Chapter 4

Genital Herpes

Selma Emre and Ayse Akkus

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Abstract

Genital herpes simplex virus (HSV) infections are among the most commonly seen sexually transmitted infections in the world. Genital herpes is a serious health problem because the infection continues through life with remissions and relapses, it causes recurring painful ulcers, and there is no known cure for it. The real prevalence of the genital herpes infection is unknown due to asymptomatic cases. The majority of infected individuals are not aware of the infection due to short duration of symptoms and signs or its asymptomatic nature. The clinical presentation of genital herpes shows certain differences in terms of the primary attack following the first encounter with the virus and recurrent attacks. There is a strong relationship between HSV-2 positivity and human immunodeficiency virus (HIV). A serious complication of genital herpes in the mother during pregnancy, neonatal herpes, has a mortality risk of 60% if not treated. Antiviral therapy is safe and effective, for both episodic treatment and chronic suppression of HSV. Epidemiology, clinical presentation, laboratory, and treatment options of genital herpes are summarized in this chapter.

Keywords: genital herpes, herpes simplex viruses, sexually transmitted diseases

1. Introduction

Genital herpes is a sexually transmitted infection which is seen throughout the world and continues through life. It is the most common cause of diseases accompanied by genital ulceration. Genital herpes is a serious health problem because the infection continues through life with remissions and relapses, it causes recurring painful ulcers, the virus transmitted from mother to infant causes serious neonatal infections, and there is no known cure for it [1, 2].

Herpes simplex viruses (HSV) are the most common human pathogens causing infections in orofacial and genital regions. Genital herpes infection is caused by herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2). HSV-1 mainly causes infection in oral, facial,

and ocular regions and in the central nervous system (CNS) and is transmitted during childhood. While in the past genital herpes infections were mostly caused by HSV-2 and orofacial infections were mostly caused by HSV-1, HSV-1 is reported to cause genital herpes at an increasing rate today, particularly in developed countries [3, 4]. One of the important reasons behind the increase in HSV-1-induced genital herpes cases in developed countries is decreased seroprevalence of HSV-1 and the fact that the host has not encountered with the virus prior to the onset of sexual activity. Another important reason is suggested to be changing sexual behaviors among the youth such as oral sex. HSV-2 is usually transmitted through sexual contact and causes genital infection. HSV-2 may cause orofacial infections as well, which cannot be clinically distinguished from HSV-1-induced infections. However, HSV-2-induced orofacial infections are very rare [5, 6].

Herpes simplex viruses stay with infected individuals latently for lifetime. Their presentation is quite variable depending on the immune condition of the host, site of entry of the virus, and whether the disease is primary or secondary [7]. Genital herpes infection has some serious results. First of all, HSVs transmitted from the mother to the neonatal cause serious mortality and morbidity. The second serious risk is the fact that genital herpes infections facilitate human immunodeficiency virus (HIV) and play a role in the spread of HIV [8].

2. Epidemiology

Genital HSV infections are among the most commonly seen sexually transmitted infections in the world. The real prevalence of the genital herpes infection is unknown due to asymptomatic cases. The most common cause of the genital herpes infection is HSV-2, but the number of primary genital herpes cases induced by HSV-1 is on the rise. The prevalence of infections induced by HSV-1 and HSV-2 varies between countries. While HSV-1 prevalence is about 60–80% worldwide, its prevalence in developing countries varies between 70 and 100%. HSV-2 prevalence is reported to vary between 7 and 80% depending on the country, age group, and sexual life characteristics. More than 500 million people are estimated to be infected with HSV-2 worldwide, which corresponds to 16% of the world population in between the ages of 15–49. It is also estimated that 20 million new cases occur every year [5, 6, 9].

HSV-1 seroprevalence is associated with age, race, geographical location, and socioeconomic status. HSV-2 is associated with age, race, geographical location, socioeconomic status, sexually transmitted disease history, onset of sexual activity, and number of the sexual partner. The most significant determining factor in genital HSV infections is lifetime sexual partner count. It was found in a study conducted in the United States that HSV-2 infection and HSV1/HSV2 co-infection are closely associated with lifetime sexual activity, smoking status, and recreational drug use [1, 10].

HSV-1 is typically transmitted during childhood and with non-sexual contact. While HSV-1-induced genital herpes prevalence varies between geographical regions, almost half of all new genital herpes cases are caused by HSV-1 in European countries [12]. HSV-1 seropositivity is estimated to be 40–63% in the United States, while HSV-2 seropositivity is estimated to be

16–18% [10]. While HSV-1 prevalence was 62% in the United States between 1988 and 1994, it dropped to 57.7% between 1999 and 2004. However, HSV-1 seroprevalence was found to increase in those who were diagnosed with genital herpes only [3]. Having orofacial HSV-1 infection during childhood may protect against genital HSV-1 infection in later years and silent HSV-2 seroconversion occurs more frequently in individuals with HSV-1 immunity. In other words, the transmission rate, duration of disease, and severity of disease are decreased in those who have immunity against a HSV type due to cross-immunity. The presence of HSV-1 antibodies does not prevent HSV-2 transmission. However, HSV-2 infection may be milder or asymptomatic in those with positive HSV-1 antibodies [7, 10, 11].

HSV-2 positivity occurs in adolescence when sexual activity begins and prevalence rate consistently increases toward adult ages. HSV-2 seroprevalence during pregnancy is reported to be 7–40% in different parts of the world. It is reported in rates varying between 60 and 95% in those infected with HIV and female sex workers [5]. The region with the highest HSV-2 prevalence and incidence is sub-Saharan Africa. Prevalence goes as high as 80% for men and over the age of 35 for women. HSV-2 seroprevalence is lower in European countries and reports vary greatly between countries. In cross-sectional studies for Europe between 1989 and 2000, HSV-2 seroprevalence was found to be 4% in Great Britain and Wales, whereas it was found to be 24% in Bulgaria. While it was 20–30% in Germany and Switzerland, it went as high as 40% in Turkey. The lowest prevalence is reported in Asian countries with 10–30% [12–14].

HSV-2 seroprevalence was found to be 17.2% in the United States in 1999–2000 and 14% between 2005 and 2010. It is believed that behaviors reducing sexual risk factors improved hygiene and life conditions, improved socioeconomic conditions, and shrinking families might have had effective in the decrease in HSV-1 and HSV-2 prevalence [3, 10].

3. Structure of herpes simplex viruses

More than 80 virus types were identified in the herpesvirus family. However, only eight herpesviruses cause diseases in humans. Herpesviruses, which are human pathogens, are HSV-1 (HHV-1), HSV-2 (HHV-2), varicella zoster virus (VZV, HHV-3), Epstein-Barr virus (EBV, HHV-4), cytomegalovirus (CMV, HHV-5), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), and human herpesvirus 8 (HHV-8). Herpesviruses, which are the first two types of HHVs and responsible for genital herpes infections, are referred to as herpes simplex viruses [15].

HSVs are members of the alpha herpesviridea subfamily of the herpesvirus family and have a large double-stranded DNA genome. The diameter of the viral nucleocapsid is approximately 100 nm and the diameter of the virus is approximately 250 nm. The structure of the virus consists of a nucleus containing the DNA in the center, an icosahedral capsid surrounding the nucleus, a tegument consisting of an amorphous protein layer surrounding the capsid, and an envelope surrounding all of these [7, 12]. The envelope is a glycoprotein outer cover and is typically derived from the host cell membrane while the DNA-containing capsid passes through the nuclear membrane of the host cell. These glycoproteins play an important role

during entry into the host cell. Even though DNA sequences of HSV-1 and HSV-2 are very similar, they have different antigenic structures due to differences in envelope proteins [16].

HSVs are required to attach to at least three different cell surface receptors to start the infection. As a result of this attachment, the plasma membrane and the virus envelope join and the virus enters into the cell as a result. The viral envelope contains at least 12 different glycoproteins involved in the virus' entry into and exit from the cell (gB, gC, gD, gE, gH, gI, gK, gL, and gM) [17]. Five different envelope proteins are involved in the virus entry process. Surface glycoproteins of HSVs mediate attachment to and entry into host cell surface and also stimulate the host's immune system [12]. Heparan sulfate proteoglycans (HSPGs) on the cell surface are attachment regions for HSVs. gB and gC bind HSPGs and are necessary for attachment. Fırst, gD binds cell surface receptor and starts changes which allow for membrane fusion of other glycoproteins. Nectin-1 is a cell adhesion molecule, which gD binds and also the main HSV receptor found in epithelial cells and neurons [12, 17, 18].

The viral genome is required to pass through the cell surface and cytoplasm and reach the nucleus for the replication of the virus. Entry of the virus into nucleus occurs in three stages. The first stage is the absorption of the virion to the cell surface, the second stage is passing through nuclear pores after passing through the plasma membrane, and the third stage is the introduction of the viral DNA from the capsid [16]. HSVs mostly use their own DNA synthesis mechanisms for genome replication; however, they are dependent on the host's RNA polymerase II for transcription of viral genes. Viral DNA synthesize requires at least seven viral proteins. At least six viral proteins allow for robust expression of viral genes and mobilize cellular proteins for effective synthesis of the viral DNA and proteins. Other viral proteins, mainly thymidine kinase (TK), ribonucleotide reductase, dUTPase, and uracyl DNA glycosylase, control viral nucleic acid metabolism. These proteins are potential targets of antiviral treatment [12].

4. Pathophysiology

Host's immune system is the most important factor which determines the transmission, severity, and frequency of recurrence of the infection. Humoral and cellular immune systems limit the spread of the virus in immune-competent individuals. In experiments with both humans and rats, CD4+ and CD8+ T lymphocytes, macrophages, natural killer cells, and inflammatory cytokines such as interferon-γ were shown to be involved in protection against HSVs [5, 19]. While individuals with mild cellular immune deficiency experience frequent recurrences and slower resolution, individuals with severe immune deficiency are at a higher risk of disseminated, treatment-resistant, and chronic disease. More frequent and severe recurrent herpes infections in acquired immunodeficiency syndrome (AIDS) patients indicate the importance of cellular immunity, CD4+ T cells in particular [9]. Humoral immune system, on the other hand, does not affect disease severity. However, it is involved in reduction of virus titer in inoculation region and neural tissues during primary infection [5, 19]. Another cell that is primarily affected in genital herpes and involved in immune response against HSV-2

is keratinocytes. Keratinocytes infected with HSV-2 show up-regulation of antiviral cytokines such as interferon alpha, beta, tumor necrosis factor-alpha (TNF-α), colony-stimulating factors, growth factors, defensins, selectins, lymphocyte function-associated antigens, and Toll-like receptors [20].

Genital HSV infections are more common in women compared to men. Studies show that women are more vulnerable to transmission than men. This vulnerability is believed to arise from anatomic characteristics of women, the structure of the genital epithelium, longer exposure to inoculum, and a higher rate of viral reactivation among men than women. When it comes to sexual transmission, the risk of transmission from man to woman is higher than the risk of transmission from woman to man. The virus is easily deactivated with water, soap, and drying and transmission through objects is not likely [21].

The virus, which enters into the body through skin or mucosa, starts the cytolytic replication within epithelial cells. In this period, virions within epithelial cells are observed histologically as intranuclear inclusions. Cells turn into multinucleated giant cells due to cytolytic properties of HSVs. Epithelial cells break up due to cell damage, and the space between separated cells is filled with liquid. Resulting blisters contain cellular debris, inflammatory cells, and virion products [5].

HSVs are neurotropic human pathogens. Following the replication in epithelial cells, the virus is absorbed by sensory neurons that innervate these tissues. The virus travels through neuron body and to neural ganglia via retrograde microtubule-associated transport and remains latently in neural ganglia without leading to cell death in neurons. It is unknown why and how HSVs remain latently. However, after a single lytic infection, the virus gains ability to protect against host's defense system. The latent virus genome is kept within sensory neurons in a balanced manner and all viral lytic genes are suppressed. The virus may reactivate to continue its replication due to various triggering factors and reaches epithelial cells via anterograde transport. Infected cells do not spread virus for the duration of latent infection and disease symptoms are not observed in the host. Trigeminal and sacral ganglia are the regions where HSV-1 and HSV-2 viruses most frequently remain latent. Recurrent genital herpes infection usually occurs as a result of reactivation of the virus remaining latent in sacral root ganglia [9, 17, 22]. Many factors such as traumas, inflammatory diseases, ultraviolet, menstruation, immune suppression, fatigue, and psychological stress may lead to reactivation of the latent virus. Following the virus reactivation, the virus reaches mucosa and skin once more from dorsal root ganglia through peripheral nerves. The infection maybe symptomatic or asymptomatic and seroconversion of type-specific antibodies takes 4–6 weeks [11].

4.1. HSV/HIV relationship

There is a strong relationship between HSV-2 positivity and HIV. The risk of HIV transmission is three times higher in women and men infected with HSV-2 [23, 24]. Among HIV-positive patients in UK, HSV-1 seroprevalence was found to be 90%, HSV-2 seroprevalence was found to be 67%, and HSV-1 and HSV-2 co-incidence was found to be 64% [25]. Worldwide, more than half of individuals infected with HIV have HSV-2 infection. Genital herpes lesions are

suggested to facilitate HIV acquisition due to disruptions in physical barriers of skin and mucosa. Another facilitating factor may be HIVs reaching a high number of CD4+ cells due to increased cellular inflammatory response. HSV-2 infection is believed to have played a facilitating role in HIV endemic in sub-Saharan Africa. HSV suppression treatment has not been shown to prevent HIV transmission [13, 20, 26]. In addition, HSV-2 infection is suggested to accelerate HIV disease and increase viral load. HSV treatment with acyclovir has been shown to slow down HIV progression in individuals co-infected with HIV and HSV-2. Some authors recommend that HIV-infected patients are checked for HSV-2 and co-infected individuals receive suppression treatment for HSV-2. However, this subject has not been fully illuminated. Although it is known that HSV-2 positivity facilitates HIV transmission, there is no evidence showing that it accelerates AIDS progression. On the other hand, HIV viral load has been reported to increase HSV-2 activity [26].

5. Clinic

Genital herpes lesions are formed by both HSV-1 and HSV-2 viruses. Severity of clinical signs varies significantly. Since the majority of individuals infected with HSV do not realize a clinical symptom, they are not diagnosed with genital herpes. Therefore, they continue to spread the virus without knowing that they are infected. While mild and moderate symptoms and signs are observed in some patients, the first attack may be as severe as to require hospitalization in others. HSV-1-induced genital herpes may be milder and recur less frequently than the infection induced by HSV-2. The incubation period after the transmission of the virus is not known with certainty. The primary infection occurs 2–12 days (4 days on average) after sexual contact. In one study, based on the data obtained from patients who were aware of having the primary attack, the time between the sexual contact and the primary attack may vary from 1 to 49 days and thus it is suggested that the incubation period may be longer than expected [27].

The majority of infected individuals are not aware of the infection due to short duration of symptoms and signs or its asymptomatic nature. For this reason, genital herpes should be considered in patients with nonspecific genital symptoms. The clinical presentation of genital herpes shows certain differences in terms of the primary attack following the first encounter with the virus and recurrent attacks [28].

5.1. Primary genital herpes

Although episodes in most primary genital herpes cases are asymptomatic or atypical, clinical signs are similar for both HSV-1 and HSV-2 in terms of the classical symptomatic first episode. In the prodromal period, patients may have headache, fever, anorexia, malaise, and painful inguinal and femoral lymphadenopathy. Following the prodromal period which lasts for 2–24 h, patients experience localized or regional pain and tingling and burning sensations. Constitutional symptoms are present in 80% of patients [11, 27]. Primary lesions begin about 4–7 days after sexual contact on labia minora, introitus, and urethral meatus in women and on penis shaft and glans in men as painful, erythematous, clustering vesicles, and papules in

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varying sizes. Painful and inflammatory vulvar edema is present in women. Other than the genital region, lesions may be seen on perineum and hips. Proctitis is one of the important initial symptoms in homosexual men. Irregular erosions and ulcers are formed due to ruptured vesicles. Since circulating antibodies are not on a sufficient level, autoinoculation may occur in other anatomical regions during or after the primary genital infection in particular. Lesions are crusted and heal without scarring after 2–3 weeks. In this period, patients may spread the virus for approximately 12 days. Atypical course may be present in women with cervical lesions, which are usually overlooked, and it is more difficult to make a diagnosis. The moist property of the genital region in women may lead to more severe clinical signs. Dysuria is also more common in women. Autonomic dysfunction and aseptic meningitis, which lead to urinary retention, are complications seen in this period. These lesions may sometimes occur without said complications. In primary genital herpes infections, aseptic meningitis is seen in 30% of women and 10% of men [7, 11]. The most common and unsettling symptom during the first episode is reported to be pain in women. In men, on the other hand, lesions are reported to be the most common and unsettling symptom. Surveys made with patients show that female patients experience more work force loss during the first genital herpes attack compared to male patients [29].

5.2. Recurrent genital herpes

The virus remaining latent in sensory neural ganglia following the primary genital herpes reactivates and causes recurrent infections. Recurrent lesions occur more commonly in men. Recurrence is observed in 70–90% of HSV-2-positive individuals and in 20–50% of HSV-1-positive individuals who have had a symptomatic primary genital infection [5]. Recurrences are six times more frequent in HSV-2 infections compared to HSV-1 infections [1]. One to two days prior to recurrent lesions, prodromal signs such as itching, tingling, paresthesia, and pain in lumbosacral dermatomes are observed. Recurrent genital herpes lesions involve less grouped lesions compared to primary genital herpes and tend to be unilateral (**Figure 1**). It

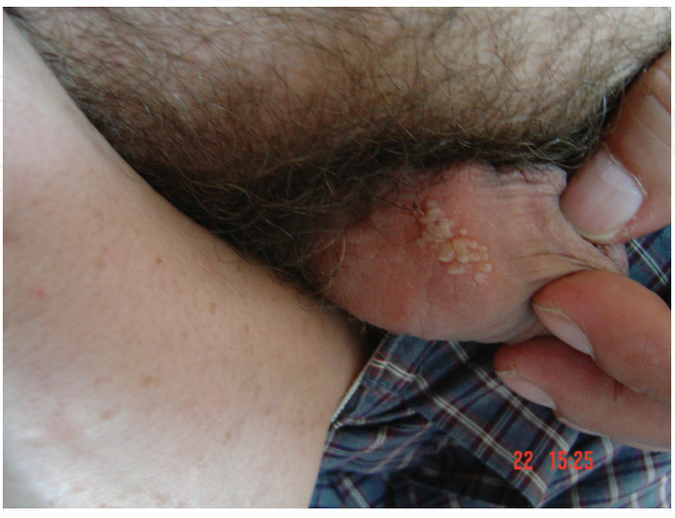

Figure 1. Painful grouped vesicles are seen. By the courtesy of Dr. Zekayi Kutlubay.

is usually not accompanied by systemic symptoms. Lesions are painful; however, the pain is milder compared to primary infection. Lesions usually heal within 7–8 days and viral spread lasts shorter and its concentration is lower. Recurrences may occur on thighs, lower abdomen, hips, and genital organs. Fissures, erythematous patches, excoriations, and linear ulcerations may be seen as atypical lesions [1, 11, 30]. Recurrent infections become sparse in time. That being said, recurrences have been reported in 25% of patients in the fourth year of infection [5].

5.3. Asymptomatic genital viral shedding

Genital herpes infections are characterized by lifelong viral shedding after the first genital herpes attack. Viral shedding in individuals infected with genital herpes continues with both lesional and asymptomatic periods. Fifty to ninety percent of transmissions occur from infected individuals who are not aware of their infections during the asymptomatic viral shedding period. Only 25% of HSV-2-seropositive individuals have genital herpes history. The majority of infected individuals either carries the infection asymptomatically or is not aware of symptoms [1, 2]. The period with the highest risk of transmission is the active disease period which involves visible lesions. Shedding continues for 1 week after symptomatic attacks. However, viral reactivation is characterized by asymptomatic viral shedding in most patients. The asymptomatic shedding property of the virus is the most significant reason behind its spread. Viral shedding is very common in HSV-2-seropositive patients, whereas it is less common in asymptomatic HSV-1 patients. The cell shredding rate is 3–5% in cell cultures obtained from women infected with genital HSV-2 in asymptomatic period; however, this rate goes up to 28% when wipe samples are examined using the polymerase chain reaction (PCR) method.

Studies show that the highest shedding rates are seen within the first year following the onset of the infection. In a study involving 377 adults with genital herpes, viral shedding was examined by applying the PCR method to anogenital swab and found to be 33.6% within the first year after the first attack, 20.6% between 1 and 9 years, and 16.7% over 10 years. Subclinical viral shedding was shown to be similar in both men and women.

5.4. Neonatal herpes

A rare yet serious complication of genital herpes in the mother during pregnancy, neonatal herpes, has a mortality risk of 60% if not treated. It may lead to mortality and permanent sequels in 30% of cases in spite of antiviral treatment. Neonatal herpes is estimated to be about 10 in 100,000 live births worldwide. This corresponds to approximately 14,000 neonatal herpes (4000 HSV-1 and 10,000 HSV-2) cases every year. The highest number of neonatal herpes cases belongs to Africa due to high HSV-2 positivity rate among women and high birth rate. HSV-1 infections cause more neonatal herpes cases than HSV-2 infections in the United States, Europe, and the West of the Pacific [31].

Transmission from the mother to the infant mostly (85%) occurs during vaginal birth due to viral shedding. Intrauterine (5%) and postnatal (10%) transmission cases are less common [2, 8]. Its

clinical manifestation involves eye, mouth, and skin infection, central nervous system disease, or disseminated disease which starts within the first 28 days of life. Eye, mouth, and skin infection is present in 45% of cases and characterized by vesicular lesions without CNS involvement or disseminated disease. CNS disease is observed in about 30% of cases and characterized by lethargy, feeding difficulty, and seizures. CNS disease may be accompanied by skin lesions. The mortality is 6% and permanent moderate and severe neurological damage is 50% with intravenous (IV) acyclovir treatment. Disseminated disease consists of the remaining 25% of cases and presents multiple organ involvement with clinical sepsis. The mortality is 30% in spite of acyclovir treatment [20].

6. Laboratory

Although genital herpes can be diagnosed via patient history and examination, herpes diagnosis may not always be easy. There may be atypical localizations such as hip and thigh or atypical presentations such as vulvar/penile/perianal fissures, recurrent erythema, recurrent pain, cystitis, urethritis, and genital discharge without lesions. On the other hand, various diseases causing ulcers in the genital region such as Behcet's disease, Crohn's disease, other sexually transmitted diseases, and fixed drug eruption may mimic herpes. In such cases, the patient may be subjected to unnecessary antiviral treatments and experience negative social and psychosocial effects due to the diagnosis. For a thorough infection management, the clinical diagnosis must be supported with laboratory confirmation. Supporting the diagnosis is also important for detection of possible cases, further consulting services, and prevention of serious complications such as neonatal herpes [32–34].

6.1. Virus detection and typing

It refers to displaying the viral genome on the skin or mucosal membrane. The best test sample is vesicle content. Samples must be sent to the laboratory in saline or virus transport medium [30]. Virus detection methods are mainly divided into four groups: cell culture, molecular methods (nucleic acid amplification tests (NAATs)), direct viral antigen detection, and cytological examinations [34]. The most commonly preferred methods are cell culture and PCR, which is a NAAT method. It is possible to distinguish between HSV-1 and HSV-2 using these two methods. It is absolutely necessary to distinguish between HSV-1 and HSV-2 in newly diagnosed genital herpes cases [35]. Because viral shedding is intermittent, the fact that no infected cell is detected does not mean that the HSV infection is not present [36].

Cell culture has lost its previous significance since it has low sensitivity in cases of healing lesions and ulcerative lesions and requires more time compared to PCR. NAAT methods such as PCR are accepted as the reference test by many centers due to their high sensitivity [30, 34, 36, 37]. Other advantages of NAAT methods include reproducibility, speed, and labor efficiency [38]. Direct viral antigen detection is a good alternative since it results in a matter of hours and

is a commercially accessible method. However, it has certain disadvantages such as low specificity and sensitivity values and inability to distinguish types. Cytological methods based on detection of cellular changes such as Tzanck are not recommended due to lack of specificity and sensitivity. Similarly, these methods do not allow for distinguishing types as well [34].

6.2. Serology

Immunoglobulin M (IgM) antibodies can be detected in blood 7–10 days after encountering the infectious agent. They remain detectable for about 1–2 weeks, while they remain positive for about 6 weeks in some individuals. They become positive again within a short time frame in recurrent infections [39]. Detection of IgG antibodies may require 2 weeks to 3 months following the transmission of the virus and they remain positive for lifetime [5]. Although IgM detection in IgG negativity during the window period in the first infection in particular may be important for primary infection diagnosis, it is not recommended for routine practice [34, 40].

HSV-1 IgG antibodies do not allow for distinguishing between genital and oropharyngeal infections, HSV-2 IgG antibodies can be used to confirm genital herpes infection diagnosis. For this reason, detection of type-specific HSV IgG antibodies, especially HSV-2, is very important to use type-specific serological tests for an accurate and effective genital herpes management [6, 34].

Detection of type-specific HSV IgG antibodies is a rapid, effective, and reliable method in infection diagnosis. Although it does not provide information related to infection time, it is possible to support primary infection diagnosis in individuals who are believed to have *the first genital herpes attack*. When used together with direct virus detection methods, primary infection diagnosis is possible with observing the initially negative IgG value, which is specific to HSV type, becoming positive in repeated PCR tests. Serology is also effective in detection of asymptomatic HSV-2 carries and possible viral shedders [30]. Especially *patients with negative direct virus detection tests, yet recurrent or atypical genital symptoms and partners of individuals diagnosed with genital herpes* are suitable indications. If the partner is HSV-2-negative, it is important to detect the infection to take protective measures. It is also important to know the HSV serology in case of pregnancy to protect against neonatal herpes, which is a serious condition, and take necessary measures. Moreover, HSV-2 infection increases the risk of HIV transmission independently and leads to disease progression in HIV-seropositive patients. Therefore, HSV serology should be explored especially for *individuals with multiple partners and/or HIV-seropositive individuals* to control sexually transmitted diseases and manage HIV. HSV serology has no indication in general population [34]. **Table 1** shows how to interpret laboratory findings in detail.

Type-specific serological tests are commercially available and the enzyme-linked immunosorbent assay (ELISA) method is widely used. They depend on detection of HSV-specific glycoprotein G1 or C1 (HSV-1) and glycoprotein G2 (HSV-2) as antigen [36]. These tests have a sensitivity of 97–100% and a specificity of 94–98% [5, 41]. Although there are multiple tests used for confirmation, the Western Blot test is accepted as the gold standard and can be found in only a number of reference centers [34].

	HSV-1 detection by direct method	HSV-2 detection by direct method	HSV-1-specific IgG	HSV-2-specific IgG	Interpretation
First assessment of genital lesions	Positive	Negative	Negative	Positive or negative	Acute HSV-1 infection. Repeat HSV-1-specific serology within 15–30 days
	Negative	Positive	Positive or negative	Negative	Acute HSV-2 infection. Repeat HSV-2-specific serology within 15–30 days
Recurrent genital lesions	Positive	Negative	Positive	Positive or negative	Recurrent HSV-1 infection
	Negative	Positive	Positive or negative	Positive	Recurrent HSV-2 infection
	Negative	Negative	Negative	Positive	Possible recurrent HSV-2 infection. Other potential causes of genital ulcerative disease should be considered
	Negative	Negative	Positive	Negative	Possible recurrent HSV-1 infection. Other potential causes of genital ulcerative disease should be considered

Table 1. Virological and serological approach to genital HSV infection.

7. Treatment

Systemic antiviral use is the essential point of genital herpes treatment. Studies have shown that systemic antiviral treatment limits the severity and duration of the genital herpes attack [42, 43]. The important point to keep in mind is that antiviral treatment does not eliminate latent infection and does not affect posttreatment recurrence risk and severity [36].

In treatment of HSV-1- and HSV-2-induced genital herpes, it is recommended to use acyclovir, valacyclovir, and famciclovir as the standard primary care [30, 36]. These are nucleoside analogs which inhibit herpesvirus DNA polymerase specifically. While acyclovir is available in IV and oral forms, valacyclovir and famciclovir are available in oral form only. These three agents have similar activities in terms of reducing disease severity, duration, and recurrence [44]. Acyclovir is the prototype drug since it is the first molecule used. It is safe and has high

tolerability. Gastrointestinal system complaints, eruption, and temporary neurotoxic effects are possible. Nephrotoxicity may develop in insufficiently hydrated cases. Concurrent nephrotoxic drug use should be avoided, liver and kidney functions should be followed closely, and the dose should be adjusted in case of renal failure [45]. Valacyclovir is the prodrug form of acyclovir. Valacyclovir is converted to acyclovir by hepatic valacyclovir hydrolase. It has higher oral bioavailability. Its use is not licensed for children, adolescents, and pregnant women. Its side effect profile is similar to that of acyclovir. Famciclovir is the prodrug form of penciclovir, which is only available in topical form. It has a quite high oral bioavailability. Similar to valacyclovir, its use is not licensed for children, adolescents, and pregnant women. Possible side effects include headache, nausea, and diarrhea [30].

The effect of topical agents is weaker than systemic agents and they do not contribute to combined treatment. They are not recommended for use in case of genital herpes since they lead to an increase in resistance. Intravenous treatment should be considered only when oral agents cannot be tolerated and in complicated cases [35]. Washing with serum physiologic and using analgesic and topical anesthetic agents are additional approaches which may be beneficial.

7.1. Primary genital herpes

Primary infections are usually more severe and longer compared to recurrent attacks. Therefore, guides recommend systemic antiviral use in all primary genital herpes cases. It is recommended that treatment is started within the first 5 days. If new lesion formation continues, treatment should be started in cases older than 5 days as well. The patient should be followed up closely in terms of systemic symptoms, complications, and new lesion formation. In such cases, it may be necessary to prolong the standard treatment [35, 36, 46]. **Table 2** shows recommended doses in detail.

7.2. Recurrent genital herpes

Recurrent genital herpes attacks are usually self-limiting and not so irritating compared to the first attack. However, attacks may sometimes be very frequent (four to six times a year or more) and severe and reduced the individual's life quality. In such cases, two different regimens are used: the suppressive treatment and the intermittent treatment. Patient compliance and cost should be considered when choosing a treatment regimen. **Table 2** shows recommended doses in detail. Acyclovir is low in cost compared to the other two agents. Intermittent treatment seems to be more advantageous than suppressive treatment in terms of both patient compliance and cost. Although studies show that both treatment regimens are effective and safe, suppressive treatment is more effective [47]. Thus, the World Health Organization (WHO) recommends suppressive treatment at first and to stop the treatment after 1 year to reassess recurrence frequency [46]. Since the patient usually experiences an attack after stopping the treatment, it is recommended to wait at least for the second attack. The treatment may be restarted after reassessment for patients who have unacceptable attack frequency and symptoms [35].

First episode for genital herpes (adult, pregnant, immunosuppressive patients)	Oral doses[a]
Acyclovir[b]	400 mg three times a day for 5–10 days or 200 mg five times a day for 5–10 days
Valacyclovir	500–1000 mg twice a day for 5–10 days
Famciclovir	250 mg three times a day for 5–10 days
Suppressive therapy for recurrent genital herpes	
Acyclovir[b]	400 mg twice a day[d] 200 mg four times daily[c]
Valacyclovir	500 mg once a day or 1 g once a day[d]
Famciclovir	250 mg twice a day 500 mg twice a day[d]
Episodic therapy for recurrent genital herpes	
Acyclovir[b]	400 mg three times a day for 5 days[d] or 800 mg twice a day for 5 days or 800 mg three times a day for 2 days
Valacyclovir	500 mg twice a day for 3 days or 1 g once a day for 5 days[d]
Famciclovir	125–250 mg twice a day for 5 days or 1 g twice a day for 1 day or 500 mg for 1 dose followed by 250 mg twice a day for 2 days 500 mg twice a day for 5 days[d]

[a]First episode oral doses vary according to guidelines.

[b]Recommended as the first choice in the WHO STI guideline.

[c]Has a usage difficulty although it is found more efficient than the usage of 400 mg twice a day.

[d]The recommended dose for the people HIV+ and have more than 10 episodes a year.

Table 2. Treatment of genital herpes.

7.3. Management of complications

Complications such as urinary retention, meningoencephalitis, disseminated disease, pneumonia, and hepatitis, which are usually observed during the first attack and in immunosuppressive individuals, should be treated by hospitalizing the patient. The patient should be administered acyclovir 5–10 mg/kg IV every 8 h for 2–7 days or until clinical recovery is observed. The initial intervention should be followed up with oral antiviral treatment and the process should be completed in a total of 10 days. The treatment should be 21 days in case of HSV encephalitis [36].

7.4. Special cases

7.4.1. HSV management in pregnancy

Neonatal herpes during pregnancy is a serious health problem with high mortality and morbidity. Herpes must be managed carefully during pregnancy to minimize the risk of transmission to fetus. Primary/recurrent character of the maternal infection, presence of transplacental neutralizing antibodies, presence of premature rupture of membranes, fetal scalp electrode use, and labor method are factors which affect transmission [48]. Maximum risk occurs with the primary infection acquired during the third trimester.

7.4.1.1. Primary attack management

Treatment should not be delayed in case of primary attack. Oral acyclovir administration in standard dose (400 mg/three times/day) is recommended as primary care. If the maternal infection is disseminated, IV use should be considered [49]. Although all three agents are accepted to be safe, valacyclovir and famciclovir are not recommended for primary care due to insufficient data [49–51]. If the attack occurs during the first or the second trimester, suppressive treatment with acyclovir may be started again from the 36th week until labor [52, 53]. If the attack occurs during the third trimester, acyclovir administration should be continued until labor. Detection of type-specific HSV antibodies is recommended for pregnant women who apply due to primary attack during the third trimester. Detection of the same antibody type with the type isolated on genital swab usually indicates recurrent attack rather than primary attack. There is no elective C-section indication in such cases. Otherwise, if there is also any doubt, attacks in the third trimester should be treated as primary attack and elective C-section should be used [49].

7.4.1.2. Recurrent attack management

Existing protective antibodies of the pregnant woman with recurrent attack protect the fetus against transplacental transmission. Thus, neonatal herpes is not common in recurrent herpes cases. While antiviral treatment is not recommended for recurrent attacks before the 36th week, standard treatment may be considered in severe cases [54, 55]. It has been shown that suppressive treatment with acyclovir from the 36th week until labor reduces viral shedding, clinical herpes lesions, and requirement for C-section [56]. Vaginal birth should be preferred if there is no other obstetric contraindication. Even though vaginal birth is recommended in case of lesion presence during birth, the final decision should be made by the mother due to low neonatal herpes risk [49].

7.4.2. HSV management in HIV-positive patients

HSV is a condition that requires careful assessment in HIV+ patients. Similar to immunocompetent individuals, reactivation is subclinical in most cases [57]. However, the form of reactivation is closely related with the rate of immunosuppression and ulcerate, necrotic, painful, massive, multiple, and atypical lesions may be observed especially in patients with

low CD4+ cell count [58]. Resistance is a high possibility in HIV+ patients. Antiviral treatment has been shown to be effective in HIV+ patients as well [59, 60]. However, antiviral treatment has not been found to be effective in preventing the transmission of HIV or HSV to the possible partner [61, 62]. **Table 2** shows doses for HIV+ patients.

7.5. Cases of resistance

Drug resistance should always be considered in cases where lesions become chronic or new attacks occur under antiviral treatment. Development of drug resistance against acyclovir and derivatives has been increasing due to high prevalence of herpes and frequent and prolonged use of accessible agents. There is a vast difference between immunocompetent and immunosuppressive cases in terms of drug resistance. Immunocompetent individuals rarely develop drug resistance, while drug resistance rates up to 36% have been reported for immunosuppressive cases in the literature. In a clinical study on patients with genital herpes, the acyclovir resistance rate has been found to be 0.18% for HIV-negative cases and 5.3% for HIV-positive cases [63–65].

Acyclovir resistance occurs through HSV thymidine kinase gene mutations. Phenotypically, it is observed as loss in TK activity, reduced TK production, or reduced affinity for substrate [66]. Acyclovir resistance is accompanied by cross-resistance against other nucleoside analogs such as valacyclovir, famciclovir, ganciclovir, and penciclovir since they share the same mechanism. While treatment with high doses of acyclovir and analogs is possible in cases of partial resistance, other treatment methods, which do not depend on TK, should be considered in cases of complete resistance [35, 67]. An oral agent other than acyclovir and analogs is not available. Foscarnet (40–80 mg/kg IV every 8 h) administration is the first choice after high doses of acyclovir in case of non-response to nucleoside analogs. Non-response to foscarnet is also possible, albeit rare. In such cases, IV cidofovir administration (5 mg/kg/week) may be considered [68]. Topical imiquimod is a good alternative in cases where IV treatment is not possible [69–71]. Although it is effective in resistant cases, topical cidofovir is disadvantaged due to lack of a commercially available preparation [72].

8. Protection from transmission

The first and most important approach is to inform asymptomatic partners and detection of possible asymptomatic carriers by assessing type-specific HSV-2 antibodies. Although it is not possible to fully protect HSV-2-seronegative partners from transmission, it is possible to minimize the risk. The primary reason behind sexual transmission is asymptomatic viral shedding. Both HSV-1- and HSV-2-induced genital herpes cases may involve asymptomatic viral shedding. Viral shedding is more common in individuals with frequent and severe attacks in particular. The first step to protection is to encourage condom use. It has been shown to have quite high effectiveness in regular use and higher effectiveness in transmission from man to woman [73]. Sexual intercourse should be avoided during active attack periods. Asymptomatic viral shedding responsible for transmission can be suppressed with all

systemic antiviral treatments [74, 75]. A reverse transcriptase inhibitor analog also approved for HIV, gel form of tenofovir, has been shown to protect HSV-seronegative women against transmission when used 12 h prior to intercourse [76]. SPL7013 gel (VivaGel®) is a microbicide developed to protect against HIV and HSV. It has been found to have strong antiviral activity when used 3 h before intercourse [77].

Efforts to develop a vaccine for HSV-1 and HSV-2 are among the priorities of WHO. Although there is no licensed HSV vaccine available as of now, there are numerous vaccines at clinical and preclinical study stages. Studies have gained pace, thanks to a better understanding of immune response against HSV [78]. Vaccines generally have two different purposes: reduction of disease activity and viral shedding (therapeutic) and prevention of infection occurrence (prophylactic). The most common HSV vaccines used in human clinical studies are glycoprotein subunit (gp D2) vaccines. A HSV subunit vaccine, HerpeVac, is a prophylactic vaccine and has the most intensive clinical study. In a study on HSV-1- and HSV-2-seronegative women, it has been found that the vaccine provides 58% protection against HSV-1; however, it has no protective effect against HSV-2 [79]. Clinical phase II studies of four prospective vaccines with therapeutic indications still continue today. First results of studies on GEN-003, a gD2/ICP4 protein subunit vaccine with Matrix M adjuvant, indicate that the vaccine reduces viral shedding by about 50% [80]. HerpV, a peptide vaccine with 32 peptides complexed with heat shock proteins and Q-21 adjuvant, is another therapeutic vaccine and reduces viral shedding by 15%. The other two vaccines (codon-optimized polynucleotide vaccine and VCL-HB01/HM01) are DNA vaccines and research results are awaited for these vaccines. Phase I studies for HSV529, a replication-defective HSV-2 vaccine, have started with both therapeutic and prophylactic indications [81].

9. Consultancy

It is very important to inform herpes-seropositive individuals and their partners accurately and completely and eliminate their concerns. Because it is possible to improve their life quality through the right consultancy, transmission can be minimized and cases such as neonatal herpes may be prevented. It is not an accurate and complete approach to provide medical services only. Patients should be provided consultancy in the first visit. A healthy consultancy and information should involve the following:

- ***General***: HSV is not a race- or gender-specific infection. While having multiple partners increases the risk, it may be seen in monogamous individuals as well. Transmission is possible without clinical lesions and symptoms (asymptomatic viral shedding). Recurrences are likely to happen.
- ***Treatment***: It is possible to reduce lesion duration and severity, attack frequency, asymptomatic viral shedding, and negative psychological effects on the patient using antiviral systemic treatment [44, 82].

- ***Protection***: It is important that current and future partners are informed by the HSV-positive individual. Partner status should be determined by serology and HSV-negative partners should be informed about possible measures. Intercourse should be avoided during active lesion presence and transmission risk should be minimized by condom use. HSV+ women should be informed about the neonatal herpes risk, and obstetricians and gynecologists should be urged to inform patients during pregnancy. In addition, it should be mentioned that HIV transmission risk is increased in HSV-2-positive individuals.
- ***Psychology***: Mental health of individuals may be negatively affected upon diagnosis due to shame, guilt, fear, and despair. Words such as "chronic, incurable, attack" should be avoided during the visit to prevent increased concern. The patient may not understand what is told during the first visit due to the shock caused by the diagnosis. For this reason, the patient should be followed up in future visits. The individual may overcome the difficulty by sharing experiences with or learning from others with the same infection. There are various support platforms which can be used for this purpose and the individual may be referred to such platforms [35, 36, 83].

Author details

Selma Emre[1]* and Ayse Akkus[2]

*Address all correspondence to: dr_semre@yahoo.com

1 Department of Dermatology, Medical School, Yildirim Beyazit University, Ankara, Turkey

2 Dermatology Clinic, Tunceli State Hospital, Tunceli, Turkey

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