

Behavioral, Virologic and Immunologic Factors Associated with the Acquisition and Severity of Herpes Simplex Virus Type 2 Infection among Women

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Abstract

Herpes simplex virus type 2 (HSV-2) is a well-known sexually transmitted virus that affects millions of people worldwide, particularly the women. In this review article, we explore the virology and the various factors related to the acquisition and severity of HSV-2 infection amongst women. Behavioral factors like high risk sexual activities, together with unprotected sex and having multiple sexual companions, have been identified as risk factors for HSV-2 infection among women. Virologic factors which include excessive viral density and common viral shedding in body fluids are also associated with high risk of transmission and severity. The immune system additionally plays a crucial role in controlling HSV-2 infection, with weakened immune system being a predisposing factor for acquiring and experiencing severe signs and symptoms of the infection. It is critical to understand these factors in order to develop robust and efficient strategies to prevent and control HSV-2 acquisition amongst women. Safe sexual practices and the use of antiviral agents can considerably lessen the risk of transmission and the severity of the infection. Women who have interplay in excessive-risk sexual conduct should be informed on the importance of safe sexual practices, and routine laboratory test for HSV-2 infection. Furthermore, antiviral agents need to be considered for pregnant women with HSV-2 infection to lessen the threat of neonatal herpes in their newborn. Finally, since, the acquisition and severity of HSV-2 infection among women is driven by different factors, a multi-faceted approach is needed to effectively control and prevent the infection.

Key words: herpes simplex virus type 2; women, risk factors; acquisition, severity

Introduction

Herpes simplex virus type 2 (HSV-2) infection is one of the most common sexually transmitted infections globally. It is estimated that approximately 500 million people are infected with HSV-2 worldwide [1, 2]. The virus is generally more prevalent amongst women, and it could have a huge effect on their reproductive health. HSV-2 is a member of the family Herpesviridae, transmitted through sexual activities. The virus causes genital herpes, characterized with painful blisters or ulcers at the genitals, anus, or mouth.

Although HSV-2 is the most common cause of genital herpes, it may moreover cause infections in other parts of the body.

HSV-2 infects both women and men alike, with women being at more risk of infection than their male counterparts due to their anatomical variations. The chance of acquiring HSV-2 increases with increase in the number of sexual companions and the frequency of sexual intercourse. People who have other sexually transmitted infections, like HIV, are also at higher risk of acquiring HSV-2 [3, 4].

HSV-2 is transmitted through sexual contact with an infected partner who has possible lesions or disseminate the virus in body fluids like vaginal secretion. The virus additionally can be transmitted through oral sex if the partner has oral herpes. The virus may be transmitted irrespective of the fact that the infected associate does no longer have visible lesions, due to the fact the virus may be shed from the pores and skin without any obvious signs and symptoms [4].

After infection, the virus enters the nerve cells and travels to the ganglia, where it establishes latency. Periodically, the virus reactivates and travels back off the nerve to the pores and skin, causing a recurrence of signs and symptoms. Recurrences may be brought on by different stressors like infection, menstruation, and sexual activity [4, 5].

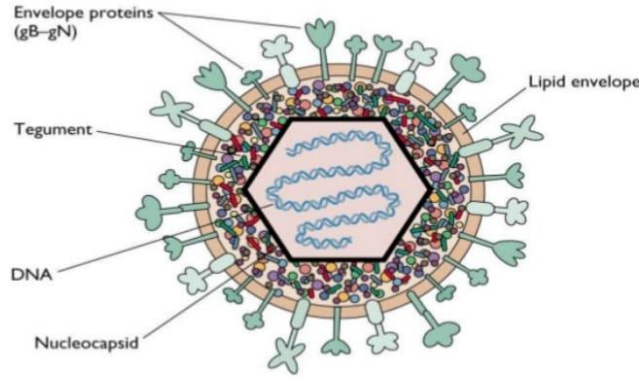
The severity of HSV-2 infections varies fom individual to individual. Some people may have one or two infections in their lifetime, while others may have several infections. In some instances, the infection may spread to other parts of the body, like the eyes, heart, brain or spinal cord, causing extra genital herpes [6, 7]. This review discusses the virology and some major contributing factors associated with the acquisition and severity of HSV-2 infection amongst the female folks.

Virology of HSV-2

Herpes simplex virus type 2 (HSV-2) is a double-stranded DNA enveloped virus (**Figure 1**), 120-200nm in diameter, belonging to the family Herpesviridae. It is a contagious sexually transmitted virus that commonly infects the genital and perianal regions of the body, however can also affect distinctive mucosal surfaces of the body including the skin. The virus has a complex shape, which incorporates an outer envelope derived from the host cell membrane, an icosahedral capsid, and a linear double-stranded DNA genome. The viral genome is spherical, 152 kilobases in length and encodes about 80 proteins [8].

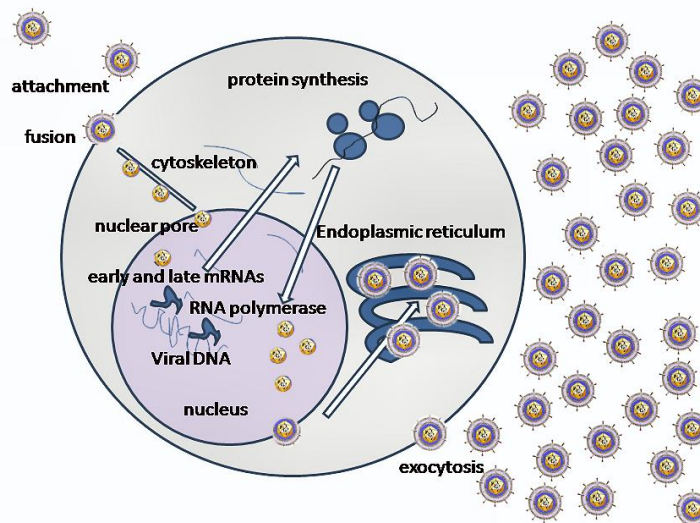
Human is the only natural host for HSV-2. The virus enters host cells via the binding of viral glycoproteins to host cell receptors, followed with the aid of fusion of the viral envelope with the host cell membrane. The virus then releases its capsid into the cytoplasm of the host cell, where it is transported to the nucleus. Replication and assembly occur in the nucleus of infected cell. Once in the nucleus, the viral DNA is transcribed and replicated, leading to the production of new viral particles which are released outside the cell through exocytosis (**Figure 2**).

The virus has a unique capacity to establish a lifelong latent infection within the host, wherein it may stay dormant inside sensory neurons until reactivated (**Figure 3**). Reactivation of HSV-2 can arise spontaneously or be triggered via various stressors including physical trauma, surgery, sunbathing, alcohol consumption, smoking, menstruation, infection, and immunosuppression due to chemotherapy or HIV/AIDS [9, 10].



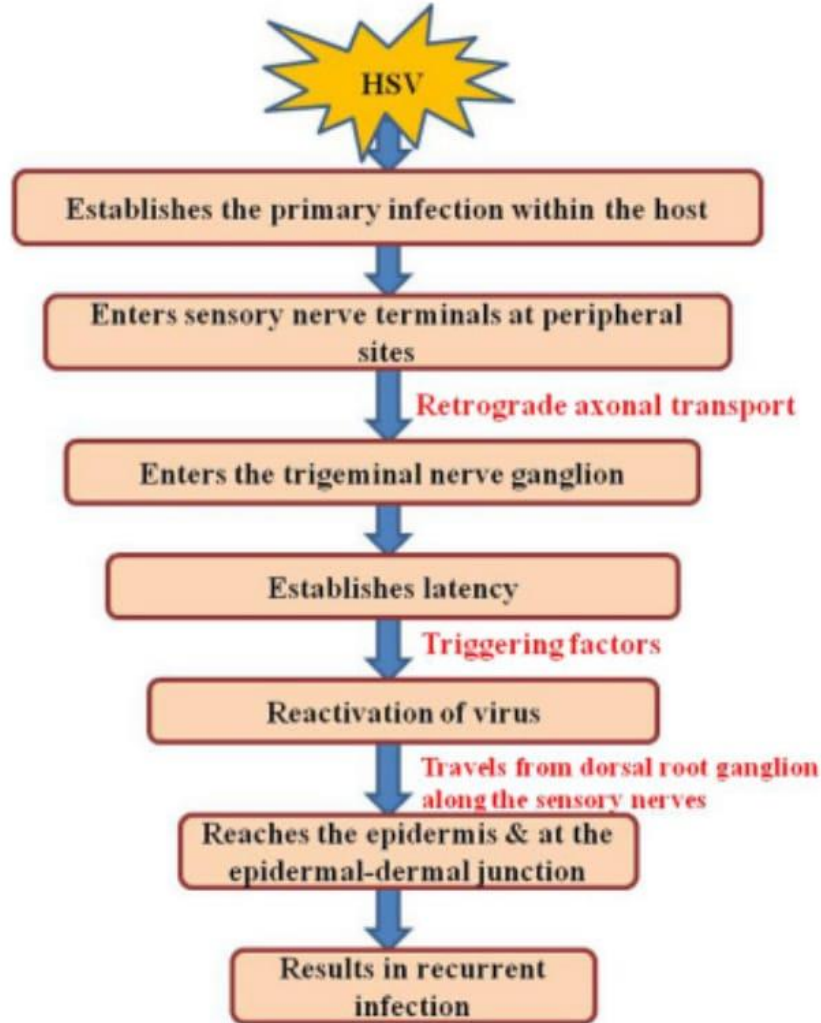
Source: Slideshare

Figure 1: Schematic diagram of Herpes Simplex Virus-2.



Source: https://en.wikipedia.org/wiki/File:HSV_replication.png

Figure 2: A simplified diagram of HSV replication.



Source: Sciencedirect

Figure 3: A flow chart illustrating the pathogenesis of HSV-2.

Clinical manifestations of HSV-2 infection can vary from lack of symptoms to fever, painful urination, excessive genital ulceration and systemic signs. It begins with tingling, burning or itching around the genitals, followed by the appearance of small blisters that rupture to leave red, open sores around the genitals (vagina and cervix), anus or buttock (Figure 4). This may take months or years. Unusual vaginal discharge may be experienced by some women. The virus can also initiate recurrent outbreaks of genital herpes, which can be characterized by painful genital lesions which can last for numerous weeks [5, 11, 12].



Figure 4: Herpes blisters/sores on the vagina (A) and buttock (B).

Factors associated with the acquisition and severity of HSV-2

Several factors are associated with the acquisition and severity of HSV-2 infection amongst female individuals [4, 13]. These review focuses majorly on behavioral, virologic and immunologic factors.

Behavioral factors

Behavioral factors play an important role in the acquisition and transmission of HSV-2. Behavioral factors including unsafe sexual practices including sharing of sex toys, number of sexual companions, and age at sexual debut had been recognized as risk factors for HSV-2 infection among women. Women who have interaction in high-threat sexual behavior inclusive of unprotected sex, having a couple of sexual companions, or engaging sexual activity at an early age are at a higher risk of acquiring HSV-2 infection. Studies have shown that the risk of HSV-2 infection will increase with the number of sexual companions someone has, and that individuals who have sex at a younger age are more likely to acquire the virus. Unprotected sexual pastime with an infected associate is the most critical factor predisposing women to acquisition of HSV-2. Women who have more than one sexual companions, engage in high-risk sexual behavior, or have a records of sexually transmitted infections (STIs) are at a higher risk of contracting the virus. The use of condoms for the duration of sexual activity can reduce the danger of HSV-2 transmission. Additionally, being in a monogamous courting with an associate who has been examined for STIs also can reduce the chance of acquiring HSV-2 [4].

Virologic factors

Virologic factors like the viral load, viral shedding, viral type, presence of viral mutations and co-infection with other virus have been recognized as factors related to the acquisition and severity of HSV-2 infection among women. High viral density had been related to a better chance of transmission and disease severity. Viral shedding, which is the release of virus particles from an infected person's body, can arise even if the person no longer show any sign or symptom. Studies have shown that women who frequently shed the virus in their body fluid are much more likely to transmit the virus to their sexual partners [4].

Viral shedding is the duration when the virus is present in the genital tract and may be transmitted to others. Women who have frequent episodes of viral shedding are at a higher risk of transmitting the virus to their sexual partners. The viral load is the quantity of virus present inside the genital tract. Women who have a high viral load are at a higher risk of transmitting the virus to their sexual partners. The viral type also plays a role in the acquisition and severity of HSV-2 infection in women. HSV-2 is more generally related to genital herpes, whereas HSV-1 is associated with oral

herpes. However, the occurrence of oral herpes due to infection with HSV-2 is increasing [8, 10].

Herpes simplex virus type 1 (HSV-1) is a related virus responsible for oral herpes, which is characterized with cold sores across the mouth. Studies have shown that people with HSV-1 infection are less prone to acquire HSV-2 infection. Presence of neutralizing antibodies due to HSV-1 can confer some level of protection against HSV-2 as the two viruses are closely related. However, if someone with HSV-1 infection eventually acquires HSV-2 infection, the infection can be very severe [4].

Studies have also shown that females infected with HIV are more likely to acquire HSV-2 infection, and vice versa. This is due to the fact each viruses can increase the threat of transmission of the other since they both share similar routes of transmission [14].

Immunologic factors

The immune system plays a critical role in controlling HSV-2 infection. The immune status, antibody response, and cytokine levels have been recognized as important elements associated with the acquisition and severity of HSV-2 infection amongst females. Immune cells particularly the T cells and antibodies help to clear the virus and prevent recurrences. However, the virus has evolved several mechanisms to circumvent the immune system, together with hiding in nerve cells and generating proteins that intervene with optimum immune performance [6, 15, 16].

Furthermore, females who have a weakened immune system, particularly those with cancer and HIV/AIDS, are more inclined and are at a higher risk of growing extreme and recurrent HSV-2 infections. Women who are infected with both HIV and HSV-2 are at a higher risk of transmitting each viruses to their sexual partners. Studies have however shown that women with higher levels of antibodies towards HSV-2 are less probable to suffer extreme symptoms of the infection [4].

Impact of HSV-2 on Public Health

HSV-2 infection among females has several public health implications. These include:

Increased Risk of HIV Transmission:

Females infected with HSV-2 are at a higher risk of acquiring and transmitting HIV. This is because HSV-2 can cause genital ulcers and inflammation, which increase the risk of HIV transmission [4, 14].

Neonatal Herpes:

Females infected with HSV-2 can transmit the virus to their newborns during delivery, which can lead to severe and potentially fatal neonatal herpes.

Therefore, pregnant females who are infected with HSV-2 require careful monitoring and management to prevent transmission to their infants [5].

Psychosocial Impact:

HSV-2 infection can have a significant psychosocial impact on females, including shame, guilt, and fear of rejection or stigma. This can affect their sexual and reproductive health and overall quality of life [5, 16].

Control and prevention of HSV-2

There are several measures that may be taken to control and prevent the transmission of herpes simplex virus type 2 infection among women [4]. Here are some of them:

Abstinence:

Abstinence from sexual pastime, inclusive of vaginal, anal, and oral sex, is the best way to protect against acquisition and transmission of HSV-2 infection. Sexual contact with companions who have viable lesions or symptoms of the virus have to be averted.

Condom use:

Consistent and accurate use of condoms can lessen the chance of transmission of HSV-2 infection for the duration of sexual intercourse. However, condoms might not offer complete protection, because the virus can be present on areas of skin that are not protected by the condom.

Limit sexual companions:

Limiting the range of sexual partners can reduce the risk of acquiring and transmitting HSV-2 infection [4].

Testing of Partner:

It is critical for individuals to be aware of their sexual partner's HSV-2 status, and for partners to be examined regularly for the presence of the virus. Available techniques for laboratory testing including: microscopy, virus culture and isolation, serology (ELISA, Neutralization test, Complement Fixation Test, Immunofluorescent test etc.) and more recently is molecular methods (e.g Polymerase Chain Reaction – PCR, DNA probe) [4,18].

Public enlightenment:

Public enlightenment campaigns can help increase the knowledge and awareness about the risk and transmission of HSV-2 infection, as well as reduce stigma and discrimination against people living with the virus [4, 5].

Antiviral drugs:

Currently, there is no specific cure for HSV-2 infection [19]. However some antiviral agents can be deployed for management of the virus. Since the introduction of the nucleoside analogs decades ago, treatment of HSV-2 infections has not seen much progress, besides the development of their respective prodrugs (Aciclovir, Fanciclovir & Valaciclovir). These antiviral agents work by suppressing viral replication, decreasing the severity and frequency of outbreaks, and decreasing the risk of transmission to sexual partners. Antiviral drugs can be particularly helpful for pregnant women with HSV-2 infection from 36 weeks of pregnancy, as it can lessen the risk of mother-to-child transmission resulting in neonatal herpes in newborn [20].

Furthermore, the development of inhibitors of the Helicase-primase complex of HSV represent a very innovative approach to the treatment of HSV-2 infection [21]. An Example of such inhibitor is Amenamevir, approved in Japan in 2017 to treat shingles (herpes zoster) [22]. However, drawbacks such as limited effectiveness and poor bioavailability of these drugs require further research if promising HSV drugs must be developed in the future. At the moment, Pritelivir, a novel treatment option for Acyclovir-resistant Herpes Simplex Virus Infections is underway as reported by Birkmann *et al.* [23]. It is hoped that this drug will do well at the clinical phase, just as it did at the preclinical.

Vaccines:

Vaccines against HSV-2 infection are currently being developed and have shown promising effects in both preclinical and clinical trials. These vaccines are designed to stimulate the immune system to provide defensive antibodies against the virus. Some of the vaccines are based totally on inactivated and live-attenuated viruses, whilst others are based on monoclonal antibodies, viral proteins, DNA or mRNA [24-26]. For instance, a novel mRNA-based genital herpes vaccine developed by Scientists from the Perelman School of Medicine at the University of Pennsylvania protected almost all animal subjects exposed to the virus [27]. Building on the new approaches for the development of many current cancer immunotherapeutics, then Pennsylvania researchers inserted a precise messenger RNA (mRNA), that can create proteins necessary for a robust immune response in their vaccine to stimulates three (3) types of antibodies: one which blocks the virus from getting into cells, and others that ensure that the virus does not “turn off” the innate immune system protective features. This technique differs from other herpes vaccines, which only work by blocking viral entry. This and other similar clinical trials have shown promising results, however, more research is needed to determine the protection and efficacy of these vaccines before they are approved and commercialized. Currently, the trials of some candidate vaccines such as Herpevac, ImmunoVEX, HerpV and VCL-HB01, have been terminated for lack of positive clinical, virologic and immunologic outcomes [28, 29].

Conclusion

HSV-2 infection has been associated with huge physical and emotional distress for the women folks. The acquisition and severity of HSV-2 infection among women are driven by various factors such as behavioral, virologic, and immunologic factors amongst others. Understanding these factors is vital for the development of effective strategies for the prevention and control of HSV-2 infection among women. While there is no specific cure for the virus, antiviral drugs and lifestyle adjustments can assist to manage signs and symptoms and reduce the risk of transmission. Preventive measures including working towards safe sexual practices, including using condoms and being in a monogamous relationship and regular laboratory testing are the exceptional ways to reduce the risk of infection. Ongoing studies with regards to vaccination and treatment might also offer new alternatives for handling and preventing HSV-2 infections in the future.

Abbreviations:

Deoxyribonucleic acid (DNA)
Enzyme-Linked Immunosorbent Assay (ELISA)
Herpes Simplex Virus Type 1 (HSV-1)
Herpes Simplex Virus Type 2 (HSV-2)
Human Immunodeficiency Virus (HIV)
Messenger ribonucleic acid (mRNA)
Polymerase Chain Reaction (PCR)
United States National Institute of Health (US NIH)

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Conflict of Interest

The authors declare that there are no conflict of interest.

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