

Herpes Simplex Virus Infection: Epidemiological Aspects and Analysis of the Type-specific Antibody Response

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ABSTRACT

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are ubiquitous viruses belonging to the Herpesviridae family, which consists of over 100 known viruses infecting organisms from oysters to humans. HSV-1 and HSV-2 often lead to asymptomatic infections in humans, nevertheless different clinical presentations can be seen including recurring oral and genital lesions, meningitis and less commonly neonatal herpes and encephalitis.

HSV type 1 and type 2 are closely related viruses carrying a genetic homology of ~50% and this resemblance has hampered the attempts to differentiate between the two types serologically. Due to the recurring and often asymptomatic nature of the HSV infection, type-specific serology can be the only way to diagnose an HSV infection and it can also be employed for epidemiological studies, for counseling in the clinical situation

and in evaluating HSV vaccine trials. The only known HSV-glycoproteins inducing type-specific antibody responses are the envelope glycoproteins G-1 (gG-1) from HSV-1 and gG-2 from HSV-2 and they have therefore been utilized as discriminating ELISA antigens. However, a prerequisite for type-specific seroassays is that these tests are based on genetically stable antigens inducing only type-specific antibodies and this prerequisite is not yet fulfilled for the type-specific HSV ELISA antigen gG-1.

In the present work, the B-cell epitopes, including an immunodominant region, were outlined for gG-1 by investigating the reactivity of purified human anti-gG-1 antibodies to cellulose-bound synthetic peptides spanning the entire gG-1 sequence, employing the pepscan method. It was demonstrated that the epitopic regions of gG-1 were localized to regions carrying a high degree of homology to gG-2, from HSV-2. In spite of this, an analysis of purified human anti-gG-1 antibodies displayed no cross-reactivity to the gG-2 antigen or to virus-infected cell-membranes from HSV-2. During the epitope-mapping, two corresponding highly homologous epitopic regions in gG-1 and gG-2 were found. However, despite this similarity a retained type-specific antibody-response was demonstrated. The molecular basis for this finding was explored and mutational analysis demonstrated that the human polyclonal antibody response

was dependant on the structural presentation of these regions and relied on single or dual key residues.

The DNA sequence of gG-1 in 108 clinical isolates was further examined, showing that missense mutations, leading to amino acid shifts, affected the immunodominant region in almost 40% of the investigated viral isolates. Two different genotypes were established by phylogenetic comparison, but when investigating the serological response in patients infected with either of these two genotypes their IgG reactivity did not differ when compared.

The type-specific HSV serology was applied in the clinical setting, using it as a tool for classifying first episodes of genital herpes and clarifying transmission routes. In an investigation of 97 consecutive patients with first episodes of genital herpes, virus isolation demonstrated that 44% of all cases were found to be caused by HSV-1, while over 60% of the cases of true primary genital infections were due to HSV-1. In 17% the first episode of genital herpes corresponded to the first clinical recurrence of an earlier acquired HSV-2 infection.

A suggested explanation to the rise in genital infections caused by HSV-1 has been a decrease of HSV-1 among children. An epidemiological study was therefore conducted in sera from 2106 Swedish children and

adolescents, aged 0–19 years, using the type-specific HSV-ELISAs. In total, HSV-1 IgG antibodies were found in 31% and HSV-2 in 0.5%. The HSV-1 infection seemed to be acquired early in life, with a seroprevalence of over 20 % in the cohort of 1–2 year olds, and increased to 37% among 15–19 year olds. The seroprevalence in the oldest age-cohort did not differ significantly from that seen in earlier Swedish studies. An evaluation of the type-specific ELISAs was also performed, demonstrating that the sensitivity of the type-specific HSV-1 and HSV-2 ELISAs were 98% and the specificity 97% and 93%, respectively, when compared to the golden standard Western blot.

Conclusions

The type-specific HSV-1 ELISA was found to be based on an antigen inducing only type-specific antibodies and the two different genotypes of gG-1, found in clinical isolates, did not seem to affect the

serological HSV-1 IgG-response. The type-specific antibody responses in homologous regions of gG-1 and gG-2 depended on the structural presentation of these regions and relied on single or dual key residues.

Type-specific HSV-serology was found to be of value in classifying first episodes of genital herpes and almost half of these episodes were found to be caused by HSV-1. Anamnestic data supported the suggestion that the oro-genital route of transmission was common in genital HSV-1 infections.

The rise in genital HSV-1 infections has been suggested to depend on a decrease in HSV-1 infections among children, but when comparing the HSV-1 seroprevalence in the oldest age-cohort in our study, with that seen in earlier Swedish studies, no statistical differences were seen.

This thesis is based on the following papers

- I. Löwhagen GB, Tunbäck P, Andersson K, Bergström T, Johannisson G. First episodes of genital herpes in a Swedish STD population: a study of epidemiology and transmission by the use of herpes simplex virus (HSV) typing and serology. *Sex Transm Inf* 2000; 76: 179–182.
- II. Tunbäck P, Liljeqvist JÅ, Löwhagen GB, Bergström T. Glycoprotein G of Herpes Simplex Virus type 1: identification of type-specific epitopes by human antibodies. *J Gen Virol* 2000; 81: 1033–1040.
- III. Rekabdar E, Tunbäck P, Liljeqvist JÅ, Lindh M, Bergström T. Dichotomy of Glycoprotein G gene in herpes simplex virus type 1 isolates. *J Clin Microbiol* 2002; 3245–3251.
- IV. Tunbäck P, Bergström T, Löwhagen GB, Hoebeke J, Liljeqvist JÅ. Type-specific reactivity of anti-glycoprotein G antibodies from herpes simplex virus infected individuals is maintained by single or dual type-specific residues. In manuscript.
- V. Tunbäck P, Bergström T, Andersson AS, Nordin P, Krantz I, Löwhagen GB. Prevalence of herpes simplex virus antibodies in childhood and adolescence – a cross sectional study. *Scand J Inf Dis* 2003; 35: 498–502.