Recent Advances in Genital Herpes
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Abstract
The majority of transmissions occur as a consequence of inapparent infection in the source contact, as asymptomatic viral excretion in individuals with recurrent infections. The development of type specific serological assays has allowed for a more accurate determination of herpes simplex virus (HSV) 2 prevalence and has revealed that the prevalence of HSV 2 in sexually transmitted disease clinic attendees varies from 8%-83%, in female prostitutes from 75%-96% and in antenatal clinic attendees from 6%-53%.

Patients treated for primary genital herpes are likely to resume sexual intercourse earlier than those who do not. Long-term suppressive acyclovir will result in decrease in clinical symptoms and viral excretion and may decrease the opportunity for HSV transmission.

Acyclovir is the drug of choice for the treatment of primary genital herpes and for long-term acyclovir suppression. Two new drugs, valaciclovir and famciclovir, are currently under investigation. Failure to respond to acyclovir may be due to inadequate dose, malabsorption, another condition, or resistance. Resistance is rare and occurs mainly in profoundly immunosuppressed individuals, and is usually due to the development of thymidine kinase deficient mutants. Treatment with intravenous foscarnet is usually successful.

Patients with genital herpes have a number of emotional problems, particularly if the condition recurs. Recent studies suggest that emotional stress does not precipitate recurrences, rather that recurrences cause stress. Long-term acyclovir suppression can decrease psychological morbidity in patients with frequent recurrences.

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Introduction
The last decade has seen several major advances in the diagnosis and treatment of genital herpes and in our understanding of the natural history, transmission and psychological morbidity associated with the disease. In addition, there has been a recognition of the complex interrelationship between herpes simplex virus (HSV) infections, in particular genital infection with HSV 2, and infection with the human immunodeficiency virus (HIV).

This article will review recent advances in our understanding of the natural history and epidemiology of genital herpes, its treatment, psychological morbidity and finally briefly consider the interrelationship between HSV and HIV.

Natural History and Epidemiology
The herpes simplex virus enters the host through the skin or mucous membranes. It is then rapidly taken up by sensory nerve terminals (which have viral receptors specific for HSV), penetrates the nerve axon, and is carried centripetally to the nerve cells in the dorsal root ganglia where latency is established. Herpes simplex viruses establish latency in neuronal cells and subsequent reactivation may give rise to repeated episodes of disease or asymptomatic viral shedding. The exact mechanisms involved in the establishment of latency and subsequent reactivation are not yet fully understood. It is believed, however, that viral replication is partially blocked by genetic mechanisms usually involved in early gene transcription. Reactivation of the virus is probably achieved by removal of the block on viral transcription. In genital herpes, factors known to be important in clinical reactivation are:

- Local trauma, mainly sexual intercourse and masturbation;¹²
- Menstruation;¹²
- Viral type (HSV 2 infections recur earlier and more frequently than those due to HSV 1);³⁸
- Psychological factors.⁶⁷

Genital herpes can be caused by either HSV 1 or HSV 2.⁶ The majority of genital infections are caused by HSV 2, and the percentage of infections caused by HSV 1 varies from 1%-86%, reflecting the differing popularity of oral sex in different communities,⁵⁷ and the prevalence of pre-existing HSV 1, mostly orolabial herpes acquired in childhood. There is some evidence to suggest, that in some communities with a greater aware-
ness of safer sex issues, an increasing number of people are having oral sex without condoms, and as a consequence, the percentage of genital infections due to HSV 1 has increased.\textsuperscript{2,23}

The first episode of genital herpes is often more prolonged and severe in women than in men.\textsuperscript{2} In contrast, the clinical features of the first infection due to the two viruses are virtually identical, and the severity of the infection is determined largely by a previous exposure to herpes simplex viruses (usually HSV 1, either symptomatic cold sores or asymptomatic oral infection).\textsuperscript{20,22} Those with no previous exposure usually have a more severe and prolonged first episode whilst in those with pre-existing HSV antibodies, the first episode is less severe. In contrast, once latency is established, antibody status appears to have little bearing on the likelihood of viral reactivation or the development of recurrences.

There are a number of additional effects of prior immunity to HSV 1 on genital HSV 2 infection, including lower acquisition rates of genital HSV 2 infection,\textsuperscript{25,27} a higher incidence of asymptomatic or unrecognised genital HSV 2 infection,\textsuperscript{22} and the possibility of less frequent HSV 2 clinical recurrences and less frequent viral shedding in the absence of symptoms.\textsuperscript{26} In addition, the acquisition of HSV 2 infection appears to be protective against reinfection with a different HSV 2 strain.\textsuperscript{29-31}

Clinical recurrences and asymptomatic viral reactivation occur in virtually all individuals following a clinically apparent first episode of genital herpes. Viral reactivation is more common in the first few months following the first episode,\textsuperscript{30} and there is some evidence that the frequency of clinical recurrences also decreases over time, perhaps related to the level of neutralising antibodies.\textsuperscript{28}

Genital HSV 2 infections recur earlier and more frequently than those due to HSV 1.\textsuperscript{24} The reasons for the difference in recurrence rates between genital HSV 2 and HSV 1 are not well understood, but it is of interest that HSV 2 oral infections recur far less frequently than HSV 1 oral infections, suggesting that both viruses have “developed” some degree of site specificity.\textsuperscript{3}

Transmission

Genital herpes is transmitted by close physical contact with someone who is shedding the virus. Infection can occur when the source partner has a clinical recurrence or more importantly, when they are shedding the virus asymptomatically.\textsuperscript{29-30}

In 1985 Merz et al\textsuperscript{21} studied 66 contacts of patients presenting with a first episode of genital herpes. Twenty-five (34%) knew that they had herpes, 15 (23%) had unrecognised genital herpes (symptoms and signs suggestive of genital herpes although they were unaware that the condition was herpes), and 3 were found by the clinical staff to have lesions compatible with herpes but were asymptomatic and consequently unaware of their condition. The remaining 23 source contacts were completely asymptomatic. Overall, the authors concluded that 42 (62%) of the source contacts were unaware that they had the infection, supporting the view that inapparent infection is more important as a source of infection than clinical disease.

There have been several studies of transmission in couples,\textsuperscript{32,33} where one had the infection and the other did not. The largest study involved 144 couples who were followed up for a mean of 334 days (range 28-1122 days).\textsuperscript{32} During this period, transmission occurred in 14, an overall transmission rate of 10% per annum. However, there was a statistically significant difference in the transmission rate between men and women (male to female 19%, female to male 4.5%, \(P = 0.05\)). The majority of transmission occurred when the source partner did not have a clinical recurrence. Other couple studies have confirmed the importance of transmission as a consequence of asymptomatic viral shedding and inapparent clinical disease.\textsuperscript{33}

Prevalence and Incidence

Genital herpes is the commonest reported ulcerative sexually transmitted disease (STD) seen in developed nations.\textsuperscript{34,35} In developing countries, little information is available, but in many of these countries syphilis and tropical infections, particularly chancre, appear to be the most important causes of genital ulceration.\textsuperscript{36,37} However, herpes is also common and is probably underdiagnosed as many individuals may regard the infection as relatively trivial and transient and consequently may not seek medical help. Herpes may be particularly important in parts of Africa and Asia, where genital ulcer disease may be a major factor in the spread of HIV infection.\textsuperscript{38,41}

The majority of people exposed to HSV never develop any signs or symptoms of the infection, and consequently studies of clinical prevalence are only able to give a partial picture of HSV epidemiology. Earlier serological studies were further complicated by the inability to distinguish between HSV 1 and HSV 2.\textsuperscript{30} However, the recent introduction of sensitive and type specific HSV antibody tests has provided a useful tool to study HSV epidemiology,\textsuperscript{24,44} and several serological surveys have been conducted throughout the world.

The first of these studies was reported by Johnson et al in 1989.\textsuperscript{45} The authors used serum and demographic data collected between 1976 and 1980 as part of a second national health and nutrition examination survey (NHANES II) in the United States of America. The NHANES II population was identified using a multi-stage, stratified, cluster sample, of noninstitutionalised civilian population between the ages of 6 months and 74
years. Twenty-seven thousand, eight hundred and one persons were entered into the NHANES II study and serum samples were available for 9943 (51%) of those aged 14 or above. A sub-sample of 3416 were selected, including all non-whites, and a random sample (20%-25% depending upon age) of whites. A random sample of 785 children were also selected.

The overall HSV 2 seroprevalence was 16.4% in adults aged 15 years or older (95% confidence interval, 14.2-18.6). Acquisition of HSV was related to age with very low prevalence in the under 15s increasing to 6.9% in the 15-29 age group, and 20.2% in the 30-34 age group. Using univariate odds ratios adjusted for age, the odds of having HSV 2 were significantly higher for women than for men, odds ratio 1.6 (95% confidence interval 1.2-2.06, P = 0.0015); and for blacks than whites, odds ratio 5.7 (95% confidence interval 4.25-7.74, P = 0.001). Other significant factors included marital status, low income, and inner city residence. Using multivariate analysis, age, race, sex, and marital status were all significantly associated with HSV 2 status.

A repeat survey was conducted between 1989 and 1990, and showed that the seroprevalence of HSV 2 amongst subjects aged 15-74 had increased from 16.4% in the earlier study to 21.7% in the later study. The biggest increase was amongst young white men, possibly related to later marriage and consequently more exposure to multiple partners. Age, gender and race were again shown to be strongly associated with HSV 2 prevalence.

The importance of age was highlighted by a study of 839 Swedish girls aged 14-15 years followed prospectively for 15 years. At age 14-15 years, only 0.5% of the girls were HSV 2 seropositive. By age 18-19 years, seroprevalence was 1.6%; by 19-20 years, it was 2.5%; by 20-24 years, it was 11% and by age 30-31, it was 25%. The annual seroconversion rate between the ages of 19-20 and 30-31 was over 2%.

Another population-based HSV 2 seroprevalence survey was conducted in white Canadians in Toronto between 1978 and 1980. However, the authors did not use a type specific antibody test and concluded that this could have underestimated seroprevalence by up to 20%. Nonetheless, they found HSV 2 seroprevalence of 17.5% in women and 12.8% in men, and a relationship between both number of sexual partners and age at first intercourse and HSV 2 antibody status. They also showed that in those who were antibody positive, less than 20% had a history of symptoms attributable to genital herpes. The final population-based study included 1212 unmarried men and women aged 20-44, in San Francisco. The overall prevalence of HSV 2 was 33%, and seropositivity was significantly related to female gender (women 41%, men 25%), number of lifetime sexual partners, older age, poor education levels, and black and Hispanic race.

Overall these population-based studies suggest that HSV 2 infections occur in a considerable minority of the population, that prevalence is related to increasing age (commencing at about 15 and peaking in the late 30s), gender (women more than men), and the number of lifetime sexual partners.

A large number of seroprevalence surveys have now been conducted using type specific assays in various selected population groups, including STD clinic attenders, women attending antenatal or family planning clinics, blood donors, homosexual men, prostitutes and others.

Amongst STD clinic attenders, HSV 2 prevalence varies from 8%-83%, in female prostitutes infection is even more common (75%-96%), particularly in some parts of Africa where virtually all the women sampled were positive. In women attending antenatal clinics it is much lower (6%-53%), and in blood donors where homosexual men and people with a history of STDs are sometimes excluded as donors, the reported HSV 2 prevalence is 5%-18%. Other groups that have been studied include university students (0.1%-4.3%), family planning clinics (10%-35%), family medical clinics (23%), and homosexual men (22%-83%).

Many of these surveys have only been reported in abstract form, and some involve very small and highly selected population groups. However, these studies provide a useful overall picture of HSV 2 prevalence in different "at risk" groups.

**Apparent and Inapparent Genital Herpes**

Several studies have attempted to evaluate the relationship between the detection of HSV 2 type specific antibodies and symptoms or signs suggestive of genital herpes. These studies suggest that only 13%-31% of individuals with HSV 2 antibodies have symptoms or clinical signs suggestive of genital herpes. However, many individuals with HSV 2 infection have genital symptoms or signs that are not recognised as genital herpes. Some have genital lesions that are misdiagnosed by health care professionals, and some have minor symptoms which can, in many circumstances, be confirmed clinically or virologically as genital HSV 2 infection. These individuals should be considered as having unrecognized symptomatic genital herpes and probably constitute the major source of new infections in the community.

Overall it is now estimated that 20% of infected people have recognised symptomatic herpes, 60% unrecognized symptomatic genital herpes and 20% asymptomatic herpes. These estimates are based on intensive studies with a small number of highly motivated women, and may not be relevant to all infected people. These
studies suggest that HSV 2 antibody tests may be extremely useful to identify infected people, and counsel them about symptoms and particularly about the risks of transmission.

Further evidence of the importance of the inapparent infection comes from studies documenting asymptomatic viral shedding, or the detection of cellular changes suggestive of HSV on cervical cytology. Inapparent viral excetration can occur in two situations. Firstly, patients with clinical herpes can shed virus asymptptomatically from time to time. Studies in women with recurrent herpes have shown that HSV can be isolated from 4%-14%,1,2,3,8,9,10 of them when they are asymptomatic. The second group of patients are those who have never had symptomatic genital herpes and yet are found to shed virus.11-14 Viral shedding of this type has been documented from both men and women, and from the internal and external genitalia. Finally, changes suggestive of HSV can be detected on cervical smears in women with and without symptomatic genital herpes,15 suggesting that inapparent cervical infection may be of particular importance.

In addition to the risk of sexual transmission, asymptomatic viral shedding in women appears to be an important source of neonatal infection, accounting for at least 50% of neonatal infections.66-68

Impact of Viral Chemotherapy

The introduction of safe and effective antiviral drugs for the treatment of genital herpes, in particular acyclovir, has the potential for altering the natural history and epidemiology of genital herpes. Acyclovir can successfully be used to treat first episode genital herpes and results in a significant reduction in the duration of lesions, symptoms and viral shedding. Consequently patients are likely to resume sexual activity earlier, with a greater chance of transmission to an uninfected partner. A more important potential problem is the widespread use of acyclovir for patients with frequently recurring herpes.69-72 Whilst this form of treatment is highly effective in reducing the frequency of recurrences, minor clinical episodes and asymptomatic viral shedding still occur, particularly with suboptimal doses.73-77 The latter problem is not uncommon and many patients (and doctors) will reduce the dose to assist with compliance or to reduce the cost. This problem may become more acute if current moves go ahead to allow acyclovir to be sold without prescription.78 Finally, patients on acyclovir suppression may be unaware that they are still potentially infectious, or may be falsely reassured by the lack of clinical recurrences, and perhaps fail to consistently use condoms.

Treatment

The introduction of acyclovir for the treatment of genital herpes, in the early 1980s,79 enabled physicians to effectively treat patients with this condition for the first time. The mechanism of action, safety profile, and clinical utility of the drug have been extensively reviewed elsewhere, and acyclovir is now considered the drug of choice for the treatment of primary and the suppression of recurrent genital herpes.80-83

Occasionally patients fail to respond to acyclovir, or relapse whilst on treatment. There are several possible reasons for this. Firstly, the dose may be inadequate. Oral acyclovir is poorly absorbed, and patients on long-term suppression with low dose acyclovir are in danger of dropping their serum acyclovir levels below the therapeutic range, particularly if tablets are missed or delayed.84-87 Secondly, the poor oral absorption84 may be further compromised by intestinal infections, diarrhoea, or other causes of intestinal hurry. Thirdly, a small number of patients with disease of the terminal ileum may malabsorb acyclovir, which is preferentially absorbed in the terminal ileum.88 Finally, the emergence of resistance to acyclovir is of growing concern. Most of the resistant isolates are thymidine kinase (TK) deficient mutants, although DNA polymerase deficient mutants, and strains with altered substrate specificity occasionally have been isolated.89-91 The vast majority of clinically significant, resistant strains have been isolated from individuals with profound immunosuppression, mostly patients with acquired immune deficiency syndrome (AIDS), who have often had repeated or prolonged exposure to acyclovir.92-98 However, the recent report of a clinically significant strain isolated from the genital site in a patient with normal immunity is of concern.99

The pathogenesis of resistance has not been fully elucidated. However, it is known that each time the virus reactivates, the resultant isolates consist of a clonal mix of viruses, most which have normal TK activity, but a minority will be TK deficient mutants.88 Prolonged or repeated exposure to acyclovir may encourage more frequent emergence of TK- mutants. In patients with normal immune function, T cells will control, and rapidly eliminate all replicating viruses, and any clinical disease will be short lived (Fig. 1). However, in patients with defective T cell function, TK-mutants will not be eliminated and may result in persistent or even progressive clinical disease (Fig. 2).

TK- mutants may successfully be treated with foscarnet, a drug that acts by competing with DNA polymerase.94-96 However, foscarnet has to be given intravenously and is nephrotoxic. Relapses following successful treatment with foscarnet are common.97-99 and resistance to foscarnet has now been described.100 Topical triflurouracil may be useful in some cases.100 Treatment of DNA polymerase deficient mutants remains unsatisfactory.

Acyclovir is an acyclic nucleoside and a number of
new analogues with similar structure are currently being evaluated. These include penciclovir and its prodrug, famciclovir, and valaciclovir (Fig. 3). The oral bioavailability of penciclovir is extremely poor and a prodrug famciclovir was developed to overcome this problem. Oral famciclovir delivers high serum concentrations of penciclovir and has a similar mode of action to acyclovir, competing as a substrate with deoxynucleotides for thymidine kinase. Penciclovir (and consequently famciclovir) and acyclovir have similar activity against HSV 1. However, penciclovir’s activity against HSV 2 is markedly weaker than that of acyclovir, an observation that may prove important in relation to the treatment of genital herpes.

The mechanism of action of all the acyclic nucleosides depends on their phosphorylation to the triphosphate, which then acts against DNA polymerase. Penciclovir triphosphate rapidly reaches high concentrations in the cell, an apparent advantage. However, the affinity of penciclovir triphosphate for HSV DNA polymerase is approximately 100-fold less than that of acyclovir.

One advantage of famciclovir is that the active com- pound (penciclovir triphosphate) has a significantly longer half-life than acyclovir triphosphate. This together with its better oral absorption than acyclovir, suggest that less frequent oral dosing may be possible, an advantage which may be particularly important for patients with frequently recurring genital herpes who require long-term suppressive treatment.

Valaciclovir is a valine ester of acyclovir and is converted in the bowel to acyclovir. It has the advantage of improved oral absorption, with serum acyclovir levels as high as are achieved with intravenous acyclovir. This may have some advantages for patients with poor oral absorption, and also for those requiring long-term acyclovir suppression.

The current generation of antiviral drugs do not prevent the establishment of latency, nor do they decrease the amount of latent virus present in the sacral ganglia. Recent research efforts aimed at understanding the pathogenesis of latency and reactivation may result in the production of novel agents capable of eliminating latent virus, or preventing reactivation.

Prevention

Prevention strategies currently rely on education, decreased exposure (a reduction in the number of sexual partners, awareness about infectivity and the use of condoms), and antiviral treatment. However, all of these approaches are unreliable. The development of herpes vaccines, which will prevent the establishment of neuronal latency, has the potential for a more rational and reliable approach to the prevention of herpes.
Several types of vaccines have been developed including live virus vaccines, attenuated live virus vaccines, live virus vectors, killed virus vaccines, and subunit vaccines, and these have been extensively reviewed elsewhere.\(^{108,109}\)

The current generation of vaccines consist of intact or truncated glycoproteins produced by using recombinant DNA technology using *Escherichia coli*, mammalian cells or baculovirus.\(^{110-112}\) Vaccination with recombinant mammalian viral glycoproteins gD2 and gB2 protects guinea pigs from genital herpes, and in those previously infected, reduces the frequency of subsequent recurrences.\(^{113,114}\)

Studies in humans using a vaccine, consisting of recombinant mammalian gD2 bound to alum, have shown that the vaccine is well tolerated and can generate an immune response to HSV 2 far higher than those seen with naturally acquired infection.\(^{115}\) A recent double-blind placebo-controlled trial using the same vaccine in patients with frequently recurring genital herpes has shown that vaccine recipients had a statistically significant reduction in the frequency of recurrences, and a marked and sustained increase in gD2 neutralising antibodies compared with placebo.\(^{116}\) However, the vaccine recipients had a statistically significant increase in “prophylactic only” episodes, perhaps suggesting that subclinical viral reactivation and the risk of transmission remain as major concerns.

Studies are now underway to determine whether similar vaccines can protect non-immune individuals from acquiring HSV 2 infections.

The Epidemiological Link between Herpes and HIV

Several studies have suggested that there is both indirect and direct epidemiological evidence linking HSV 2 and HIV infection. Indirect evidence comes from studies suggesting a link between genital ulcerative diseases (mostly undiagnosed and presumed to be largely chancreoid and syphilis) and HIV.\(^{38-43,117-119}\) and it is beyond the scope of this review to explore these studies in detail.

The direct evidence comes from serological studies suggesting that individuals with HSV 2 antibodies are more likely to be HIV-antibody positive than those without.\(^{120,121}\) However, although there are several studies that suggest an association, this may not be as straightforward as the studies would indicate. The first problem is that the majority of studies showing a link between HSV 2 and HIV were cross-sectional, and consequently were unable to show a clear temporal relationship between prior acquisition of HSV 2 and the subsequent acquisition of HIV. Secondly, several studies failed to control for sexual behaviour of the participants. Risk factors for the acquisition of HSV 2 and HIV are not independent. The relationship is confounded by the sexual behaviour of those infected, and as discussed above, several studies have shown that infection with HSV 2 is strongly associated with the lifetime number of sexual partners, and a history of previous sexually transmitted diseases.\(^{122}\) Finally, several of the studies involved small numbers of highly selected patients, including homosexual men with and without proctitis, and Haitian women.

One study which did not show any relationship between the two viruses was a case control study in homosexual men in the United States. The authors compared prior HSV 2 serostatus in HIV seroconverters and non converters. Forty-three percent of both groups had HSV 2 antibodies before acquisition of HIV, supporting the view that the link between the two viruses is casual rather than causal.\(^{123}\)

Psychological Morbidity Associated with Genital Herpes

Many people who have genital herpes find it difficult to deal with the emotional aspects of the infection. Common concerns include the recurrent nature of the infection, and the fact that it is sexually acquired and may be transmitted to any future sexual partners. This may result firstly in the individual feeling “dirty” or unloved; secondly, in an inability to establish new sexual relationships; and finally, in social inadequacy or withdrawal.\(^{124,125}\)

A syndrome akin to bereavement has been described in patients when they are first diagnosed to have genital herpes: denial, belief that there is a cure, realisation that they have genital herpes, loneliness, anger towards sexual partners, fear of sexual deprivation, and development of poor self image.\(^{126}\) A recent prospective study has confirmed that at the time of presentation, many patients have profound psychological morbidity, in particular anxiety and concern about their illness, when compared with patients attending a sexually transmitted disease clinic with another diagnosis, or young patients attending dermatology outpatient clinics with chronic dermatoses.\(^{127}\)

The relationship between recurrences and psychological morbidity has been the subject of debate for many years. It has been suggested from retrospective studies that recurrence rates are higher in patients with pre-existing psychiatric or psychological illness.\(^{52,128,129}\) However, prospective studies, where patients were followed from the date of their first episode, do not support this view, but suggest that psychological morbidity is high in all patients at the time of initial presentation, and only remains high in those who have recurrences.\(^{130}\)

An additional difficult issue to unravel is whether “stress” or emotional or psychological problems can trigger recurrences. Retrospective reports support this hypothesis.\(^{131}\) However, a study where patients were asked to keep prospective diaries of stressful events,
and to monitor their recurrence rate failed to confirm this. It is likely that the perceived relationship between emotional stress and recurrent genital herpes is due to the profound feelings of depression that occur with frequent recurrences.

Counselling patients with genital herpes firstly involves the provision of accurate information about the infection, including clinical features, natural history, risk of transmission and approaches to treatment, and secondly, ongoing psychological support. Finally, patients with frequent recurrences should be considered for long-term acyclovir suppression as this may have dramatic and long-lasting psychological benefits.

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