

## CLINICAL REPORT

# Proportion of Herpes Simplex Virus (HSV) Type 1 and Type 2 Among Genital and Extragenital HSV Isolates

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Herpes simplex virus type 1 (HSV-1) has been associated with orofacial infections and HSV type 2 (HSV-2) with genital infections. This tropism of the virus seems to have changed and in clinical reports an increasing number of genital herpes infections caused by HSV-1 have been recognized. The aim of this study was to estimate the proportion of HSV-1 and HSV-2, respectively, among isolates from different anatomical sites typed in our laboratory during the years 1994–1998. Out of a total of 3,085 anogenital isolates, 29% were typed as HSV-1 and 71% as HSV-2. The highest prevalence of HSV-1 was registered among isolates from young women. Of 631 orofacial isolates, 4% were typed as HSV-2 and 96% as HSV-1. Of 69 finger/hand isolates, 54% were typed as HSV-1 and 46% as HSV-2, and of 95 isolates from other regions (abdomen, foot, etc.), 60% were typed as HSV-1 and 40% as HSV-2. It was found that HSV-2 was as common as HSV-1 in the extra-genital regions with the exception of the orofacial area, in which HSV-2 was seldom detected. Furthermore, the study showed an increasing proportion of HSV-1 among anogenital isolates during the study period. Taken together, these results suggest that a clear HSV type-related tropism might be limited to the permissiveness of the orofacial region for HSV-1, and that both serotypes may readily establish infections below the neck. *Key words: epidemiology; genital herpes; labial herpes.*

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Infection with herpes simplex virus type 1 (HSV-1) has primarily been associated with orofacial infections and HSV-2 with genital infections. During recent decades, an increasing number of cases of genital herpes caused by HSV-1 have been reported, especially from Europe (1–4). Conversely, an increase in the proportion of HSV-2 isolates from oral or other extra-genital sites has not been documented. In most textbooks, oral HSV-2 is said to be an uncommon infection, although few studies have addressed this issue (5). Most investigators consider that the presence of HSV-2 antibodies reflects an anogenital infection (6, 7). The aim of this study

was to estimate the proportion of HSV-1 and HSV-2, respectively, among genital and extra-genital isolates typed in our laboratory during the years 1994–1998. Isolates from the STD Clinic at Sahlgrenska Hospital during this period were analysed separately for comparison with data from the same clinic in the 1980s (8).

## METHODS

The Virological Laboratory at Sahlgrenska Hospital serves clinics in Gothenburg and its surroundings. The majority of specimens are from STD clinics and gynaecological clinics. Information regarding HSV isolates analysed by typing in the laboratory from 1994 to 1998 was collected. For most isolates, data were available concerning the age and sex of the patient and from which site the sample was taken. Anogenital isolates from the STD Clinic at Sahlgrenska Hospital were analysed separately.

*Isolation and typing of virus*

Material from blisters or eroded lesions was collected with a cotton-tipped swab and at the laboratory directly inoculated on cultures of green monkey kidney (GMK) cells. Cytopathic effects were registered daily and after passage, typing of isolated virus was performed by means of an enzyme-linked immunosorbent assay (ELISA) using monoclonal antibodies type-specifically reacting with either HSV-2 glycoprotein G or HSV-1 glycoprotein C (9).

*Statistics*

The proportions of isolates typed as HSV-1 and HSV-2 are presented with 95% confidence intervals (CI). The  $\chi^2$  test for trend was used to analyse changes in HSV-1 prevalence from 1994 to 1998 and a logistic regression analysis to test independent correlations between HSV type and sex and HSV type and age.

## RESULTS

There were 4,437 typed HSV isolates registered during the period 1994–1998. The area from which the sample was taken was registered in 3,880 cases. Most isolates originated from the anogenital region, and included gluteal, herpetic infections (Table I). The proportion of HSV-1 and HSV-2 in isolates from finger/hand, orofacial and other regions was the same during the study years, while the proportion of HSV-1 among anogenital isolates increased from 1994 to 1998 ( $p < 0.01$ ) (Table II).

Table I. Origin and proportion (%) of HSV-1 and HSV-2 in 4,437 typed HSV isolates from 1994 to 1998

Origin of isolates	No.	HSV-1 (%)	HSV-2 (%)
Anogenital	3,085	29	71
Orofacial	631	96	4
Finger-hand	69	54	46
Other regions (abdomen, foot, etc.)	95	60	40
Unknown	557	48	52

Table II. Proportion of HSV-1 (%) among anogenital isolates during the years 1994 to 1998

Year	No. isolates	HSV-1 (%)	CI 95 %
1994	572	23	20–27
1995	651	27	23–30
1996	687	26	23–29
1997	591	34	30–38
1998	584	35	31–39

$\chi^2$  test for trend  $p < 0.01$ .

### Anogenital HSV-isolates

Of 3,085 isolates, 29% (CI, 27–31%) were typed as HSV-1 and 71% (CI 69–73%) as HSV-2. For 129 isolates, the sex of the patient was unknown. Altogether, 32% (CI 30–34%) of female isolates and 20% (CI, 18–24%) of male isolates were typed as HSV-1 (Table III). The women were younger than the men: mean age for women  $\pm$  SD was  $34 \pm 14$  years and for men  $37 \pm 13$ . The HSV-1 isolates were from younger patients than the HSV-2 isolates (Table III). Both age and sex were independently correlated with HSV type ( $\chi^2$  for sex 21.7 and for age 193.3,  $p < 0.001$ ).

Of 425 (277 male, 148 female) anogenital HSV isolates from the STD Clinic at Sahlgrenska Hospital, 78 (18.4%, CI, 15–22) were typed as HSV-1 and 347 (81.6%, CI, 78–85) as HSV-2.

## DISCUSSION

The question of differences in tropism between HSV-1 and HSV-2 has been of long-lasting interest since discrimination of the two serotypes was made almost 4 decades ago, and has stimulated clinical as well as experimental studies (5, 10, 11). The present study reports the typing of a large number of consecutively received HSV isolates of which the body localization was documented in more than 3/4

Table III. Sex and age distribution of anogenital HSV-1 and HSV-2 infections

	HSV-1 <i>n</i> (%)	HSV-2 <i>n</i> (%)	Total <i>n</i>
Women	712 (32)	1,507 (68)	2219
Men	151 (20)	586 (80)	737
Age (years, mean $\pm$ SD)	29.1 $\pm$ 10.5	37.3 $\pm$ 13.7	34.9 $\pm$ 13.4

of the material. The results demonstrate a substantial contribution of HSV-1 to genital infections, although HSV-2 dominates as a causative agent. Furthermore, despite a rare occurrence of HSV-2 in the orofacial region, this virus was as well represented as HSV-1 in infections of the finger-hand and other regions.

There are obvious limitations in the interpretation of laboratory data when there is no access to clinical information. During the study period, there was no significant change of the catchment area of the laboratory or of the laboratory test routines. Isolates originating from clinical studies were not included.

Of isolates from the anogenital tract, altogether 70% were typed as HSV-2 and of orofacial isolates 96% as HSV-1, which supports the selective tropism for HSV-1 and HSV-2, respectively. Of 631 isolates from the orofacial area, 4% were typed as HSV-2, which is the same proportion as reported from this laboratory during the 1980s (8). The interaction between the virus and cellular host factors of skin, mucosa and/or ganglia cells decides whether an infection (clinical or subclinical) will be established. It may be that more specific cellular host factors are required for an HSV-2 infection compared with those required for HSV-1. The infrequent occurrence of orofacial HSV-2 infection might also be related to the fact that up to 40–70% of young adults, when exposed to HSV-2, have a prior HSV-1 infection of the trigeminal nerve group ganglia (6), which may be associated with the development of local immune responses that decrease the ability of HSV-2 to colonize the ganglia (12). In isolates from the finger-hand and other body sites such as the back, the same proportion of HSV-1 and HSV-2 was registered, which might indicate that host cells in these dermatomes do not discriminate between HSV-1 and HSV-2. Taken together, the results indicate that both viruses seem to be well adapted to infect most regions of the body, with one clear exception: the restricted ability of HSV-2 to establish an infection in the orofacial region. Therefore, the concept of HSV-2 as a virus occurring “below the waist” might be revised to “below the neck”.

The epidemiological pattern of HSV infections differs in different parts of the world. From the US, an increasing incidence of HSV-2 infections is reported (7), especially among young people, while some data from Sweden indicate a decreasing incidence of HSV-2 in young people (13). From the UK, several studies (2, 3) since the 1980s have reported an increasing number of first episode genital herpes infections caused by HSV-1. In the 1990s an increase in HSV-1 infections was observed in STD clinics in Sweden, and in a study comprising 108 first episodes of genital herpes seen in the STD clinic at Sahlgrenska Hospital between 1995 and 1999, 44% were HSV-1 infections (4).

In the present study, 29% of all anogenital isolates sent to the laboratory between 1994 and 1998 were

typed as HSV-1, which is in accordance with European studies. In the UK, Scoular et al. (14) reported an HSV-1 prevalence of 29–38% in genital isolates analysed between 1985 and 1988. In the US, genital HSV-1 infections seem to be less frequent, and in a recent report from an STD clinic, 17% of 1,145 genital isolates analysed during the period 1993–1997 were typed as HSV-1 (15). In clinical studies of genital herpes, the highest prevalence of HSV-1 has been reported in young women (2, 4, 14, 16). The same pattern was seen in the present study, and we found age and sex to be independently correlated to HSV type.

In an earlier study comprising anogenital isolates from our STD Clinic at Sahlgrenska Hospital during the years 1980–1987, we found that 10.4% of 1,087 isolates were type HSV-1 and during those years no trend towards an increase in HSV-1 was observed (8). Among isolates collected in the same clinic during the years 1994–1998, the proportion of HSV-1 infections was 18.2%. The indication for testing and the spectrum of patients attending has not changed since the 1980s, supporting a real increase in genital herpes caused by HSV-1 in this population. The lower figure (18.4%) in isolates from the STD Clinic, compared with the overall HSV-1 prevalence of 29%, probably reflects the fact that in an STD clinic more patients with recurrent genital herpes are sampled and also that the majority are males. Genital HSV-1 infections are less likely to recur than HSV-2 infections and in the STD Clinic at Sahlgrenska Hospital 94% of recurrent episodes of genital herpes were caused by HSV-2 (17).

In conclusion, these retrospective laboratory data are in agreement with clinical studies, showing, at least in the STD population, an increase of anogenital herpes caused by HSV-1. The selective tropism for HSV-1 and HSV-2 is illustrated. It is important to note that our results reflect the spectrum of HSV infections in patients attending a medical clinic and thus may not reflect the spectrum of HSV infections in the general population. Although 4% of orofacial HSV isolates were typed as HSV-2, this may not reflect the prevalence of HSV-2 labial herpes in general. In an ongoing study, we are looking at the clinical features and viral characteristics of orofacial herpes caused by HSV-2 compared with that caused by HSV-1.

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