

Testing for type-specific antibody to herpes simplex virus—implications for clinical practice

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Recently, assays that can distinguish between antibody to herpes simplex virus (HSV) types 1 and 2 have become available. These tests not only make it possible to better define infection in symptomatic patients and their sexual partners but also to identify asymptomatic infected individuals who may, nevertheless, be infectious. Type-specific antibody tests for HSV have several potential applications. They have a clear role in helping to define the worldwide distribution and pattern of HSV infection, and a potential role in the management of individual patients, although this has yet to be formally established and evaluated. Because of the high costs and potential disadvantages of targeted screening, particularly in the absence of effective interventions to prevent acquisition or transmission of infection, the public health benefits of screening need to be formally evaluated before its widespread introduction.

Introduction

Herpes simplex virus (HSV) is responsible for one of the most common human viral infections. HSV-1 is the usual cause of orolabial herpes, whereas HSV-2 is the usual cause of genital herpes, although either viral type can cause either clinical syndrome. HSV-2 is almost always transmitted sexually. HSV-1 is usually transmitted horizontally during childhood, although improvements in socioeconomic circumstances in many countries have resulted in a dramatic decline in the rate of childhood infection. Consequently, adolescents in these countries often remain unexposed to HSV infection until onset of sexual activity. A significant proportion of those infected with HSV are asymptomatic.¹

In this paper I review the characteristics of type-specific serological assays for HSV infection and their role to date in determining the pattern and distribution of HSV infection in different populations around the world. The potential uses for these tests in clinical practice, and their utility as tools for screening for HSV infection in the general population, are also discussed.

Characteristics of type-specific antibody assays

HSV-1 and -2 are closely related viruses. Antibodies to these two viruses cross-react extensively and proteins from

them contain cross-reactive epitopes, but type-specific epitopes are present within glycoproteins G and C (gG and gC).

Assays based on detecting these type-specific epitopes (gG or gC) using either Western blot or solid-phase enzyme-linked immunosorbent assay (ELISA) can reliably differentiate between antibodies to HSV-1 and -2 and have recently become commercially available. It should be noted that type-specific antibody responses may take up to 6–8 weeks to develop and the response may be blunted if the infection has been treated previously with antiviral drugs.

Western blot

Western blot detects antibodies that react with up to 50 HSV proteins including gC and gG and is therefore more sensitive than assays that rely solely on detection of type-specific epitopes. Western blot is considered to be the 'gold standard' for type-specific assays and is particularly useful for detecting seroconversion to HSV-2 in individuals previously infected with only HSV-1. This method has been exhaustively tested to determine its accuracy, but it is time consuming, expensive and technically difficult to replicate on a large scale.²

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Solid-phase ELISA

The gG or gC type-specific immunoassays are more widely available than Western blots and several of these have been developed into commercial ELISA tests. Most of these tests are designed for use in the laboratory, although one manufacturer (Diagnology, Belfast, UK) has developed a point-of-care test (POCKit) for detection of HSV-2, but not HSV-1, antibodies. Most of the commercially available assays are based on the detection of type-specific IgG rather than IgM, although type-specific assays of IgM antibodies are available in some laboratories.^{3,4}

Potential application for type-specific antibody assays

Type-specific assays have several potential applications. Firstly, in seroepidemiological studies, they have been used to determine the prevalence and incidence of HSV infection in various populations and the rates of transmission of infection between serodiscordant sexual partners, and to

examine the co-factor effect of HSV-2 infection in the acquisition of human immunodeficiency virus (HIV). Secondly, type-specific antibody tests are likely to be useful in specific clinical situations (see 'Clinical utility of type-specific HSV antibody tests') although they have not yet been formally evaluated for this purpose. Thirdly, type-specific antibody tests could be used to screen for latent HSV infection, although the advantages of this for public health are not clear.

Seroepidemiological studies

Seroprevalence studies

The prevalence of HSV-1 and -2 infection has been determined in several populations around the world (Tables I and II). The prevalence of HSV-2 infection varies markedly, being high in developing countries and the USA and lower in Europe.⁵⁻⁹ Irrespective of geographical location, these studies show that the prevalence of both HSV-1 and -2 antibodies increases with age, and that HSV-2 antibody is more common in women than in men. An increased prevalence

Table I. Prevalence of HSV-1 antibody, from European and USA studies

Country	Year of study	Setting	Test used	Population	Estimate of prevalence (%)	Sample size
USA	1983-84	college students 18-23 years	immunodot	male	33.7	1063
				female	48.6	
USA		family planning clinic (female)	immunodot	17-20 years	52.1	1435
				21-24 years	55.8	1567
				25-28 years	63.8	875
				29-32 years	70.0	404
				>32 years	71.1	246
				total	58.2	4527
USA	1988-89	unmarried, 15-44 years (inner city)	Western blot	male	61	601
				female	63	611
USA	1985-88	obstetrics practice	Western blot	pregnant women	59.9	1355
USA	1984-86	STD clinic	Western blot	female	58.0	776
UK	1980-81	antenatal clinics, HSV-2-negative women	ELISA (native gG2)	<20 years	74.9	521
				20-24 years	77.3	1122
				25-29 years	76.6	911
				30-34 years	80.9	444
				>34 years	90.9	164
				total	77.9	3166
UK	1992	blood donors	Western blot	male	3.2	
				female	12.4	
	1990-91	GUM clinic		male	21.2	486
				female	24.5	347
Sweden	1969	antenatal clinics (HSV-2-negative women)	ELISA	1969	69	777
	1983			1983	63	1200
	1989			1989	69	670
				total		2647

Testing for type-specific antibody to HSV

Table II. Prevalence of HSV-2 antibody, from selected studies around the world

Country	Year of study	Setting	Test used	Population	Estimate of prevalence (%)	95% CI	Sample size
USA	1976–80	household	immunodot	male	13.2	10.5–15.9	4201
				female	19.4		
				15–29 years	6.9	14.2–18.6	
				30–44 years	20.2		
				60–74 years	23.4		
				total	16.4		
UK	1989–91	household	immunodot	12–19 years	5.6	4.3–7.2	2396
				20–29 years	17.2	15.0–19.7	2750
				30–39 years	27.8	24.8–31.2	2567
				40–49 years	26.6	23.5–30.0	2061
				50–59 years	25.1	21.5–29.4	884
				60–69 years	24.3	20.2–29.1	1069
UK	1980–81	antenatal clinics	ELISA	>70 years	27.7	24.6–31.1	1367
				<20 years	4.4	545	
				20–24 years	9.5	1240	
				25–29 years	11.3	1027	
				30–34 years	13.8	515	
				>34 years	18.8	202	
UK	1992	blood donors	Western blot	total	10.4	3533	
				male	3.2		
	1990–91	GUM clinic		female	12.4		
				male	21.2	486	
Sweden	1969	antenatal clinics	ELISA	female	24.5	347	
				1983	19	941	
				1989	33	1759	
Italy	1990s	STD clinic, Milan	ELISA	1989	33	2700	
				antenatal/GUM, Modena	Western blot	24.6	909
					STD clinic, Rome	12.5	945
					blood donors, Rome	15	202
Tanzania	1993	firemen	MAB blocking ELISA	blood donors, Rome	6	182	
				firemen	3.9	156	
				male 15–54 years	19	14–24	231
				female	42	36–48	259
				15–54 years			

of HSV-2, and to a lesser extent HSV-1, infection is associated with an increased number of sexual partners, early age at first sexual intercourse and years of sexual activity. In fact, the prevalence of HSV-2 antibody has been proposed as a surrogate marker of level of sexual activity that would be of particular use in adolescent populations to reflect the lifetime experience of sexual risk-taking.

Seroepidemiological studies have demonstrated a dramatic increase in the seroprevalence of HSV-2 in the USA between the late 1970s, when the seroprevalence in a randomly selected sample of adult Americans was 16.4%, and the early 1990s, when the seroprevalence in a similar population sample was 21.8%.⁵ This rise in seroprevalence was largely a result of an increase in prevalence amongst young white men and women, and this in turn has been

attributed to increasing ‘unsafe sexual practices’, but may also reflect a decline in the background prevalence of HSV-1 antibody over time, since infection with HSV-1 has been shown to reduce susceptibility to subsequent infection with HSV-2 in some studies.

Seroincidence studies

There have been relatively few prospective studies on HSV seroincidence. One of the few published studies was conducted among antenatal patients from the USA and demonstrated an annual seroincidence of 1–2% for both HSV-1 and HSV-2 (Table III). Importantly, neonatal herpes in general only occurred when infection occurred close to the time of delivery.¹⁰

Table III. Frequency of antenatal HSV seroconversion among 7046 initially HSV-susceptible women

Type of seroconversion	Number with seroconversion/ number at risk ^a	Observed rate (%)	Adjusted rate ^b
Any seroconversion	94/7046	1.3	2.1 ± 0.2
HSV ⁻ to HSV-1 ⁺ or HSV-2 ⁺	49/2033	2.4	3.7 ± 0.5
HSV ⁻ to HSV-1 ⁺	30/2033	1.5	2.3 ± 0.4
HSV ⁻ to HSV-2 ⁺	19/2033	0.9	1.4 ± 0.3
HSV-1 ⁺ to HSV-1 ⁺ and HSV-2 ⁺	45/4075	1.1	1.7 ± 0.3
HSV-2 ⁺ to HSV-1 ⁺ and HSV-2 ⁺	0/939	0	0

^aThe median period of observation was 202 days.

^bThe adjusted rate is the estimated (± S.E.M.) chance of seroconversion adjusted for 280 days of gestation and is based on the assumption of a uniform rate of seroconversion during the entire pregnancy.

Sexual transmission studies

Type-specific antibody tests have been used to help determine the rate of transmission of HSV infection, particularly in the context of vaccine studies or antiviral drug trials aimed at reducing sexual transmission of HSV. Several such studies are either currently under way or are due to be published in the near future. The largest published study indicates that the overall risk of sexual HSV-2 transmission is high (approximately 10% per annum), that the risk is higher for transmission from men to women (17% per annum) than vice versa (3% per annum) and that previous infection with HSV-1 is at least partially protective against HSV-2 infection,¹¹ although this has been rejected recently.¹²

Co-factor studies

Type-specific assays that detect asymptomatic HSV infection in addition to clinically apparent genital herpes have been useful in determining the role of HSV in facilitating transmission or acquisition of HIV infection. This has also enabled the population attributable fraction (i.e. the proportion of new HIV infection in a population that can be attributed to HSV infection) to be calculated in different settings.¹³

Clinical utility of type-specific HSV antibody tests

Unequivocal diagnosis of genital herpes relies upon isolation of the virus directly from genital lesions. However, HSV isolation may be problematic, particularly from atypical or early-aborted lesions. Typing of the viral isolate may be a useful adjunctive diagnostic test particularly for counselling, since genital HSV-1 infection is associated with a lower recurrence rate than genital HSV-2.¹⁴

First-episode genital herpes

People presenting with their first episode of genital herpes are often concerned about the source of acquisition. Establishing the timing of infection is also of particular clinical importance in pregnant women where primary infection close to term poses considerable risk to the neonate.¹⁰ A negative antibody test in the presence of a positive viral culture would confirm recent acquisition.

Sexual partners of persons with genital herpes

It may be helpful to determine whether the sexual partner of an individual with genital herpes is already immune or is at risk of acquiring infection. This is likely to be of particular importance in the pregnant female partners of infected men.

Pregnant women

As indicated earlier, women who have primary HSV infection close to the time of delivery are at high risk for vertical transmission to their baby. Type-specific testing of women presenting with their first clinical episode during pregnancy is useful for distinguishing a new infection from a recurrence. In addition, in women whose sexual partners have a history of recurrent genital herpes, testing can determine whether or not they are at risk of primary infection by testing for seroconcordance.

Persistently culture-negative genital ulceration

Type-specific serology may be helpful in the management of individuals with recurrent genital ulceration that is persistently culture negative. Absence of HSV antibodies will rule out genital herpes as the cause of ulceration, whereas presence of HSV-2 antibody will increase the likelihood

Testing for type-specific antibody to HSV

that symptoms result from genital herpes and may warrant a trial of antiviral therapy. As genital HSV-1 can cause recurrent genital ulceration—although it more commonly causes orolabial lesions—a positive HSV-1 antibody test will neither confirm nor refute a diagnosis of genital herpes.

Screening for HSV antibody

It has been suggested that targeted population screening for HSV antibodies may be helpful in reducing both sexual and vertical transmission of HSV infection. Two groups that have been suggested for screening are antenatal patients and those who attend sexually transmitted disease (STD) clinics. Proponents argue that antenatal screening could identify women at risk of acquiring HSV infection during pregnancy, while opponents state that an effective means of preventing sexual and vertical transmission has not yet been established, and that the public health benefits of screening are unclear.^{10,15,16} The case for screening STD clinic attendees is also unclear.¹⁷ The development of an effective prophylactic vaccine for HSV would greatly strengthen the rationale for screening.

Conclusion

Type-specific antibody tests for HSV have several potential applications. They have a clear role in helping to define the worldwide distribution and pattern of HSV infection, and a potential role in the management of individual patients, although this has yet to be formally established and evaluated. Because of the high costs and potential disadvantages of targeted screening, particularly in the absence of effective interventions to prevent acquisition and transmission of infection, the public health benefits of screening need to be formally evaluated before its widespread introduction.

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