

Genital Herpes Simplex Virus Infection

ARVID NILSEN

Department of Dermatology, Haukeland University Hospital and University of Bergen, Bergen Norway.

Arvid Nilsen, dermato-venereology consultant in Bergen, Norway, recently defended his doctoral thesis at the University of Bergen on studies regarding genital herpes simplex virus infection in Norwegian and Tanzanian populations.



The aim of the studies was, firstly, to investigate possible epidemiological changes over time in genital herpes virus simplex (HSV) disease in Norwegian individuals; secondly, to investigate the prevalence of HSV-2 infection among Tanzanian and Norwegian patients with sexual transmitted diseases (STD), identify possible demographic or behavioural differences between African and Norwegian patients, and investigate whether risk factors for genital HSV-2 infection differs from risk factors for other STDs; and, thirdly, to evaluate a novel serological test for identification of HSV-2 infection.

Genital ulcer disease has been documented to be a risk factor for the sexual transmission of HIV, and HSV-2 infection shows the highest association with HIV transmission. The laboratory diagnosis of genital HSV infection has traditionally been based on analysis of lesional specimens by culture on cell media. However, modern polymerase chain reaction (PCR)-based methods on lesional specimens increases the sensitivity considerably. Type-specific serological methods provide additional information in selected clinical cases. Additionally, HSV-2-specific serology is the best tool for monitoring HSV-2 incidence and prevalence. However, most of these types of tests are too expensive for use in the developing world, where they are most needed.

Paper I retrospectively investigated genital HSV infection in Bergen, Norway, and possible differences between three periods in the 1980s and 1990s (1). In primary disease, HSV-2 was the major cause of genital disease during the late 1980s (64%), whereas HSV-1 constituted a greater part of the cases in the early and late 1990s (66% and 51%, respectively), especially in female patients (73% and 63%, respectively) and in young patients (up to 70–90%). In recurrent genital HSV infection, HSV-1 accounted for 4% of cases during the late 1980s, compared with 15% during the 1990s. HSV-1 recurrent disease was at least twice as frequent in females as in males in all three periods. The highest proportion of recurrent HSV-1 disease was found in patients younger than 25 years in the late 1990s (37%).

The retrospective design of the study does not allow any conclusions to be drawn as to the reason(s) for the observed change in viral type. An increase in orogenital sexual practice among young people might, at least in part, be an explanation, as oral sex has been demonstrated in prospective studies to be an independent risk factor for genital HSV-1 infection. Furthermore, oral sex seems to be practised by many adolescents, often before the first intercourse experience, and to be more common than vaginal sex. The introduction of HIV during the 1980s and fear of being sexually infected with HIV could be a reason for people practising more orogenital sex than before. Another possible explanation for the epidemiological change in HSV-1 might be a decrease in HSV-1 seropositivity among young people, rendering this population more susceptible to genital HSV-1 infection. The same change has been reported previously from Europe and Japan.

Paper II compared the diagnostic utility of a novel enzyme-linked immunoassay (ELISA) test (the peptide 55 method) with two different ELISAs (the Ho assay and the Gull assay) for detection of anti-HSV-2 IgG antibodies (2). Multimerization of peptides has long been recognized as a valuable approach to amplify peptide immunogens. Such multiple antigen peptides (MAPs) are nearly pure antigens and therefore are immunologically focused, in contrast to conventional peptide-protein conjugates. In the peptide 55 assay, four copies of a peptide sequence corresponding to residues 561–578 of gG-2 were attached to the lysine core. Furthermore, a glycine spacer was introduced between the core and the peptides, increasing the sensitivity of the assay. The use of receiver operating characteristic (ROC) methods on known sera enabled us to calculate optimal cut-off values.

The peptide 55 assay reached a sensitivity of 100% and a specificity of 98.6%, compared with sensitivity/specificity figures of 97.2%/94.4% and 93.5%/96.8% for the Ho assay and the Gull assay, respectively. This assay also gave a better discrimination between patient and control sera than did the two other tests. We suggest that this low-cost assay is suitable

when type-specific HSV serotesting is indicated, particularly in settings with restricted resources. The peptide 55 assay should also be evaluated as a possible confirmatory test for existing FAD (Food and Drug Administration)-approved methods (and vice versa).

Paper III investigated the prevalence of HSV-2 antibodies in different cohorts and evaluated risk factors for HSV-2 seropositivity (3). The prevalence of HSV-2 antibodies was significantly higher in Tanzanian than in Norwegian STD patients (70% versus 17%). Female STD patients had the highest prevalence in both countries, and the prevalence increased with age. In sera collected in 1989–93, HSV-2 prevalence in Tanzanian STD patients was 43% (4), indicating that HSV-2 seroprevalence has increased considerably among Tanzanian STD patients during the 1990s. The much lower seroprevalence figures among Norwegian STD patients compare reasonably well with other European STD studies. We know of no previous report on HSV-2 seroprevalence in Norwegian STD patients. A much larger proportion of genital herpes is caused by HSV-1 in Norway and Europe than in Africa, where almost exclusively HSV-2 genital infection is reported.

In the Tanzanian STD patients, a higher HSV-2 seroprevalence was associated with female gender, previous STD (other than HSV), homo- or bisexual preference, and HIV seropositivity, with a non-significant association with increasing age. In the Norwegian STD patients, a higher HSV-2 seroprevalence was associated with female gender, increasing age, previous genital HSV disease, and coitarchal age below 15 years. In logistic regression analysis of the Tanzanian STD patients, HSV-2 seropositivity was non-significantly associated with increasing age (odds ratio (OR) 1.37, 95% confidence interval (CI) 0.97–1.92). This can probably be explained by the fact that a very high proportion of patients had already been infected by the age of 25 years. Lower age and high HSV-2 seroprevalence was particularly evident among female Tanzanian STD patients, of whom almost 50% were infected before the age of 20 years. In contrast, the steepest increase in HSV-2 seropositivity in Norwegian STD patients was seen between 30 and 40 years.

The lack of association between higher HSV-2 seroprevalence and patient-reported previous genital HSV-infection in the Tanzanian STD cohort, as well as the very high association in their Norwegian counterparts (OR 7.94), are probably due to incorrect information from the Tanzanians, as few of them have had a laboratory-proven diagnosis, questioning the validity of the questionnaire.

A history of previous STD (other than HSV) was predictive for HSV-2 seropositivity in the Tanzanian, but not in the

Norwegian, STD group. However, the two groups are hardly comparable in this respect, as the majority of the Tanzanians reported syphilis, gonorrhoea or genital ulcer disease, whereas the Norwegians almost exclusively reported Chlamydia and human papillomavirus (HPV) infections. Also, the use of syndromic diagnosis and management in Tanzania might result in some cases of previous genital HSV infection being reported as previous STDs.

An independent positive association between HSV-2 seropositivity and HIV seropositivity was found in Tanzanian STD patients and pregnant women, but not in blood donors, in line with numerous other studies. The very high prevalence of HSV-2 antibodies among Tanzanian STD patients, particularly the large increase over only one decade, is alarming.

Paper IV investigated whether social/cultural, behavioural or demographic factors differed between Tanzania and Norway as possible risk factors for STDs (other than HSV) (5). Reporting previous STDs was more common in the Tanzanian patients, mainly gonorrhoea and syphilis, whereas the Norwegian patients mainly reported previous Chlamydia or HPV infections. There were no significant differences between the two cohorts with regard to age, gender, coitarchal age and sexual preference. Thirty-three percent of the Tanzanian STD patients tested positive for HIV antibodies, females more often (43%) than males (26%), and approximately one-third of the female HIV-positive patients had seroconverted by the age of 25 years, and approximately two-thirds by the age of 30 years.

To avoid a potential report bias, the questionnaire procedure should have been repeated among the same patients. However, it was not possible to reach the Tanzanian cohort for a second time. Face-to-face interviewing in Kiswahili was used in the Tanzanian populations, as some participants were unable to read and write. The Norwegians completed the questionnaire by themselves. Self-completion might give more valid results, as the respondent does not have to disclose information in front of the interviewer. Our finding of similar sexual preference in the two groups was unexpected, as same-sex sexuality is assumed to be less accepted in Africa than in Europe. The high figures for same-sex preference, reported by the Tanzanian participants, do not indicate reduced disclosure of potential sensitive information in a face-to-face interview.

Tanzanian STD patients reported lower numbers of lifetime sexual partners than Norwegians. We suspect that the reporting of partnerships by the female Tanzanian participants might be an expression of “social desirability bias”. African women, both STD patients and in general, are less likely than men to report non-marital sex. The reported number of partners in male Tanzanian STD patients is also significantly lower than in

male Norwegian STD patients, indicating an underreporting. Risk factors for STDs (other than HSV) among Tanzanian and Norwegian STD patients were similar, but not identical, to risk factors for HSV-2 infection, as reported in paper III.

The main supervisor for the studies was Professor Lars Haarr. Members of the dissertation committee were Professor Are Dalen, Trondheim, Professor Harald Moi, Oslo, and Professor Claus Ola Solberg, Bergen.

References

- 1 Nilsen A, Myrmel H. Changing trends in genital herpes simplex virus infection in Bergen, Norway. *Acta Obstet Gynecol Scand* 2000; 79: 693–696.
- 2 Nilsen A, Ulvestad E, Marsden H, Langeland N, Myrmel H, Matre R, Haarr L. Performance characteristics of a glycoprotein G based oligopeptide (peptide 55) and two different methods using the complete glycoprotein as assays for detection of anti-HSV-2 antibodies in human sera. *J Virol Methods* 2003; 107: 21–27.
- 3 Nilsen A, Mwakagile D, Marsden H, Langeland N, Matre R, Haarr L. Prevalence of, and risk factors for, HSV-2 antibodies in sexually transmitted disease patients, healthy pregnant females, blood donors and medical students in Tanzania and Norway. *Epidemiol Infect* 2005; 133: 915–925.
- 4 Langeland N, Haarr L, Mhalu F. Prevalence of HSV-2 antibodies among STD clinic patients in Tanzania. *Int J STD AIDS* 1998; 9: 104–107.
- 5 Nilsen A, Mwakagile D, Chalamila G, Langeland N, Matre R, Haarr L. Demographic and behavioural factors in Tanzanian and Norwegian patients with sexually transmitted infections. *Acta Derm Venereol* 2006; 86: 320–328.