chicago, IL) for statistical analysis. For cross-sectional part we calculated the prevalence proportion and the proportion variance of the study population. For the case-control part we applied chi-square test in the univariate analysis; in the multivariate analysis we used logistic regression, adjusted for age, sex, and study site (Elias Hospital or "Matei Bals" Institute).

Results

A total of 1058 subjects (761 females, 297 males) were enrolled in the study. More than half of women (452) were pregnant at the time of examination. The median age of enrolled subjects was 29 years (range between 15 and 44 years). The median age for both males and females was 29 years, with the same range (between 15 and 44 years).

The overall HSV-2 seroprevalence was 15.2%. Women had a statistically significant higher HSV-2 seroprevalence compared to men (17% *versus* 10.8%, $p<0.05$) (Figure 1). The prevalence among the pregnant women included in the study was 15%.

Almost a quarter of HSV-2 seropositive patients (23%) had a history of genital herpes (Figure 2). Symptomatic genital herpes was more common in men (28.1% vs 21.7%), without statistical significance.

Analysis by age group showed a progressive increase of HSV-2 seroprevalence (Figure 3). In men,

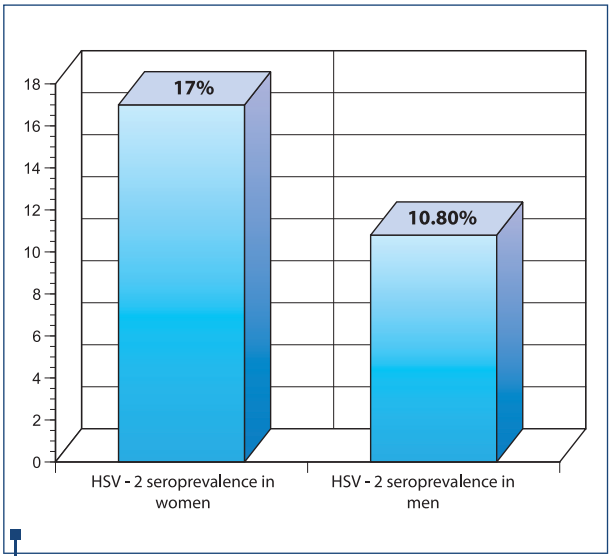

Figure 1. Comparison of HSV-2 prevalence between men and women ($p<0.05$)

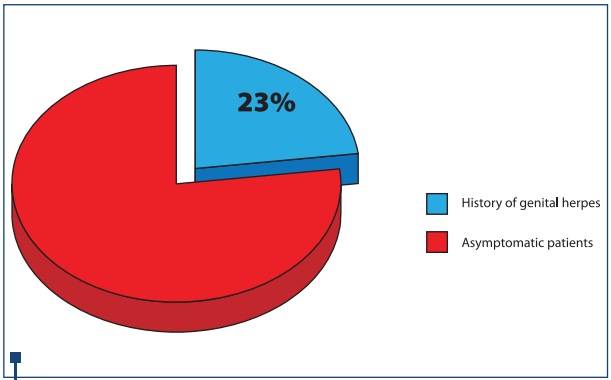

Figure 2. Prevalence of history of genital herpes in HSV-2 seropositive patients

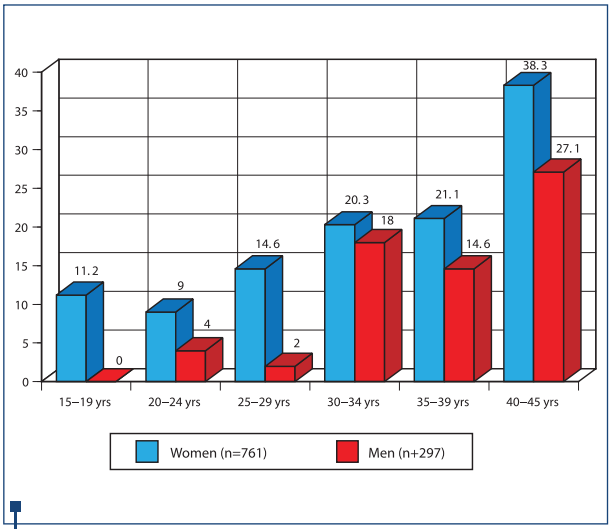

Figure 3. Age group HSV-2 seroprevalence

the seroprevalence increased from 4% (between 15 and 19 years group) to 27% (between 40 and 44 years group). Among women, the prevalence increased from 11% (between 15 and 19 years group) to 38.3% (between 40 and 44 years group). In all age groups the seroprevalence of HSV-2 was higher in women.

Discussion

The prevalence of HSV-2 infection has been estimated in different countries, but the nature, selection of samples and size vary widely from study to study[11]. Generally, the lowest seroprevalence is found in Asia (<7% in Japan) and the highest in Africa (sometimes reaching more than 80% in women and men >35 years)[11]. Both Western and Southern Europe prevalences are generally lower than those found in Northern Europe and North America[11]. Centers for Disease Control and Prevention reported an HSV-2 seroprevalence of 16.2%, in a National Health and Nutrition Examination Survey which took place between 2005 and 2008. In this survey the seroprevalence was highest among women (20.9%) and non-Hispanic blacks (39.2%). Similar to our study, most patients (81.1%) had no history of genital herpes[4].

To our knowledge this is the first estimate of HSV-2 seroprevalence in Romania and one of the few studies in Eastern Europe. Smith and contributors estimated in 2006 an overall seroprevalence of HSV-2 of 9.3% in Poland[12]. Pebody and colleagues reported that HSV-2 seroprevalences ranged from 23.9% in Bulgaria to 6% in Czech Republic[13]. Our study found an overall HSV-2 prevalence in Romania of 15.2%, which is in the range of Eastern Europe countries that have so far carried out seroprevalence studies.

Moreover, few studies have compared HSV-2 seroprevalence in men and women. For most studies, HSV-2 seropositivity was higher in females that in males[11]. We also found a significantly higher prevalence in women compared to men, which concurs with most reports that state the infection could be more easily transmitted from men to women than reverse. The higher risk of HSV-2 acquisition by women than men appears to be consistent across several geographic sites.

We also report a progressive increase with age of HSV-2 seropositivity, an epidemiological feature reported also by other authors. In a 2002 review that summarized data from peer-reviewed publications of type specific HSV seroepidemiologic surveys, Smith and contributors reported that HSV-2 prevalence was strongly associated with age, increasing from negligible levels in children younger than 12 to almost 80% in populations at risk[11].

Most seropositive subjects in our study were asymptomatic but probably contagious during subclinical episodes and during episodes of asymptomatic viral excretion, a finding consistent with other studies. This asymptomatic viral reservoir could be responsible for most new infections and public epidemiological strategies for reducing HSV-2 prevalence should target this important viral pool.

Conclusions

Our study reports a seroprevalence of HSV-2 in Romania of 15.2% which falls within the range of Eastern European countries being similar to other countries like USA prevalence. There was a significant increase of seroprevalence with age, being in the same accordance with previous reports. Women had a statistically significant higher HSV-2 seropositivity, which could be attributed to the higher risk of viral transmission from men to women. The reservoir of infection was asymptomatic in most cases and the main factor of transmission could be asymptomatic viral excretion. ■

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