Acta Derm Venereol 2005; 85: 248–252

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CLINICAL REPORT

Acceptance and Outcome of Herpes Simplex Virus Type 2 Antibody Testing in Patients Attending an STD Clinic – Recognized and Unrecognized Infections

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The majority of herpes simplex virus type 2 (HSV-2) genital infections are asymptomatic. We wanted to evaluate the acceptance of HSV-2 antibody testing among people attending an STD clinic and to estimate, after counselling, the percentage of recognized and unrecognized HSV-2 infections. First visitors to an STD clinic were invited to participate by answering a questionnaire and taking a blood test for HSV-2 antibodies. HSV-2 seropositive individuals, who were unaware of having genital herpes, were offered an HSV-2 counselling visit and follow-up. Of 1769 patients offered testing, 57% accepted. Of 152 (15%) HSV-2 seropositive individuals, 41% had a self-reported history of genital herpes, approximately 30% had genital symptoms and 30% had no genital symptoms. The percentage of patients reporting genital symptoms was much higher in HSV-2 seropositives (45%) without a history of genital herpes than in an HSV-2 seronegative group (28%). HSV-2 antibody testing should be performed generously in all cases of uncharacteristic genital symptoms. ***Key words: genital herpes; herpes simplex virus; seroepidemiology; STD.***

(Accepted October 4, 2004.)

Acta Derm Venereol 2005; 85: 248–252.

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The majority of herpes simplex virus type 2 (HSV-2) genital infections are asymptomatic. Nowadays, commercial type-specific tests are available to discriminate between type 1 and type 2 HSV infections (1). As HSV-2 with few exceptions infects the anogenital region, the presence of HSV-2 antibodies is considered to reflect genital herpes.

Although Scandinavian countries are noted for their wide public awareness of STDs in general, and genital herpes in particular, HSV-2 testing is not routinely performed at most STD clinics. The proponents of HSV-2 screening have argued that a patient attending an STD clinic is entitled to have a test for HSV-2 antibodies (2). The prevalence of HSV-2 seropositives among people attending an STD clinic varies in different parts of the world from 14% to 46% (3–11). A self-reported history of genital herpes is noted in 18–50% of HSV-2 seropositive individuals (3–5, 8, 9). However, after being informed about the clinical spectrum of genital herpes, a number of seropositive asymptomatic individuals might be able to recognize the clinical reactivation of their infection (=unrecognized symptomatic disease) (12). Without a diagnosis, these cases of 'atypical genital herpes' may be misdiagnosed as recurring balanitis or vulvovaginal candidiasis, for example. By being made aware of the HSV infection, the patient could stop having sex at the time of symptoms and, in the event of more severe symptoms, antiviral treatment could be introduced. It is known that the virus is shed intermittently from the genital tract of infected asymptomatic and symptomatic individuals (13, 14). The risk of transmitting the virus to a partner when the patient has lesions should be considerably higher and patients with unrecognized infections are thus of great importance in this context. In the present study, we wanted to determine the acceptance of testing for HSV-2 antibodies and estimate the percentage of recognized and unrecognized infections after thorough information and educational counselling at a Swedish STD clinic.

PATIENTS AND METHODS

Consecutive patients (first visitors) attending the STD clinic at Sahlgrenska University Hospital in Göteborg, the second largest city in Sweden, were invited to participate. There are two STD clinics of about the same size in Göteborg and visits are free of charge. Recruitment took place between January 2000 and May 2001, apart from three summer months (June–August 2000) and some additional days when the clinic was too busy. All first visitors were given a leaflet with information about the study, including a description of the natural course of HSV infections, especially subclinical ones, and an invitation to undergo testing for HSV-2 antibodies (Fig. 1).

All those attending the clinic, both those who accepted HSV-2 testing and those who did not, filled in a self-administered questionnaire dealing with reasons for attending, symptoms and sexual behaviour. The alternative answers to the question 'Have you had genital herpes?' were 'Yes', 'No' and 'Don't know'. Testing for chlamydia infection, gonorrhoea, HIV and syphilis was also offered.

After reading the information about the study and before agreeing to participate, the patients had the opportunity to put

 ISSN 0001-5555
DOI: 10.1080/00015550510025588

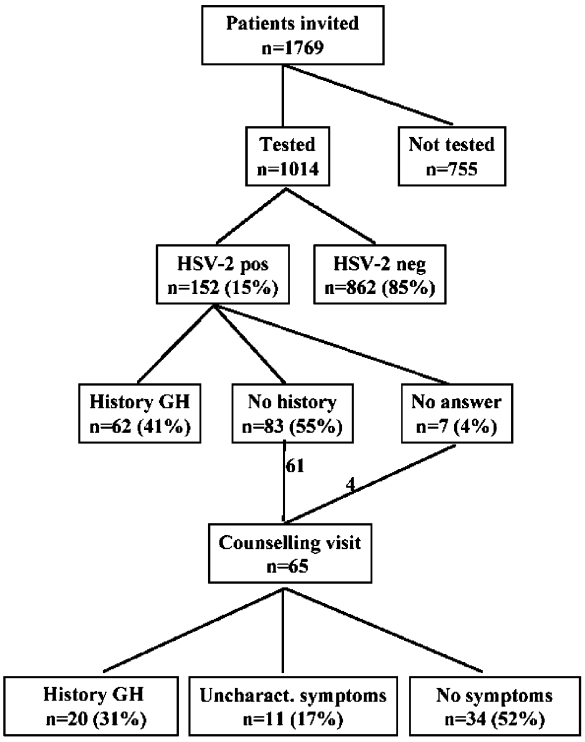

Fig. 1. Description of patient recruitment and the testing procedure and the outcome of the process. GH, genital herpes.

questions about genital herpes to a nurse trained for this purpose and to a physician.

Those who agreed to participate in the study answered questions about the history of genital symptoms, such as eczema and candida, and whether they considered themselves to have a low threshold for developing genital symptoms= 'sensitive skin'. For sensitive skin, the following question was used, 'Do you consider that you easily develop redness, itching and/or pain after friction and/or washing?'.

The study protocol was approved by the Ethics Committee at the Medical Faculty at Göteborg University.

Of 1769 eligible patients, 1014 (57%) agreed to take part (Fig. 1) in the study. The demographic data and sexual history of those who accepted testing for HSV-2 antibodies and those who abstained are shown in Table I. Males were predominant in both groups; male preponderance is the rule at the clinic. There was no difference between the two groups in terms of age.

HSV-2 counselling visit

Patients who tested positive for HSV-2 antibodies were informed by letter and those who, according to the questionnaire, had no history of genital herpes were offered a new appointment with one of the physicians responsible for the study (G.-B.L., E.B.). Patients who were HSV-2 seropositive and presented with typical lesions of genital herpes on their initial visit were not invited to this counselling visit.

The duration of this follow-up visit varied from 15 to 60 min. The transmission implications of a positive test for HSV-2 antibodies were discussed. Counselling also included information about atypical symptoms of genital herpes. Answers to questions about recurring genital symptoms during the last year were analysed and grouped according to the following definitions. 1) 'typical history of herpes'=recurring ulcers or vesicles in the genito-anal or gluteal region; 2) 'uncharacteristic symptoms'=periods of itching, eczema, balanitis and unspecific urethritis; 3) 'no genital symptoms'.

Table I. *Demographics and answers concerning sexual behaviour and STDs in patients tested for HSV-2 and for those who abstained from a test*

	Patients, *n* (%)	
Parameter	not tested	tested
Total	755 (100)	1014 (100)
Range[a]	595–755	889–1014
Men	562 (74)	724 (71)
Women	193 (26)	290 (29)
Age		
<25 years	226 (30)	324 (32)
25–35 years	355 (47)	477 (47)
>35 years	174 (23)	213 (21)
Present STD	452 (66)	640 (67)
History of chlamydia		
Yes	147 (23)	182 (20)
Don't know	47 (7)	70 (8)
History of gonorrhoea		
Yes	27 (4)	44 (5)
Don't know	40 (6)	54 (6)
History of genital herpes		
Yes	24 (4)	81 (9)***
Don't know	56 (9)	101 (11)
History of condyloma		
Yes	92 (14)	139 (15)
Don't know	45 (7)	101 (11)
Sex debut		
<15 years	219 (35)	270 (30)
16–20 years	374 (61)	582 (64)
>20 years	25 (4)	52 (6)
Number of lifetime partners		
1	26 (4)	28 (3)
2–4	94 (16)	141 (15)
5–10	171 (28)	263 (29)
>10	313 (51)	490 (53)
Number of partners last 6 months		
0	2	
1–2	469 (79)	658 (74)
⩾3	124 (21)	231 (26)
Steady partner	345 (53)	530 (56)
Use of condoms		
Always	174 (29)	255 (28)
Sometimes	388 (64)	572 (64)
Never	49 (8)	74 (8)
Test for HIV	268 (36)	861 (85)***
Test for chlamydia	704 (93)	868 (86)***
positive	93/704 (13)	76/868 (9)**
Test for gonorrhoea	137 (18)	126 (12)**
positive	16/137 (12)	3/126 (2)*

*$p<0.05$, **$p<0.005$, ***$p<0.0001$.
[a]The range of values indicates the response rates for different items below.

Follow-up

HSV-2 seropositive patients who were unaware of having genital herpes were asked to contact the clinic if they experienced any genital symptoms, even if they were only suggestive of genital herpes. Sampling for culture and/or tests based on the polymerase chain reaction (PCR) for HSV was then performed.

Patients who accepted were contacted and interviewed at the clinic or by telephone after about 6, 12 and/or 24 months. The interviews comprised questions about genital symptoms, as well as attitudes and feelings about knowing that their HSV-2 serostatus was indicative of infectiousness (to be published, results not shown).

Laboratory methods

Antibodies for HSV-2 were determined in an ELISA test using a *Helix pomatia* lectin-purified glycoprotein G (gG) 2 antigen (15). Positive sera were further tested in another ELISA test – Gull/Meridian. Sera with inconclusive results and/or discordance between the two ELISA tests were analysed using a Western blot assay previously characterized at our laboratory (16). Virus isolation and typing were performed as described previously (17). The PCR technique used was based on primers from the type-unique promoter region of the glycoprotein D gene (18).

Statistical methods

The data were analysed in the Epi Info program. Differences of proportions were compared using the chi-squared test with the level of significance set at 5%.

RESULTS

HIV serology was performed in 85% of the patients tested for HSV-2 and 36% of the untested ones. A history of genital herpes was reported more frequently in the former group, but the percentages of diagnosed gonorrhoea and chlamydia infections were higher in the latter. Sexual behaviour, however, as reflected in the answers to questions about the number of sexual partners and condom use, did not differ between the groups.

HSV-2 seropositive individuals

One hundred and fifty-two (15%) of the patients (12% of the male patients and 23% of the female patients) who were tested were HSV-2 seropositive, according to our testing algorithm (Fig. 1).

According to the initial questionnaire, 62 (41%) of 152 patients with HSV-2 antibodies stated that they had a history of genital herpes. Twelve patients presented at the initial visit with their first clinical recurrence of genital herpes, verified by culture or PCR in seven cases, and no further follow-up of these patients took place in the study. Eleven of these 12 patients had no history of genital herpes and one patient did not answer.

Sixty-five (78%) of the invited patients without a history of genital herpes attended the clinic for the counselling visit. Data from these interviews revealed that another 20 patients had a history compatible with genital herpes – recurring vesicles/ulcers in the genito-anal region – and some admitted, after counselling, that they had suspected that they had genital herpes, but that they had tried to suppress their anxiety. Six patients had experienced most of their recurrences in the peri-anal or gluteal region and, due to the localization, had not realized it could be herpes.

Of 11 patients with 'uncharacteristic symptoms', two had been previously diagnosed with balanitis, two with unspecific urethritis and one with candida vulvovaginitis. Thirty-four patients said they had no genital symptoms whatsoever.

Genital symptoms in HSV-2 seropositive and seronegative patients without a history of genital herpes

A higher proportion of patients with HSV-2 antibodies had a history of candida (42% vs 26%) and easily developing redness, itching and pain after friction/washing of the genital skin (45% vs 28%) (Table II).

Follow-up

Forty-five (54%) HSV-2 seropositive patients without a self-reported history of genital herpes agreed to continue in the study and to contact the clinic if they developed genital symptoms. Thirteen patients with a typical history of genital herpes were followed for a median of 13 months, eight patients with 'uncharacteristic' genital symptoms for a median of 19 months and 24 patients with no initial genital symptoms for a median of 18 months. Of 13 patients with a typical history of genital herpes, 7 attended with new lesions and the diagnosis could be verified by culture in 4 cases. One of eight patients with 'uncharacteristic' genital symptoms presented after 11 months with penile erosive lesions, verified as herpes simplex by culture. Two further patients in this group had unscheduled visits because of lesions which were not verified as genital herpes – one case of urethritis and one of balanitis. Of the 24 with no genital symptoms suggestive of genital herpes, one patient experienced her first recurrence of genital herpes after 24 months. The diagnosis was verified by culture. In all, 11 unscheduled visits were registered and genital herpes was verified in only 6 cases.

DISCUSSION

After receiving information about the study, more than half the patients at our STD clinic agreed to be tested for HSV-2 antibodies. This was similar to an STD clinic in Seattle; when testing was offered free of charge, 52% accepted. Acceptance was associated with the test being free and older age (21). In the UK, 90% of STD patients

Table II. *Genital symptoms in HSV-2 seropositive (*n=*83) and seronegative (*n=*758) patients without a history of genital herpes*

	seropositive *n* (%)	seronegative *n* (%)	*p* value
History of			
Candida	32/77 (42)	180/706 (26)	<0.001
'Sensitive skin'	36/80 (45)	195/705 (28)	0.006
Genital eczema	9/79 (11)	62/707 (9)	0.69

(19) and 80% of people attending an antenatal clinic (20) agreed to be tested for HSV-2. In a study from an STD clinic in the UK, 21% of 241 clients who declined HSV serology testing maintained that they did not like blood tests. More males than females did not want to know the result, 21% and 15% respectively (22).

In the present study, the reasons for abstaining were not routinely recorded, but of 53 consecutive interviewed patients the majority gave the reasons 'Don't like blood tests' (34%) and 'Don't want to know if I have a silent HSV-2 infection' (17%). Four patients had language difficulties and 20 (34%) said they were not interested and did not want to dwell any further on why they abstained from the test. We did not find any association between age and willingness to be tested. Slightly more women, 60% compared with 56% of the men, were prepared to be tested.

There were no differences between the tested and non-tested groups in terms of medical history of STDs and sexual behaviour. The non-tested patients underwent more tests for chlamydia infection and gonorrhoea and a relatively larger number of them were diagnosed as having these STDs, which could reflect the fact that many patients have decided in advance which afflictions they wish to rule out. For patients with a suspicion of HIV, HSV-2 is a minor inconvenience and a blood test is needed in any case.

Needless-to-say, the wish to be tested is initially governed by a genuine suspicion of having been infected. From a professional point of view, the testing should often encompass more than just one infectious agent. It can be assumed that agreement to be tested for something you do not think you have, or for something you have a nagging suspicion you might have, is largely dependent on the way the information is given at the STD clinic. In the above study by Mullan & Munday (22), only 41% of the males and 37% of the females chose to be tested; the information here stressed the disadvantages of being tested. Although our information was less negative, e.g. informing about the opportunity to recognize atypical symptoms as genital herpes and to avoid silent transmission to partners by using condoms, only just over half the invited patients accepted.

There are many aspects to consider when it comes to HSV-2 screening. In recent decades, an increasing percentage of first episodes of genital herpes has been shown to be caused by HSV-1, which means that a negative test for HSV-2 antibodies does not exclude genital herpes (23). A diagnosis of genital herpes may have significant psychosocial consequences for the patient and his/her partners (24). It is therefore of the utmost importance that the diagnostic tests are reliable (1). Tests with low sensitivity and specificity have limited use, especially in low prevalence populations. Most clinicians agree that the antibody tests available today should only be used in populations with a large probability of being infected (25). ELISA HSV-2 serology screening requires verification, ideally with a Western blot assay. The prevalence of HSV-2 varies with the occurrence of individual risk factors. An alternative way of applying the test is to select candidates with a scoring system using information on age, gender, sexual behaviour and symptoms (26). This would single out high-risk groups where the predictive value of a testing algorithm like the one suggested above should be quite acceptable. In the present study, we attempted to minimize the risk of false-positive results by starting with an ELISA test with a high sensitivity of $>99\%$ (16) and further verification with the Gull/Meridian ELISA test with a specificity of 98% (6) and/or a Western blot assay.

The percentage of allegedly symptomatic infections among HSV-2 seropositive individuals varies between studies (3–5, 8, 9). In general, higher figures are reported from STD clinics than from antenatal clinics or blood donors (4). There is a wide clinical spectrum of genital herpes. A reactivation of the herpes virus could present as a typical infection with vesicles/ulcers or just as a discrete redness. Atypical manifestations of genital herpes, such as fissures, soreness, urethritis, vaginitis and proctitis, have not been fully appreciated. After thorough information and educational counselling, 'asymptomatic' individuals may become aware of having recurrent genital symptoms corresponding to herpetic infection. The term 'unrecognized symptomatic' genital herpes was first introduced by Langenberg et al. in 1989 (12). A group of 'asymptomatic' HSV-2 seropositive women, who had been educated about the various symptoms of genital herpes, were followed in their study and as many as 42% recognized a clinical reactivation of genital herpes within 5 months. In a study from an antenatal clinic, 264 pregnant HSV-2 seropositive women without a history of genital herpes were followed closely until birth and, of these, 16% recognized genital lesions corresponding to herpes for the first time (27).

In most HSV-2 seroprevalence studies, the patients have been asked 'Do you have genital herpes?'. In this study, we were able to show that, of those answering 'No' or 'Don't know' to a similarly worded question, almost one-third turned out to have a history compatible with genital herpes. We found that most of these patients were not prepared to return during an attack to have their infection verified. The reasons could be that the symptoms of the infection were mostly mild and that the patient had been well informed at the counselling visit. In many cases, candida-like symptoms and unspecific genital symptoms may reflect unrecognized recurrences of genital herpes. The percentage of patients who admit having a history of candida and 'sensitive' skin was almost twice as high in HSV-2 seropositive

patients without a history of genital herpes, compared with HSV-2 seronegative patients.

Another explanation of this difference, albeit less likely, is an enhanced susceptibility to acquiring HSV in patients with candida and 'sensitive' genital skin.

In our opinion, HSV-2 antibody testing should be generously performed in all cases of uncharacteristic genital symptoms and also in some situations if the patient requests it, such as when he/she has a partner with genital herpes. Cases of unrecognized symptomatic genital herpes may be identified by taking a more careful history of genital symptoms. However, the experience acquired from this study indicates that some patients prefer not to accept their infection until they are convinced by a positive test. One of the strongest arguments against HSV-2 screening is the possible psychosocial effect of giving a young asymptomatic person information about having a sexually transmissible, incurable, lifelong infection. This issue is being addressed in an ongoing study.

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