

Is HSV serology useful for the management of first episode genital herpes?

J Page, J Taylor, R L Tideman, C Seifert, C Marks, A Cunningham, A Mindel

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See end of article for authors' affiliations

Correspondence to: A Mindel, Sexually Transmitted Infections Research Centre, The University of Sydney, Marian Villa, Westmead Hospital, Westmead, NSW 2145 Australia; adrianm@icpmr.wsahs.nsw.gov.au

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Background: First episode genital herpes simplex virus (HSV) infections can be classified into three groups, primary genital herpes (no previous exposure to HSV), non-primary first episode (IgG antibody to HSV of the non-presenting type), and first episode with pre-existing IgG HSV antibodies. The use of IgM to classify first episode genital herpes has not been evaluated.

Objective: To evaluate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of HSV-1 and HSV-2 IgM antibodies for the diagnosis of first episode genital herpes, when compared with clinical diagnosis.

Methods: Patients with a first clinical episode of genital herpes were recruited. Sera were tested for IgG antibodies to HSV-2 using an indirect enzyme linked immunosorbent assay (ELISA). Equivocal results were resolved by western blot. HSV-1 IgG and IgM and HSV-2 IgM antibodies were detected using western blot.

Results: 157 patients were recruited. 31 were excluded (missing data or no detectable antibodies and negative viral isolation). Therefore, 126 patients were included in the analysis. 23 (18.3%) had primary genital herpes, 34 (27.0%) non-primary first episode, and 69 (54.8%) had pre-existing genital herpes. The specificity and PPV of HSV IgM was 100%; the sensitivity was 79% and the NPV 85%.

Conclusion: IgM HSV serology may be useful in the management of some patients with first episode genital herpes and provide an indication of the source of infection. Drawbacks include the low sensitivity and NPV, lack of availability, IgM antibodies may occasionally be produced in response to recurrent infection and, finally, IgM antibodies may take up to 10 days to develop and last 7–10 days.

The first clinical episode of genital herpes varies from a severe infection characterised by extensive, painful genital and perigenital ulceration and systemic symptoms to a mild infection with minimal localised vesiculation and ulceration.¹ Some individuals report no symptoms or minor signs and symptoms only when questioned either when a sexual partner develops genital herpes or in the context of a sexual health screen.^{2,3}

The severity of symptoms associated with genital herpes is dependent on several factors including viral load, breach of the genital mucosa, previous exposure to herpes simplex virus (HSV), and genetic factors determining epidermal cell and immune restriction of viral replication.^{1,4} Both HSV type 1 (HSV-1) and HSV-2 can cause genital herpes. Severe first episodes are more likely to occur when the individual has never previously been exposed to either virus (that is, true primary infections). Individuals who have previously been exposed to HSV (usually to HSV-1) tend to have a less severe first episode (non-primary first episode).¹ Recently, a group of patients has been described where the individual develops clinical herpes for the first time, but has serological evidence of previous infection with that virus.⁵ There appears to be considerable overlap in the severity of symptoms between these groups.

The extensive antigenic cross reactivity between HSV-1 and HSV-2 previously has limited the practical clinical use of HSV serology. However, the development of IgG and IgM type specific serological tests may be an important tool in the diagnosis, treatment, and counselling of patients presenting with primary/first episode genital HSV infection.⁶

The time required for the development of IgG antibodies following HSV infection varies from 21 to over 42 days with most individuals having detectable IgG 21–28 days after exposure to the infection and probably lasting for life.^{7–9} IgM antibodies are usually detectable 9–10 days after exposure and last 7–14 days, although they may remain detectable for up to

6 weeks in a minority of individuals.^{9–11} IgM antibodies may be detectable during recurrences of the infection, particularly with some of the commercial ELISAs.¹¹ Therefore, serological testing soon after the first development of symptoms suggestive of genital herpes may help to determine if an infection is new (presence of IgM antibody in the absence of type specific IgG antibody), or pre-existing (presence of IgG antibody alone). An accurate diagnosis can be helpful in counselling couples or individuals about how this infection may have occurred.

Consequently, we decided to conduct a study using serology in patients presenting with a first clinical episode of genital herpes. The objective of the study was to determine the clinical utility of HSV type specific serology in this setting and whether the information derived would be of benefit to clinicians in providing information and counselling to patients and their sexual partners.

METHODS

Study setting and patient recruitment

Patients who presented to the Sydney Sexual Health Centre (SSHC) between September 1995 and November 1998 within 4 weeks of the first onset of genital symptoms suggestive of genital herpes were asked to participate in the study. The study was approved by the South Eastern Sydney Area Health Service research ethics committee and written informed consent was obtained from all participants. A self administered questionnaire was completed, to obtain details of diagnosed or suspected previous oral and/or genital herpes infections, other past sexually transmitted infections (STIs), and recent sexual practices including condom use. In addition, information regarding recent sexual partner(s) was obtained including whether the partner(s) had oral and/or genital herpes or symptoms suggestive of herpes and whether antiviral medication was being used. The SSHC clinical staff performed

Table 1 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IgM antibodies for the diagnosis of first episode genital herpes

IgM antibody	Diagnosis of "new" genital herpes		
	Yes	No	Total
Present	45	–	45
Absent	12	69	81
Total	57	69	126

Sensitivity 45/57 (79%), specificity 69/69 (100%), PPV 45/45 (100%), NPV 69/81 (85%).

a genital examination and a swab for viral culture was taken from genital vesicles and/or ulcers. Serum was taken for type specific HSV serology. Patients who were HIV antibody positive were excluded. Tests to exclude other STIs were performed if appropriate.

Patient classification

Using the clinical history, examination findings, viral culture and serology, we were able to classify the patients into three groups.

Primary genital herpes—first clinical genital HSV infection with no previous exposure to HSV—that is, no IgG to HSV-1 or HSV-2.

Non-primary first episode genital herpes—first clinical genital HSV infection with IgG antibody to HSV of the other type—for example, new HSV-2 genital infection with pre-existing IgG to HSV-1.

Pre-existing genital herpes—first genital herpes episode with pre-existing IgG HSV antibodies of the same type.

HSV serological testing

Sera were stored at -20°C and tested for antibodies to HSV-1 and HSV-2. HSV-2 IgG antibodies were detected using an "in house" indirect enzyme linked immunosorbent assay (ELISA) specific to glycoprotein G2 (gG2). The assay has levels of sensitivity and specificity of greater than 98%. Equivocal ELISA results were resolved by western blot. The available HSV-1 IgG ELISA tests all have poor levels of sensitivity and specificity. Consequently, HSV-1 IgG was detected using western blot. These methods allowed us to accurately detect IgG antibodies to HSV-2 and HSV-2 and in particular to readily identify individuals with dual infection. HSV-1 IgM and HSV-2 IgM antibodies were detected using western blot.^{9 10}

Data entry and analysis

Questionnaire responses and the serological results were entered onto a study database. The SPSS computer program was used to derive descriptive and comparative statistics.¹²

RESULTS

In all, 157 patients who presented with clinical symptoms of first episode genital herpes agreed to participate in the study. Eighty four of the 157 patients were female (53.5%), 64 (40.8%) were heterosexual males, and nine (5.7%) homosexual males. Overall, 31 patients were excluded including 11 who had no detectable antibodies and negative viral isolation after 4 weeks, two with virus isolated by swab but no serological evidence of HSV after 4 weeks and 18 where the serology was considered unreliable because of the timing of the blood test (3–4 weeks after the onset of symptoms). Consequently, 126 patients were included in the analysis.

Twenty three (18.3%) were considered to have primary genital herpes (11 with HSV-2, 11 with HSV-1, and 1 with HSV-1 and HSV-2—that is, IgM to both types), 34 (27%) non-primary first episode, and 69 (54.8%) with pre-existing genital herpes. Combining the first two groups, 57 of the 126

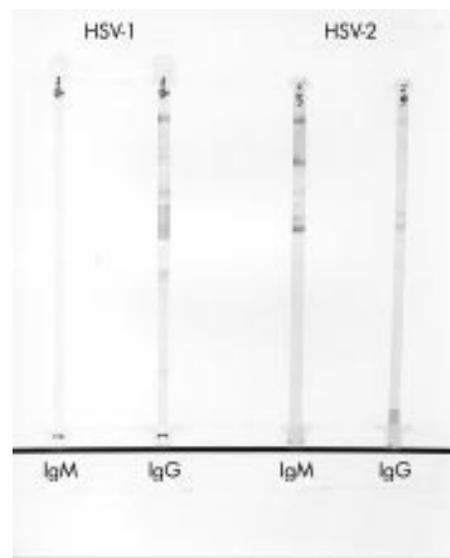


Figure 1 Western blot from patient 1. HSV-1 IgM negative, HSV-1 IgG positive, and HSV-2 IgM positive and IgG negative—interpretation, new HSV-2 infection and previous HSV-1 infection.

(45.2%) patients had a definite diagnosis of new clinical genital herpes.

The sensitivity and specificity of HSV IgM antibodies for the diagnosis of primary genital herpes was compared to that of the clinical diagnosis of first episode genital herpes (table 1). The specificity and positive predictive value were both 100%. However, the sensitivity was only 79% and the negative predictive value 85%.

Some typical cases

Patient 1

Mr B presented to the clinic with a 6 day history of blisters on his penis and a urethral discharge. He had had a regular female sexual partner for the past 8 months and she recognised the lesions to be similar to those experienced by an old boyfriend diagnosed with genital herpes. She had never had any symptoms. HSV-2 was isolated from Mr B's penile blisters. Mr B's serology showed HSV-1 IgG positive, HSV-2 IgG negative, HSV-1 IgM negative, HSV-2 IgM positive. Interpretation—non-primary first episode HSV-2 infection, (previous HSV-1 infection, fig 1). The serology was not helpful in this case.

Patient 2

Ms A presented to the clinic complaining of genital discomfort, dysuria, and a vaginal discharge of 3 days' duration. She was in a new sexual relationship, and had vaginal and orogenital sex with her partner. They used condoms intermittently for vaginal sex and never for orogenital sex. Her partner had no symptoms or signs suggestive of genital herpes but did have occasional cold sores. On examination, Ms A was noted to have several vesicles and shallow ulcer on both sides of the vulva. Viral culture from the affected area revealed HSV-2. Serology showed HSV-1 IgG and IgM negative, HSV-2 IgM positive, and HSV-2 IgG negative. Serology indicated a primary HSV-2 infection (fig 2) and was useful in providing information to the couple about the probable source of the infection.

Patient 3

Ms S presented with genital discomfort, ulceration, and dysuria of 5 days' duration. A small crop of vesicles was noted on the left side of the vulva as well as a superficial ulcer close to the urethra. HSV-2 was grown on culture of the lesions.

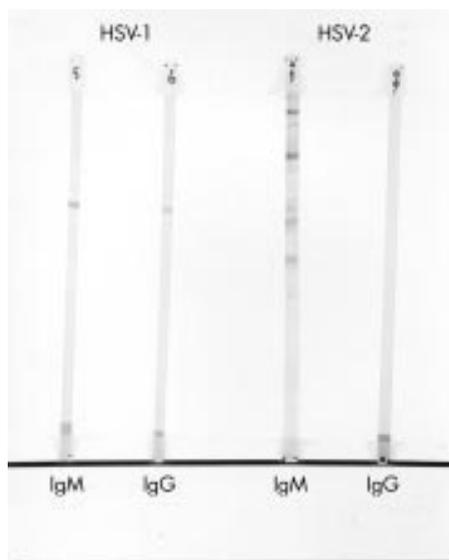


Figure 2 Western blot from patient 2. HSV-1 IgM negative, HSV-1 IgG negative, and HSV-2 IgM positive and IgG negative—interpretation, new HSV-2 infection and no previous HSV-1 infection.

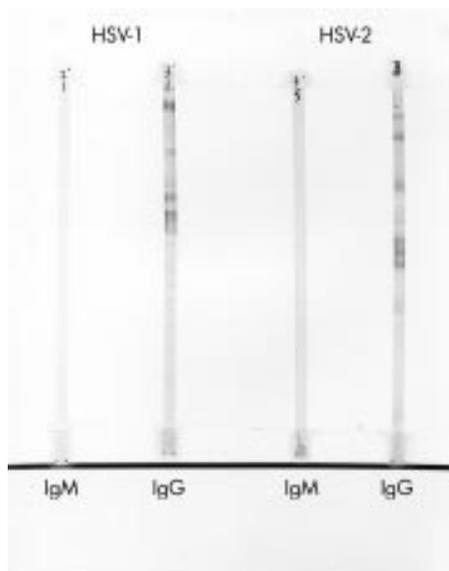


Figure 3 Western blot from patient 3. HSV-1 IgM negative, HSV-1 IgG positive and HSV-2 IgM negative and IgG negative—interpretation, pre-existing HSV-1 and HSV-2 infection.

Serology showed HSV-1 and HSV-2 IgG positive HSV-1 and HSV-2 IgM negative, indicating pre-existing HSV-2 infection (fig 3) and was considered to be helpful in that it indicated that this was not a new infection.

We compared the demographic and sexual characteristics of patients with “new” (primary and non-primary) and pre-existing genital herpes. No significant differences were found for age, sex, having a current partner, duration of sexual relationship, age at first sexual intercourse, condom use, number of lifetime sexual partners, past STIs, current sexual partner, having had genital HSV in the past 4 weeks, ever had or taking antiviral medication.

Sixty one per cent (n=28) of women and 33% (n=21) of heterosexual men contracted HSV-2 within 6 months of starting their relationship. All the women and 86% of the men infected with HSV-2 for the first time had a regular sexual partner.

DISCUSSION

This study has shown that patients who present with a first clinical episode of genital herpes may be classified into three categories on the basis of history, clinical features, viral isolation, and serology. The categories are true primary infection (IgM positive and/or viral culture positive and IgG negative at the time of presentation), non-primary first episode (IgG positive for one of the two viruses with IgM antibody to the other) and previous infection (both HSV-1 and HSV-2 IgG positive and IgMs negative).

This classification is useful in defining the natural history of first episode genital herpes and in providing patients and their partners with helpful information about the source of the infection. Many individuals acquire genital herpes in the context of monogamous relationships and knowing whether the infection is new or pre-existing may be very reassuring or at least help to unravel what is sometimes seen as an illogical situation. In this study, in patients presenting with a first episode of genital HSV infection, the specificity and positive predictive value of HSV IgM antibodies was 100%. However, this test has low sensitivity (48%) and negative predictive value (60%).

The use of HSV IgM antibodies has a number of drawbacks. Firstly, IgM type specific HSV serology is not widely available. Secondly, IgM antibodies may take up to 10 days from exposure to develop and last 7–10 days and patients may present before or after this time interval making the test relatively impractical. Finally, IgM occasionally may be produced in response to a severe recurrence rendering interpretation more difficult. On the other hand, the test has high specificity and positive predictive value in patients with “new” genital herpes, making it useful as a confirmatory test.

Patients having the test will require careful assessment and counselling. Information on the timing of the antibody responses and the meaning of positive and negative tests will need to be provided before the test is taken.¹³ Follow up will be required to explain the result, and provide support. Patients who discover that they have pre-existing infection may be concerned about where they acquired it from, whether they have infected their current and/or previous sexual partners, and whether they can transmit it to future partners. If the current partner has not acquired the infection, careful advice about strategies to reduce transmission will need to be provided including condom use and the possible benefits of suppressive antiviral therapy.^{14 15}

Serology should not be relied upon to make treatment decisions and all patients presenting with a first episode of genital herpes should immediately be considered for a course of antiviral therapy.¹⁶ Overall, IgM type specific serology offers some benefits for individuals presenting with a first episode of genital herpes and their partners, particularly those who are anxious to know more about the possible source of the infection. However, all patients offered the test will need to be provided with detailed information about the test’s interpretation and limitations. Ongoing counselling and support for patients and partners will also be essential.

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CONTRIBUTORS

The study was conceived and designed by AM and AC; JT and CS performed the serological tests. The study was coordinated by RLT. Data collection and patient recall was the responsibility of JP and CM performed the statistical analysis. The manuscript was drafted in collaboration with all the authors.

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Authors' affiliations

J Page, R L Tideman, C Marks, A Mindel, Sexually Transmitted Infections Research Centre, The University of Sydney, Marian Villa, Westmead Hospital, Westmead, NSW 2145 Australia
J Taylor, C Seifert, A Cunningham, Centre for Virus Research Westmead Millennium Institute, Westmead Hospital, Westmead NSW 2145 Australia

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