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Epidemiology of Genital Herpes Infections in Sweden

GUN-BRITT LÖWHAGEN,[1] ELIN JANSEN[1], ERIK NORDENFELT[2] and ERIK LYCKE[3]

[1]*Department of Dermatology, University of Göteborg,* [2]*Department of Virology, University of Lund, and* [3]*Department of Clinical Virology, University of Göteborg, Sweden*

The epidemiological pattern of genital herpes infections was studied by evaluating virus isolations and serological results based on samples collected from Göteborg and Malmö, the two largest urban areas of southern Sweden. 1087 strains of herpes simplex virus isolated from cases of clinical herpes in Göteborg during the period 1980 to 1987 were evaluated for type relatedness. It was found that type 1 constituted 10% of the overall number of strains isolated with insignificant variation from year to year and type 1 and 2 occurred in same proportions in men and women. The HSV type 2 specific seroprevalence in 1158 pregnant women from Malmö during the years 1973, 1979, 1987 and 1989 was studied. A significant increase in prevalence figures was noted from 1973 to 1987. The age-related seroprevalence of 1211 men and 531 women in Göteborg suggested a 5 to 10% increase per 5-year period. Generally, higher prevalence was observed in women than in men, and about 10% of the men and 20% of the women might have been asymptomatically infected.

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E. Lycke, Department of Clinical Virology, University of Göteborg, Guldhedsgatan 10B, S-413 46 Göteborg, Sweden.

The natural history and epidemiology of genital herpes has received much attention, in particular in the USA (1-4). The complexity of the epidemiological picture of genital herpes simplex virus (HSV) infection, reflecting i.a. ethnical and socio-economic influences, indicates that marked geographical variations in the epidemiological pattern exist. In some western countries, genital herpes is recognized as a disease of increasing public health importance (5-7). This concern and the introduction of efficient antiviral therapy has called for more and updated information.

Information about epidemiological patterns of genital herpes in Sweden is scarce. During 1974, HSV was isolated from 4 to 5% of patients attending a venereal disease clinic (8). HSV type 2 was reported to cause 97% of infections in males and was found in 88% of isolations from females. In the present study we report on the occurrence and type-relatedness of strains isolated from patients of sexually transmitted disease clinics and of antibody prevalence of some different patient cohorts. The study groups consisted of patients from the two largest urban areas of southern Sweden. The two cities are socio-economically similar and should be representative of a Swedish urban population.

MATERIAL AND METHODS

Outpatients attending STD clinic (Göteborg)

All first-time patients attending the STD clinic of Sahlgrens' Hospital from October 1986 to March 1987, and from February to October 1988 were examined serologically for occurrence of type common and type 2 specific antibodies. Additionally, the patients were interviewed with regard to history of genital herpes, previous sexually transmitted diseases, time for sexual debut, number of life-time sexual partners and condom use.

Pregnant women (Malmö)

Serum specimens taken from pregnant women at time of delivery were stored at -20° C. Four cohorts of women, all with healthy children delivered during the period March to May in 1973, 1979, 1987 and 1989 at the clinic of obstetrics of Malmö Allmänna Hospital, were studied.

Isolation of virus

Specimens from blisters and eroded mucocutaneous efflorescences were collected with cotton-tipped (ENT) swabs and directly introduced into cultures of green monkey kidney cells. The cultures were transported to the laboratory, incubated and, when cytopathic effects were observed (as a rule the following day), passage and typing of virus were performed.

Typing of HSV

Virus isolated from clinical specimens was typed in a multiwell cell culture system by means of enzyme-linked immunosorbent assay (ELISA) and monoclonal antibodies type-

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Table I. *HSV type 1/type 2 ratio of genital herpes (1980-1987).*

Results of typing of genital HSV strains isolated from outpatients attending STD clinic in 1980-1987 (Göteborg).

Year	HSV 1	%	HSV 2	%
1980	10	10	89	90
1981	13	12	100	88
1982	14	9	142	91
1983	23	14	137	86
1984	15	10	131	90
1985	9	7	118	93
1986	15	11	122	89
1987	14	9	135	91
Total	113	10.4	974	89.6

specifically reacting with HSV type 2 glycoprotein G (gG-2) and antibodies reacting with type common HSV antigens. The principal performance of the technique was described previously (9).

Serology

Antibodies reacting with type common and type 2 specific (gG-2) antigen were assayed by an ELISA-based method (10). The same antigen preparations were used in all assays.

RESULTS

The HSV type 1/type 2 ratio of HSV isolates

Virus isolates from patients of the dermato-venereological outpatient clinic at Sahlgrens' Hospital in Göteborg from 1980-1987 were evaluated for HSV type-relatedness. Numerically, the venereal clinic's patients represented approximately 40% of all patients attending hospital-associated care for venereal disease in Göteborg. Of these patients 3-4% were clinically diagnosed as genital herpes cases. All patients involved in the study demonstrated clinical signs compatible with a possible HSV infection. Positive virus isolations were obtained in average in 45% of the specimens examined. The material available, with a complete record of clinical data including the localization of the infection, consisted of 1087 isolates from the genitals, as well as the anal, inguinal and femoral areas, and of 418 strains isolated from lips and face, and 53 strains isolated from hand lesions.

Table I demonstrates that of the 1087 genital strains, 820 strains originated from men and 267 from women. 974 strains were typed as HSV type 2

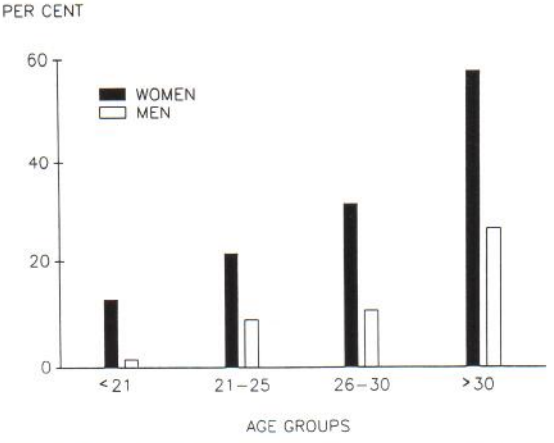

Fig. 1. Age-related prevalence of antibody reacting with HSV type 2 (gG-2) antigen (Göteborg 1987-1988). Relative no. of patients (%) in different age groups.

and 113 strains as HSV type 1. The type 1 strains represented 7 to 14% of the isolates, with 10.4 as mean and a mean percentage of 11 and 10 for men and women, respectively. There were no discernible trends showing an increase or decrease of the relative number of HSV type 1 strains during the period studied.

103 isolates originated from gluteal skin efflorescences. 100 of these were typed as HSV type 2. Of the 53 strains isolated from fingers and hands, 42 (79%) were type 2. For comparison, it should also be noted that of the 418 isolates from facial herpes, 394 (94%) were of type 1 origin.

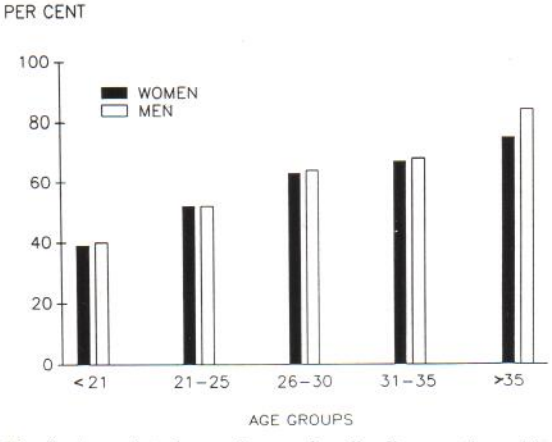

Fig. 2. Age-related prevalence of antibodies reacting with HSV type common antigens (Göteborg 1987-1988). Relative no. of patients in different age groups.

Table II. *Antibodies against HSV type 2 and number of partners.*

Number of sexual partners of HSV type 2 antibody-positive and -negative patients.

No. of partners	HSV type 2 seropositive (n = 223)		HSV type 2 seronegative (n = 759)	
	No.	%	No.	%
1	5	2	30	4
2–10	94	42	392	52
≥10	124	56	337	44

HSV type 2 specific seroprevalence

A total of 1211 men and 531 women were included in the study. The age and sex distribution indicated similar patterns for both sexes with a majority of patients in the 21-25 year-old age group. Fig. 1 demonstrates the age-related prevalence of antibodies against HSV type 2. A seroprevalence gradually increasing with age (12.5% seropositive women in the below-20 age group vs. 58% in the >30-year age group) and with generally significantly higher prevalence figures for women than men ($p < 0.001$) were noted. The difference seemed specifically related to type 2, inasmuch as essentially the same antibody distribution for men and women was noted with regard to the type common antibody prevalence figures (Fig. 2).

Of 1143 men and 475 women interviewed and tested for HSV type 2 antibodies 90 (8%) men and 46 (10%) women gave a history compatible with genital herpes infection and 155 (14%) men and 125 (26%) women were seropositive. Of the 90 (8%) men with history of lesions interpreted as genital herpes 46 (4%) were seropositive and 44 (4%) seronegative. 109 (10%) men were seropositive without having experienced any symptoms of infection. Of the 46 (10%) women with a history of genital herpes 32 (7%) were seropositive and 14 (3%) were seronegative. As many as 93 (19%) of the studied women were seropositive without previous symptoms of genital HSV infection.

Patients seropositive against HSV type 2 more frequently gave a history of chlamydia ($p < 0.05$) or gonorrhoea ($p < 0.001$) than seronegative patients. In contrast, patients seronegative against HSV type 2 more often reported occurrence of genital warts.

The mean age for sexual debut was the same (16 years) for both men and women and showed no correlation to seroprevalence. Although there was an association ($p < 0.05$) of high HSV type 2 antibody prevalence and number of sexual partners (Table II), the difference to the group of seronegative patients was moderate. Somewhat surprisingly, we found no correlation between seroprevalence figures and condom habits, perhaps as a consequence of the relatively low number of regular condom users (Table III). Statistically the HSV type 2 seropositivity covaried with age ($p < 0.001$), history of genital herpes ($p < 0.001$) and chlamydia ($p < 0.01$) while no covariance was noted for gonorrhoea ($p = 0.5$), condylomata ($p > 0.1$), number of sexual partners ($p < 0.3$) and condom use ($p > 0.6$).

The observed HSV type 2 antibody prevalence figures (Table IV) indicated an increased rate of immunization against HSV type 2 from 1973 to 1987 ($p < 0.001$) with a less pronounced progression from 1979 to 1987 and no significant change from 1987 to 1989. A decrease in seroprevalence seemed to have occurred in the youngest age group (≤25 years) from 1987 to 1989 (21% to 8%, $p < 0.02$).

DISCUSSION

The results of the present study demonstrated an increasing seroprevalence against HSV type 2 in cohorts of pregnant Swedish women from 1973 to 1987 but which remained unchanged from 1987 to 1989. The observation suggesting a gradually increased incidence of genital herpes during the last decades is in line with reports from the USA (11, 12) and the UK (13) and other unpublished Swedish seroepidemiologic findings (Forsgren et al., personal communication). The prevalence of HSV type 2 antibodies

Table III. *Antibodies against HSV type 2 and use of condoms.*

Condom use of HSV type 2 antibody-positive and -negative patients.

Frequency	Seropositive (n = 218)		Seronegative (n = 763)	
	No.	%	No.	%
Never	47	22	139	18
Seldom	103	47	397	52
Often	60	28	197	26
Always	8	3	30	4

Table IV. *Prevelence of HSV type 2 antibodies in pregnant women (1973-1989).*

Antibodies against HSV type 2 in pregnant women (Malmö). Age groups, number of patients, number and percent of seropositive individuals.

Age	1973			1979			1987			1989		
	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%	No.	Pos.	%
≤25	120	15	13	116	17	15	84	18	21	108	9	8
26-30	116	11	9	105	26	25	93	19	20	90	25	28
31-40	61	12	20	72	18	25	86	29	34	97	36	37
25-40	297	38	13	293	61	21	273	66	24	295	70	24

was age-related with less than 10% positives in the youngest age group (≤20 years) studied and a 5 to 10% increase during a 5-year period ending up with approximately 35% seropositives in the group of individuals 36 years of age. The somewhat higher seroprevalence in Sweden than in the UK and in white middle-class individuals in the US might reflect the influence of ethnic and socioeconomic conditions (14, 15) but might also depend on technical assay differences.

It is interesting that in the youngest age group (≤25 years) of pregnant women a decrease in seropositivity against HSV-2 seems to have occurred during the last years. This could be a sign of changed sexual habits, a result of the information campaigns concerning sexually transmitted diseases during the last five years.

We consistently noted higher prevalence figures for women than for men. This discrepancy was obviously specifically related to seropositivity against type 2 since it did not appear in type 1 serology with oro-labial herpetic infections. Sex-related differences have been reported previously (12) but have been referred to more widely practiced multi-partnerism among men than women and the dominance of type 2 infections in recurrent genital infections. We believe that a higher susceptibility to type 2 infections among females cannot be excluded.

The remarkable variation in reported frequencies of genital type 1 infections from different countries is intriguing (reviewed in 11). One important reason is probably the often relatively small and heterogeneous materials examined, in addition to the geographic and socio-economic influences on the epidemiologic pattern. Regrettably, the present study does not distinguish between primary, non-primary first-episode or recurrent infections. All patients studied demonstrated symptoms and were admitted for the first time to the clinic, but the relative number of primary infections is unknown. HSV type 1 infections are more frequently associated with primary infections and then more frequently in women than in men (15). Only 25% of our isolates originated from women. However, the proportion of males and females remained essentially the same for all of the years we evaluated. Moreover, recurrent type 2 infections probably constituted the main source of our isolations, but we have no reasons to assume that the relative proportions of primary and recurrent infections would differ significantly from year to year. In spite of the lack of some important data we therefore believe that the observed rates of type 1 and 2 infections indicate the relative importance of type 1 genital infections. During the period 1980 to 1987 type 1 genital infections constituted approximately 10% per cent of the overall number of genital herpes cases attending sexually transmitted diseases clinics in Sweden and type 1 infections occurred in about the same proportion in men and women.

Shedding of HSV without clinical symptoms has been documented as occuring in varying degrees depending upon the group of patients selected and criteria for inapparent infections (16, 17, 18). 25% of American college women with a positive virus culture have been reported to be inapparently infected; other studies with a multiple culture procedure have suggested considerably lower figures. In 13 Swedish men with genital herpes followed daily for 30 days with culturing from the urethra, asymptomatic shedding was probable in 6 individuals (19). The results of the present study would indicate a possible percentage of subclinical infection in 10% of men and 20% of women. It is now generally accepted that

asymptomatic infections are responsible for a substantial part of the virus circulation and spread of genital herpes. This awareness must be taken into account when risks for and strategies against neonatal infections are considered.

The risk for acquisition of genital herpes is, as with other sexually transmitted diseases, related to the degree of sexual activity, and thus indirectly to factors like the age at first intercourse and type and use of contraceptives (12, 14). As reported by others, we found an association between type 2 seropositivity and history of gonorrhea and chlamydia, but not with condylomata. The reason for the latter observation is not clear but might reflect that different age-groups, mainly teen-agers, are predominantly exposed to the ongoing human papilloma virus epidemic, whereas genital herpes is associated with individuals of 20 years-of-age or older. In agreement we observed no covariance between HSV-2 seropositivity and gonorrhoea. Our study also indicates that condoms were apparently not used in such a way as to provide any efficiency in the control of genital herpes. This was perhaps not surprising with regard to the irregularity in condom praxis generally observed and the frequent occurrence of inapparent genital herpes infections.

REFERENCES

1. Straus SE, Rooney JF, Sever JL, Seidlin M, Nusinoff-Lehrman S, Cremer K. Herpes simplex virus infection: Biology, treatment, and prevention. Ann Intern Med 1985; 103: 404-419.
2. Corey L, Spear P. Infection with herpes simplex viruses. N Engl J Med 1986; 314: 686-691, 749-757.
3. Becker TM, Stone KM, Cates W Jr. Epidemiology of genitalherpes infections in the United States. The current situation. J Reprod Med 1986; 31: 359-364.
4. Wheeler CE. The herpes simplex problem. J Am Acad Dermatol 1988; 18: 163-168.
5. Genital herpes infection - United States, 1966-1984. MMWR 1986; 35: 402-404.
6. Epidemiologic Reports. Laboratory reports of herpesvirus infections in Canada in 1984. Can Med Assoc J 1986; 134: 249-251.
7. PHLS report. Sexually transmitted disease surveillance in Britain - 1984. Br Med J 1984; 293: 942-943.
8. Jeansson S, Molin L. On the occurrence of genital herpes simplex virus infection. Acta Derm Venereol (Stockh) 1974; 54: 479-485.
9. Nilheden E, Jeansson S, Vahlne A. Typing of herpes simplex virus by an enzyme-linked immunosorbent assay with monoclonal antibodies. J Clin Microbiol 1983; 17: 677-680.
10. Svennerholm B, Olofsson S, Jeansson S, Vahlne A, Lycke E. Herpes simplex virus type-selective enzyme-linked immunosorbent assay with Helix pomatia-lectin purified antigens. J Clin Microbiol 1984; 19: 235-239.
11. Guinan ME, Wolinsky SM, Reichman RC. Epidemiology of genital herpes simplex virus infection. Epidemiol Rev 1985; 7: 127-146.
12. Johnson RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA Snowden CB. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. N Engl J Med 1989; 321: 7-12.
13. Ades AE, Peckham CS, Dale GE, Best JM, Jeansson S. Prevalence of antibodies to herpes simplex virus types 1 and 2 in pregnant women, and estimated rates of infection. J Epidemiol Community Health 1989; 43: 53-60.
14. Stavraky KM, Rawls WE, Chiavetta J, Donner AP, Wanklin JM. Sexual and socioeconomic factors affecting the risk of past infections with herpes simplex type 2. Am J Epidemiol 1983; 118: 109-121.
15. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: Clinical manifestations, course, and complications. Ann Intern Med 1983; 98: 958-972.
16. Rattray MC, Corey L, Reeves WC, Vontver LA, Holmes KK. Recurrent genital herpes among women: symptomatic v. asymptomatic viral shedding. Br J Vener Dis 1978; 54: 262-265.
17. Wittek AE, Yeager AS, Au DS, Hensleigh PA. Asymptomatic shedding of herpes simplex virus from the cervix and lesion site during pregnancy: correlation of antepartum shedding with shedding at delivery. Am J Dis Child 1984; 138: 439-442.
18. Corey L. First-episode, recurrent and asymptomatic herpes simplex infections. J Am Acad Dermatol 1988; 18, 169-172.
19. Strand A, Vahlne A, Svennerholm B, Wallin J, Lycke E. Asymptomatic virus shedding in men with genital herpes infection. Scand J Infect Dis 1986; 18: 195-197.