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Serologic Screening for Herpes Simplex Virus Among University Students: A Pilot Study

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Abstract

Objective—The authors examined the feasibility of conducting serologic testing for the herpes simplex virus 2 (HSV-2) among university students and assessed the psychosocial impact of an HSV-2 diagnosis.

Methods—The authors recruited a convenience sample of 100 students (aged 18–39 years) without a history of genital herpes from 1 university between September 2004 and March 2006. Participants received HSV-2 antibody testing by Focus ELISA and Western Blot assays and completed a questionnaire that addressed psychological functioning. Twenty-eight participants completed the questionnaire again at a 3-month follow-up visit.

Results—The study revealed (1) low test-reliability in the student population, (2) that positive test results may cause a decline in psychological well-being, and (3) that substantial resources are required to support students with positive HSV-2 results.

Conclusions—Test performance, psychological impact, and availability of resources for counseling students with positive diagnoses should be considered before implementing HSV testing programs.

Keywords

clinical medicine; mental health; sexually transmitted disease

In the United States, approximately 17% of adults are infected with herpes simplex virus type 2 (HSV-2) and 58% are infected with herpes simplex virus type 1 (HSV-1).¹ More than two-thirds of those infected are unaware of their infection, and the majority of infections are transmitted by these individuals.² Herpes infections are associated with substantial morbidity and transmission and acquisition of the human immunodeficiency virus (HIV).³

University students (at either the undergraduate or the graduate level) often engage in sexual behaviors that put them at high risk for contracting HSV and other sexually transmitted diseases (STDs). Several studies have documented high levels of sexual risk behavior among college students in the form of inconsistent or no condom use, multiple lifetime sex partners, and alcohol and other drug use combined with sexual activity.^{4–7} The most recent national survey on HSV rates indicates that 10.6% of 20-to 29-year-olds are infected with HSV-2 and 54.4% are infected with HSV-1.¹ Although HSV-1 has historically been the primary cause of oral-

labial herpes and HSV-2 the cause of genital infection, a recent study of college students found that HSV-1 accounted for 77.6% of newly diagnosed genital herpes infections.⁸ It is postulated that this may be related to a change in sexual behaviors, such as an increase in oral-genital transmission in lieu of sexual intercourse and increased use of condoms for intercourse but not for oral sex.

In the last decade, type-specific serologic assays that detect HSV-1 and HSV-2 antibodies have become commercially available, and a debate about the value of screening asymptomatic individuals has ensued. Proponents of screening argue that identifying people with unrecognized HSV-2 may result in a decreased risk of transmission from such persons to others^{9–11} and that students at some universities have voiced an interest in being tested.¹² Opponents of screening express concerns about the accuracy of the tests, the burden on health care practitioners to provide counseling, and the psychosocial distress that may accompany a positive test result in a student.^{13–15}

Our purpose in this study was to determine the feasibility of implementing serologic screening among students with no history of genital herpes. We report on the reliability of 1 commonly used screening test, the psychological impact of a positive test result, and the resources needed for counseling and testing.

METHODS

Participants

The research protocol was reviewed and approved by the University Institutional Review Board. We recruited 100 students from 1 urban university between September 2004 and March 2006 via several strategies. Fliers were posted around the university campus, including the student health center; announcements were made in classrooms in the nursing and medical schools; information was posted on student Web sites and e-mail listservs; and the study was advertised in the major undergraduate student newspaper. Eligible participants were (1) aged 18 to 40 years, (2) full or part-time students, (3) sexually active (ie, self-reported oral, anal, or vaginal sex in the past 6 months), and (4) without a known history of genital sores or genital herpes. Investigators determined students' eligibility in brief phone calls and scheduled appointments for informed consent, questionnaire completion, and phlebotomy.

Procedure

The first study visit included written informed consent, pretest counseling, completion of several self-administered questionnaires, and phlebotomy. Pretest counseling included information on the rates of HSV in the general population, HSV signs and symptoms, the frequency of subclinical presentation, transmission, the published sensitivity and specificity of the blood test, and an individual assessment of risk. The questionnaires assessed demographic characteristics, depression, anxiety, and sexual behavior.

All HSV results were provided over the phone. Giving HSV results over the phone is not uncommon in HSV research, and a large HSV-2 vaccine trial currently underway recruiting women aged 18 to 30 years gives all HSV results over the phone.¹⁶ Participants in the current study were given the phone number of a study staff member during the first study meeting and were asked to call within 2 weeks of testing for their results. Study staff also requested phone numbers at which the participants could be reached if they did not call for their results. Participants were told that their results would not be left on an answering machine or with another party. Each participant was informed of the availability of free additional posttest counseling, which included additional meetings with a physician with board certification in

infectious diseases, clinicians at the student health center, and student psychological services. Participants received \$20 in cash at the conclusion of the first study visit.

All participants who tested positive for HSV-2 were asked to return within 2 weeks of receiving their results to meet with study staff to ensure that all questions were answered and to remind the participants of the availability of referrals. Participants who tested positive for HSV-2 and a randomly selected 25% of those who tested negative were asked to return 3 months after receiving test results to complete a follow-up questionnaire. Those who returned to complete questionnaires at the 3-month follow-up appointment were compensated \$25.

Laboratory Methods

Samples were initially tested by HerpeSelect HSV-2 ELISA IgG (Focus Diagnostics) at the laboratory of 1 of the investigators (JZ) and then stored. The HerpeSelect HSV-2 enzyme-linked immunosorbent assays (ELISA) are among the most commonly used tests for serodiagnosis of HSV infection.¹⁷ Studies gathered at the start of this study reported that the Focus HerpeSelect had a sensitivity of 99% to 100% and specificity that ranged from 96% to 98%, as compared to the Western Blot (WB) gold standard.

In response to new concerns about the reliability of the HSV ELISA tests that emerged during the study, WB testing was added to the protocol for all collected samples after approximately three-quarters of the participants had already been enrolled. After this point, in addition to ELISA testing in the Zenilman laboratory, all samples were further tested by WB at the University of Washington Diagnostic Virology Laboratory (UWDVL). All previously collected samples were sent for confirmation testing by WB.

Instruments

The questionnaire addressed sociodemographic characteristics and included other measures. All scales were administered at baseline and at the 3-month follow-up appointment. General psychological status was measured by the Center for Epidemiological Studies of Depression Scale (CES-D)¹⁸ and the General Health Questionnaire (GHQ).¹⁹ The CES-D is a 20-item instrument used to measure depression in clinical and general populations and asks respondents to indicate how often they have felt a certain way (eg, sad) in the previous week, with possible answers ranging from rarely to most. The CES-D has been used extensively in college-aged populations and has high internal consistency, acceptable test-retest stability, and good construct validity.^{20–21}

The GHQ is a 30-item screening test that is designed to identify short-term changes in mental health (depression, anxiety, somatic symptoms, and social dysfunction). Respondents rate their experience of symptoms over the previous few weeks. Questions ask whether a range of symptoms have recently been worse or better than usual, including, “Have you recently lost much sleep over worry?” and “Have you been able to concentrate on whatever you’re doing?” A score of ≤ 30 indicates feeling the same or better than usual on all the symptoms. Scores > 30 indicate experiencing more distress symptoms than usual. The GHQ has been used successfully in other studies that measured the impact of genital herpes on the mental health of adults and adolescents.

Statistical Methods

We computed descriptive statistics (frequency distribution, mean) to examine sample distribution of demographic and psychosocial measures, initially for the entire sample and then for a subset of the individuals at 3 months from test date. An internal consistency reliability test indicated Cronbach’s alpha of these scales and subscales on the total sample to be between .71 and .92. Additionally, we computed the differences in the baseline and follow-up scales and

subscales of psychosocial measures to examine changes in these scores between those who tested negative and those who tested positive for HSV-2 using analysis of variance. Because confirmation testing by WB was initiated after most of the participants had been enrolled and received ELISA test results, there were 2 groups of participants in the test positive group for this analysis: those who had received only positive ELISA test results at the time of follow-up and those who had received a positive ELISA and a negative WB result at the time of follow-up. We combined these groups on the basis of the supposition that positive and contrasting HSV results may cause distress. SPSS-15 was used for conducting all analyses.²²

RESULTS

Study Participants

One hundred participants enrolled in the study. Study participants were, on average, 24.5 years of age (range 18–39; $SD = 4.4$). Almost two-thirds were female (64%), and more than two-thirds (69%) were white, reflecting the ethnic composition of the university student body. Two of five participants were enrolled in graduate programs (see Table 1).

Most of the participants (86%) described themselves as heterosexual. Three-fourths of the participants reported 1 main sex partner in the prior 3 months, and one-fourth reported at least 1 casual sex partner during the same period. Almost half of the participants (47%) reported using a condom most of the time or always with a main sex partner during the prior 3 months. Among those who reported having casual sex partners, 45% reported always using condoms during sex and 12% reported never using condoms during sex with their casual partners (see Table 1).

HSV-2 ELISA Test Performance

A detailed analysis of the ELISA test performance has been reported elsewhere.²³ Figure 1 displays the test results. In summary, 100 participants enrolled in the study. WB testing was initiated after approximately three-fourths of the participants had been enrolled; 8 of the first samples had inadequate serum for WB testing and were excluded from analysis. In addition, 3 inconclusive ELISA results for HSV-2 were excluded from the analysis.

Eighty-nine samples were tested for HSV-2 by Focus ELISA and WB. Eight of the 89 samples were HSV-2 positive by the Focus ELISA tests (9% prevalence). Three of the 8 positive samples were confirmed HSV-2 positive by WB (3.4% prevalence). All of the samples that were determined to be HSV-2 negative by the Focus ELISA tests were confirmed negative by the WB. Compared with HSV-2 WB analysis, sensitivity of the HSV-2 Focus ELISA was 100% (95% CI, 30.9–100), and specificity was 94.1% (95% CI, 86.3–97.8). Positive and negative predictive values of the Focus ELISA were 37.5% (95% CI, 10.2–74.1) and 100.0% (95% CI, 94.3–100), respectively (see Figure 1).

Psychosocial Impact

As mentioned previously, the protocol called for 3-month follow-up with all of the participants who tested HSV-2 positive and with 25% of those who tested HSV-2 negative. Follow-up was completed by 5 of the 8 participants who tested HSV-2 positive (63%) and 23 of the 81 participants who tested HSV-2 negative (28%). The 3 participants who tested ELISA HSV-2 positive but did not complete the follow-up did not differ in baseline demographic, behavioral, or psychosocial factors from the participants who tested ELISA HSV-2 positive and did complete the follow-up. Of the 5 ELISA HSV-2 positive participants who completed follow-up, 2 completed follow-up after having received only positive ELISA results and 3 completed follow-up after having received a positive ELISA and negative WB test result.

To examine the psychosocial impact of receiving a HSV-2 positive test result, we compared changes in psychosocial (CES-D and GHQ-30) scores between baseline and follow-up in the test negative and test positive group. We found that, on average, the test negative group had a 3-point decrease in GHQ-30 scores at follow-up compared with a 13-point increase in GHQ-30 scores in the test positive group. Both groups started with average scores of 30 or below, indicating a consistent mood in the past few weeks, but the test positive group had an average score of 46 at follow-up, indicating more than usual symptoms of distress over the past few weeks. The difference between the 2 test groups was statistically significant ($p < .05$). CES-D scores were only slightly different between the 2 groups. The test positive group had only slightly higher CES-D scores between baseline and follow-up ($M = 0.2$, $SD = 14.0$) compared to the test negative group, who had slightly lower CES-D scores ($M = -1.6$, $SD = 6.6$). The difference between the 2 test groups on the CES-D was not statistically significant.

Resources Used

Of the 8 participants who tested positive for HSV-2 by the Focus ELISA, 6 (75%) requested and received additional contact with study or student health center staff to discuss the meaning of their results and transmission and treatment questions. Four of these students had additional appointments with clinicians at the student health center, 3 had additional appointments with study staff members, and 2 had additional phone contact with study staff members. These meetings were in addition to pretest counseling, posttest counseling via telephone, and a posttest visit with study staff. Field notes indicate substantial psychosocial morbidity among students who tested positive for HSV-2, which included terminated romantic relationships, relationship conflict over results, and anxiety. Students who tested negative for HSV-2 did not request additional counseling.

COMMENT

The value and risks of screening university students for HSV are of considerable concern to campus health officials. The findings in the current study suggest important issues that should be considered before conducting such screening. First, it is important to consider the performance data on the selected test (ie, published sensitivity and specificity) in conjunction with the prevalence of HSV-2 in the student population to be tested. Because the positive predictive value (the proportion of patients with positive test results who actually have the disease [ie, true positives]) is a function of sensitivity, specificity, and the prevalence of disease in the population to be tested, in low-prevalence settings, even tests with high sensitivity and specificity can have poor positive predictive values. In this study population, with a 3.4% prevalence of HSV-2, only 38% of the samples that tested positive by the Focus ELISA test were confirmed positive by WB. Several other recent investigations have also raised concerns about the frequency of false-positive HSV results in select patient groups.^{24–27} Because confirmation testing by WB is expensive (approximately \$100/test) and available only at select sites, it is unlikely that university health centers will be able to offer this additional testing to their students. In addition, if confirmation testing is offered, the possibility and implications of contrasting ELISA and WB results should be considered. An understanding of the accuracy and limitations of type-specific serologic assays is crucial for campus officials who grapple with whether to offer serologic screening and for staff who counsel students on the meaning of HSV test results and the possibility of false-positive or false-negative results.

Second, campus health officials should consider the possibility of negative psychological repercussions (depression, anxiety, and distress) among students who test positive for HSV-2. In our small sample, testing positive for HSV-2 resulted in a decline in mental health and in symptoms of depression and anxiety at the 3-month follow-up visit as measured by the GHQ, and no changes in mental health as measured by the CES-D. One possible explanation for the

different findings generated by these 2 measures is the greater variability we found in scores on the CES-D versus the GHQ. Given the small sample size, these findings should be interpreted with caution but suggest that there may be negative psychological reactions to receiving positive HSV-2 results. In the last few years, several studies with small samples have been conducted on the psychological impact of a positive HSV-2 serology in adults with no history of genital herpes.^{28–32} Although none of these studies found a long-term effect of testing HSV-2 positive, some evidence suggests that a positive HSV-2 diagnosis is associated with considerable short-term distress and impact on quality of life.^{28,30} Consistent with this finding, despite receiving in-depth pretest and posttest counseling, a majority of participants in this study who received a positive HSV-2 test result requested additional contacts with study and clinic staff to discuss the meaning of their results and treatment. Several students related considerable relationship distress, including terminated romantic relationships and anxiety related to their positive test results.

According to the 2005 Youth Risk Behavior Survey, approximately one-third of adolescents have not had intercourse by 12th grade.³³ These students, as well as those sexually active students with limited sexual experience, are still exploring issues surrounding sexuality and intimacy in college. As such, they may be uniquely vulnerable to negative psychological outcomes after being diagnosed with genital herpes. Hence, experiences testing adults may not be generalizable to a college population, and the potential psychosocial impact and resultant counseling and education needs should be carefully considered if a university is considering an HSV-2 screening program. Campus officials should have in place the resources needed to respond to requests for additional counseling in a timely manner.

Limitations

This study has a few limitations. First, this was a small sample that was not sufficient to narrowly define the sensitivity and specificity of the tests or to conclude the psychological impact of study results. In addition, the small sample limited our ability to perform stratified analyses on the relationship between testing HSV-2 positive and sexual risk behaviors. Clearly, the findings of this study must be replicated in larger samples. However, our findings are not dissimilar to those found by others in these areas. Also, we used a convenience sample of students at 1 university. These findings cannot necessarily be generalized to other populations or even to students at other universities. Future research is needed in a diversity of populations. Despite these limitations, the results of this study highlight some important issues to consider when grappling with screening students with no history of genital herpes for HSV-2. Reasonable arguments exist for screening and not screening students for HSV-2. We hope the results from this study provide student health officials with additional perspectives as they consider this challenging decision.

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FIGURE 1.

Overall results of HSV-2 ELISA and Western Blot (WB) serological testing. HSV-2 = herpes simplex virus 2.

TABLE 1

Sociodemographic and Sexual Behavior Characteristics of Study Participants ($N = 100$)^a

Characteristic	<i>n</i>	%
Age (y)		
18–22	37	37
23–25	29	29
26–30	24	24
31–39	10	10
Sex		
Female	64	64
Male	36	36
Race/Ethnicity		
Asian/Pacific Islander	12	12
Latino	2	2
African American/Black	6	6
White	69	69
Caribbean/West Indian	2	2
Multiracial	7	7
Other	2	2
Sexual orientation		
Heterosexual	86	86
Homosexual	5	5
Bisexual	6	6
Unknown	3	3
School year		
Freshman	4	4
Sophomore	5	5
Junior	14	14
Senior	22	22
Graduate student	41	41
Special student	14	14
Number of main sexual partners in past 3 months		
None	14	14
1	75	75
2 or more	8	8
Unknown	3	3
Frequency of condom use during intercourse with main partner		
Never	20	24.1
Less than half of the time	14	16.9
Half-most of the time	12	14.4
Always	26	31.3
Unknown	11	13.3
Not applicable	17	—
Number of casual sexual partners in past 3 months		
None	73	73
1	14	14
2 or more	10	10
Unknown	3	3
Frequency of condom use during intercourse with casual partner		
Never	3	12.5
Less than half of the time	2	8.3
Half-most of the time	1	4.2
Always	11	45.8
Unknown	7	29.2
Not applicable	76	—

^a Adapted with permission from the American Sexually Transmitted Diseases Association.²³