ORIGINAL ARTICLE

HSV type specific serology in sexual health clinics: use, benefits, and who gets tested

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Objectives: To determine which sexual health clinic clients were tested for herpes simplex virus (HSV) type specific antibodies and whether this test was useful for patient management.
Methods: Demographic, sexual and reproductive history, reasons for performing type specific serology, results, and benefits were derived from patient records from Parramatta Sexual Health Clinic for all patients who were tested between 13 September1993 and 31 December 2001. The value of serology was defined under five categories—diagnostic, counselling, initiating suppressive antiviral therapy, pregnancy counselling, and not useful. To establish whether patients tested for HSV were representative of clinic attendees, a sex matched "control" group was randomly selected.
Results: 382/886 (43.1%) were HSV-2 antibody positive and 774/884 (80.8%) were HSV-1 positive. The commonest reasons for requesting serology were having a partner with genital herpes (30%), undiagnosed recurrent genital ulceration (26%), and first episode of genital ulceration (22%). The test was of value in confirming the diagnosis in 57% of men and 60% of women with recurrent genital ulceration and in 28% of men and 40% of women with first episode genital herpes. In patients with a partner with genital herpes the test was of value in making a diagnosis in 27% men and 50% of women and in counselling 50% of women and 73% of men. Patients offered serology were older and more likely to have had genital herpes in the past than controls.
Conclusion: Type specific serology should be recommended for the management of couples where one has genital herpes and the other apparently does not and in individuals with genital complaints suggestive of herpes.

Genital herpes infection caused either by herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) has become an important public health problem.[1] It is one of the most common sexually transmitted infections (STIs) with an estimated 20 million new infections annually worldwide. In addition, there is considerable evidence that the majority of individuals infected with these viruses are either asymptomatic or have symptoms that neither they nor their healthcare providers identify as being caused by herpes.[2–6]

A number of HSV type specific antibody tests have been developed and evaluated.[7–9] These have been used mainly in seroepidemiological studies to determine the prevalence and incidence of HSV infection in populations and to identify risk factors for HSV-2 infection.[3 10–15] However, it has been suggested that HSV type specific antibody testing may be useful in some clinical settings, in particular within the context of sexual health screening.[16–20] The results of a previous study showed that the test contributed to patient management in 79% of patients with recurrent genital ulceration of unknown cause. It was also useful for counselling.[21] However, this study had only a small sample size (127 patients) and the results might not be representative of other sexual health clinics. Type specific HSV serology has been available at the Parramatta Sexual Health Clinic (PSHC), Sydney, Australia, for more than a decade. This study investigated who was tested and whether type specific HSV serology was useful in the management of patients attending PSHC.

METHODS

A list of all patients from PSHC who were tested by type specific HSV serology tests (western blot assay) between 13

September 1993 and 31 December 2001 was obtained from the Virology Department, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital. Data were then derived from patient records and recorded on a computerised database. Data recorded included demographic information, sexual and reproductive history, reasons for performing type specific HSV serology tests, results of type specific HSV serology using a western blot assay (WBA) test, results of HSV culture, and benefits to clinical management. The study was approved by the Western Sydney Area Health Service human ethics committee.

The value of type specific serology was defined under five categories:

(1) Diagnostic (if the diagnosis of genital HSV infection was made according to serological test results when other tests yielded negative results or were not done)

(2) Useful for counselling (for example, if patients were at risk of acquiring genital herpes from a sexual partner, or if they had recently acquired first episode genital herpes)

(3) Useful for initiating suppressive antiviral therapy (HSV confirmed serologically)

(4) Pregnancy counselling (if pregnant women were at risk of acquiring genital herpes from a partner or at risk of transmitting the infection to the baby)

(5) Not useful—did not provide extra useful information.

These categories were defined for each patient after considering the reason for type specific HSV testing, the type specific HSV serology results and HSV culture results. The clinic has no policy protocols based on HSV serology and the decision to offer the test was made by the physician in consultation with the client. All assessments were performed

Table 1 Reasons why HSV type specific serology was requested

Reasons for testing	Men No (%)	Women No (%)	Total No (%)
Partner with known genital herpes*	148 (29.5)	115 (29.9)	263 (29.7)
Undiagnosed recurrent genital ulceration or recurrent signs and symptoms suggestive of herpes	137 (27.3)	93 (24.2)	230 (25.9)
First episode of genital ulceration or signs and symptoms suggestive of first episode genital herpes	109 (21.7)	84 (21.8)	193 (21.6)
Routine screening	79 (15.7)	41 (10.7)	120 (13.5)
HSV isolated without typing	6 (1.2)	14 (3.6)	20 (2.3)
Seropositive (EIA) previous	8 (1.6)	11 (2.9)	19 (2.1)
No reason	6 (1.2)	9 (2.3)	15 (1.7)
Patient pregnant†	0	12 (3.1)	12 (1.4)
HSV isolated and check serological status	4 (0.8)	3 (0.8)	7 (0.8)
HSV change on PAP smear†	2‡ (0.4)	2 (0.5)	4 (0.5)
Patient's wife pregnant†	3 (0.6)	0	3 (0.3)
Total	502 (100)	384 (100)	886 (100)

$\chi^2 = 15.62$, df = 2, p = 0.08.
*23 men and 28 women also had genital lesions at the same time.
†Not included in the calculation of χ^2.
‡Patient's partner had HSV change on Papanicolaou smear.

by a single assessor (BS) who had no connection with patient management. The results were analysed for men and women separately.

In order to establish whether patients tested serologically for HSV were representative of all clinic attendees, a ''control'' group was selected. The same number of clients was randomly selected from all clients who attended PSHC for the first time over the same period (13 September 1993 to 31 December 2002) but who did not have HSV serology performed. The only matching was by sex. Data were then derived from patient records and recorded on a computerised database. Data recoded included demographic information and sexual and reproductive history.

Virology
Sera were stored at −20°C and tested for antibodies to HSV-1 and HSV-2 using a western blot assay.[22–24]

Data analysis
Univariate analysis using Pearson's χ^2 or Fisher's exact test was used to compare the differences in demographics, sexual behaviour, and past STIs between cases and controls.

Unconditional logistic regression, with performing or not performing the type specific HSV serology test as the dependent variable, was conducted for cases and controls to assess which variables were significantly correlated with performing the test after adjusting for other factors. By using stepwise backward elimination, based on the likelihood ratio test, the initial predictive logistic model was constructed with only those variables at p<0.1 by univariate analysis. The final model and adjusted odds ratios with 95% confidence intervals were finally given.

RESULTS
In all, 910 type specific serology tests were performed between 13 September 1993 and 31 December 2001. After excluding missing notes and duplicate results, 886 patients' data (502 men and 384 women) were retrieved from their medical notes; 442 patients had an HSV-1 IgM test performed and 13 (2.9%) were positive and 884 patients had an HSV-1 IgG test performed and 774 (80.8%) were positive. Among 442 patients who had an HSV-2 IgM tests, 32 (7.2%) were positive. All 886 patients had an HSV-2 IgG tests performed and 382 (43.1%) were positive. The prevalence of HSV-2 IgG of female patients 194/384 (50.5%) was

Table 2 Clinical value of HSV type specific antibody testing in the management of STD clinic patients

Testing reasons	Diagnostic No	(%)	Counselling No	(%)	Therapy* No	(%)	Not useful No	(%)	Total No	(%)
Men										
Undiagnosed recurrent genital ulceration or signs and symptoms suggestive of herpes	78	(56.5)			1		59	(42.7)	138	(100)
First episode of genital ulceration or signs and symptoms suggestive of first episode genital herpes	30	(27.5)	3	(2.8)			76	(69.7)	109	(100)
Sexual partner with known genital herpes†	40	(27)	108	(73)					149	(100)
Routine screening	21	(26)			1		58	(74)	79	(100)
Miscellaneous reasons‡	6	(30)	2	(10)			12	(60)	20	(100)
Women										
Undiagnosed recurrent genital ulceration or signs and symptoms suggestive of herpes	54	(60)			3		39	(40)	68	(100)
First episode of genital ulceration or signs and symptoms suggestive of first episode genital herpes	34	(39.5)	7	(11.6)	2		43	(50)	86	(100)
Sexual partner with known genital herpes†	58	(50)	57	(50)	1				115	(100)
Routine screening	20	(49)					21	(51)	41	(100)
Miscellaneous reasons‡	6	(20)	3	(10)			21	(70)	30	(100)
Total	347	(41)	80	(9)	8		429	(50)	856	(100)

*Initiate suppressive therapy.
†Patients symptomatic or asymptomatic themselves.
‡See text.

Table 3 Demographics and sexual characteristics comparing male patients who had type specific serology (cases) with controls (those who did not have serology)

	Cases		Controls		Crude OR	Adjusted OR*
	No	(%)	No	(%)	(95% CI)	(95% CI)
Age						
Median (range)	35	(18–80)	31	(17–81)		
17–19	4	(0.8)	20	(4.0)	1	1
20–24	54	(10.8)	75	(14.0)	**3.60 (1.16 to 11.13)**	2.80 (0.87 to 8.85)
25–29	92	(18.2)	115	(22.8)	**4.00 (1.32 to 12.11)**	2.72 (0.88 to 8.41)
30–34	101	(20.1)	104	(20.6)	**4.86 (1.60 to 14.70)**	**3.15 (1.01 to 9.75)**
35–39	86	(17.1)	64	(12.7)	**6.72 (2.19 to 20.61)**	**4.58 (1.45 to 14.42)**
40–44	67	(13.3)	38	(7.5)	**8.81 (2.81 to 27.70)**	**5.92 (1.83 to 19.17)**
>45	98	(19.5)	89	(17.6)	**5.51 (1.81 to 16.72)**	**3.87 (1.24 to 12.08)**
	$\chi^2 = 28.35$		p<0.0001		p_{trend}<0.0001	p_{trend} =0.013
Sexual orientation*						
Heterosexual	469	(94.6)	417	(86.3)	1	1
Homosexual	9	(1.8)	29	(6.0)	**0.28 (0.13 to 0.59)**	**0.32 (0.15 to 0.72)**
Bisexual	18	(3.6)	37	(7.7)	**0.43 (0.24 to 0.77)**	**0.39 (0.21 to 0.75)**
	$\chi^2 = 19.97$		p<0.0001		p<0.0001	p<0.001
HIV status						
Never test	55	(11.2)	79	(16.6)	1	1
Negative	431	(87.4)	385	(81.2)	**1.61 (1.11 to 2.33)**	**1.78 (1.19 to 2.66)**
Positive	7	(1.14)	10	(2.1)	1.01 (0.36 to 2.80)	2.57 (0.82 to 8.05)
	$\chi^2 = 7.05$		p<0.03		p<0.03	p<0.002
Had genital herpes						
No	392	(78.1)	489	(96.6)	1	1
Yes	110	(21.9)	17	(3.4)	**8.07 (4.76 to 13.67)**	**6.69 (3.90 to 11.46)**
	$\chi^2 = 78.77$		p<0.0001		p<0.0001	p<0.0001
Had non-gonococcal urethritis						
No	419	(83.5)	468	(92.5)	1	1
Yes	83	(16.5)	38	(7.5)	**2.44 (1.63 to 3.66)**	**1.96 (1.27 to 3.04)**
						p<0.002

*Excluding 29 patients (6 cases and 23 controls) whose sexual orientation was not recorded.

significantly higher than that of male patients 188/502 (37.5%).

Table 1 shows the reasons that were documented for requesting type specific serology. Both in men and women the commonest reasons for the request were having a partner with known genital herpes (30% of requests), undiagnosed recurrent genital ulceration or recurrent signs and symptoms suggestive of herpes (26% of requests), and first episode of genital ulceration or signs and symptoms suggestive of first episode genital

Table 4 Demographics and sexual characteristics comparing female patients who had type specific serology (cases) with controls (those who did not have serology)

	Cases		Controls		Crude OR	Adjusted OR*
	No	(%)	No	(%)	(95% CI)	(95% CI)
Age (years)						
17–19	14	(3.6)	29	(7.6)	1	1
20–24	62	(16.1)	80	(21.1)	1.61 (0.78 to 3.30)	1.16 (0.52 to 2.58)
25–29	97	(25.3)	64	(16.8)	**3.14 (1.54 to 6.40)**	**2.24 (1.02 to 4.93)**
30–34	62	(16.1)	39	(10.3)	**3.29 (1.55 to 6.99)**	**2.30 (1.04 to 5.47)**
35–39	40	(10.4)	31	(8.2)	**2.67 (1.21 to 5.90)**	**2.47 (1.01 to 6.03)**
40–44	48	(12.5)	23	(6.1)	**4.32 (1.93 to 9.70)**	**3.97 (1.58 to 9.98)**
>45	61	(15.9)	114	(30.1)	1.11 (0.55 to 2.25)	1.37 (0.61 to 3.06)
	$\chi^2 = 45.49$		p<0.0001		p_{trend} <0.0001	p_{trend} =0.004
Sex worker						
No	369	(96.1)	339	(89.0)	1	1
Yes	15	(3.9)	42	(11.0)	**0.33 (0.18 to 0.60)**	**0.12 (0.06 to 0.25)**
	$\chi^2 = 14.05$		p<0.006		p<0.03	p<0.041
Condom use						
Always use	19	(5.3)	32	(9.5)	1	1
Inconsistent use	200	(55.4)	120	(35.5)	**2.81 (1.52 to 5.17)**	**1.41 (9.67 to 2.96)**
Never use	142	(39.3)	186	(55.0)	1.29 (0.70 to 2.36)	0.91 (0.43 to 1.97)
	$\chi^2 = 28.49$		p<0.0001		p<0.0001	p<0.042
Unknown	23	(6.0)	43	(11.3)		
HIV status						
Never test	50	(13.4)	161	(46.0)	1	1
Negative	324	(86.6)	189	(54.0)	**5.52 (3.83 to 7.95)**	**5.91 (3.84 to 9.11)**
	$\chi^2 = 93.23$		p<0.0001		p<0.0001	p<0.0001
Unknown	10	(2.6)	31	(8.1)		
Had genital herpes						
No	288	(75.0)	364	(95.5)	1	1
Yes	96	(25.0)	17	(4.5)	**7.14 (4.17 to 12.22)**	**7.56 (4.17 to 13.76)**
	$\chi^2 = 64.8$		p<0.0001		p<0.0001	p<0.0001

herpes (22% of requests). A variety of other reasons were listed in a small number of cases. In 120 patients (13.5%) ''routine screening'' was listed as the reason for testing.

Table 2 lists the clinical value of type specific serology separately for men and women considering each of the reasons for testing. The test was assessed as being of the most value in relation to patients presenting with recurrent genital ulceration or other recurrent signs and symptoms suggestive of genital herpes where it was of value in confirming the diagnosis in 57% of men and 60% of women. The test was also considered to be of considerable value in patients presenting with a first episode of genital ulceration or signs and symptoms suggestive of first episode genital herpes. In this situation the test was of assistance in making a diagnosis in 28% of men and 40% of women and of use in counselling 3% of men and 12% of women. Finally, in patients presenting with a partner who has genital herpes, the test was assessed to be of value in making a diagnosis in 27% of men and 50% of women and in counselling 29% of women and 19% of men.

Representativeness of the sample tested for HSV by type specific serology

There were a number of demographic and sexual differences comparing patients who had type specific serology and controls and these can be seen in tables 3 and 4. Male patients were independently significantly more likely to be older, to have had a negative HIV antibody test, to have had non-gonococcal urethritis in the past, and to have had a history of genital herpes than controls. Female patients tested for HSV serologically were more likely to be older, less likely to be involved in the commercial sex industry, more likely to have had a negative HIV antibody test, and more likely to have had genital herpes in the past.

DISCUSSION

This study showed that in the context of a sexual health setting where HSV type specific serology was readily available the test was requested for three main reasons—having a partner with known genital herpes (30% of presentations), presenting with undiagnosed recurrent genital ulceration or recurrent signs and symptoms suggestive of herpes (26%), or presenting with a first episode of genital ulceration or signs and symptoms suggestive of first episode genital herpes (22%). In an additional 14%, tests were performed as part of a ''routine screen.''

HSV-2 type specific serology assisted the diagnosis of 57% of male and 60% of female patients presenting with undiagnosed recurrent genital ulceration or signs and symptoms suggestive of recurrent herpes. The test was also helpful in confirming the diagnosis of first episode of genital ulceration, or signs and symptoms suggestive of first episode genital herpes (27% of men and 50% of women). In patients whose partner already has the infection, the test was able to help in the diagnosis of 27.5% of men and 50% of women. The test was also helpful in providing useful information for counselling in 73% of men and 50% of women whose partner had genital herpes.

This study suggests that the selective use of HSV-2 type specific serology in a sexual health setting maybe of considerable benefit to both patients and clinicians and should be recommended for the management of couples where one has the infection and the other apparently does not and in individuals with genital complaints suggestive of herpes where culture and/or PCR are repeatedly negative. This finding is in keeping with previous recommendations.[19] [25] However, clinicians need to bear in mind that HSV serology confirms that the individual has been exposed to that virus in the past, but will not establish whether particular signs and symptoms are caused by herpes. There are other drawbacks to testing including psychological morbidity associated with the tests itself and the infection,[26] [27] the increased clinical burden placed on STI clinic staff, cost, and the variable sensitivity and specificity of the HSV type specific ELISA tests.[7]

The routine use of HSV-2 type specific serology as a screening test has been debated in a variety of settings, in particular in patients attending sexual health/STD clinics[25] [28] and in pregnancy.[29] [30] This study and others have shown that a considerable proportion of patients attending STD clinics (22–65%) are HSV-2 antibody positive.[2–4] [12] [31–38] Consequently, testing in this setting will result in the detection of a large number of individuals with HSV-2, all of who will require counselling and advice about symptoms and transmission. At least some will require antiviral treatment. Copas et al have published a ''risk score'' based on four well described populations to assist in the interpretation of positive HSV-2 serology.[39] While the scores were helpful in test interpretation, common risk variables for use in all populations were not identified. Within STD clinic populations, knowledge about the expected seroprevalence and possible risk factors and behaviours may help to determine whether testing will be worthwhile.

Not surprisingly, patients who were tested for herpes were not representative of clinic clientele. Some of the important differences were that those tested were older and more likely to have had herpes in the past than controls. However, some groups that may be at high risk for the acquisition of herpes (including female sex workers and homosexual men) were less likely to be tested and future testing policies will need to carefully consider the demographic characteristics and risk profiles of their patients.

The strengths of this study are that it represents ''actual'' clinical practice and involves a large number of patients. The weaknesses are that the data were analysed retrospectively and that the evaluation of benefit was a subjective assessment based on what the clinician and or counsellor had written in the notes.

In conclusion, this study has demonstrated that selective use of HSV type specific serology is of benefit both to patients and healthcare providers and should be considered as one of the tests offered to patients with undiagnosed genital ulceration and for those who have a partner with genital herpes.

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