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CLINICAL VIGNETTE

Diagnosis and Management of Genital HSV-2

Angela Ruman, MD

A 21-year-old female presented to my office to establish care. She is a healthy college student without significant past medical history, on no medications. She is currently in a monogamous relationship with a male who is her only sexual partner. She has no prior history of sexually transmitted diseases, uses condoms and had a Pap smear a year ago that was normal.

She reported a two-week history of a burning sensation in her vaginal area. She denies similar symptoms in the past and was free of fever, chills, dysuria, urgency or urinary frequency. Her menstrual periods were regular and she had no vaginal discharge. She had tried over the counter antifungal agents without relief.

On exam there were small fissures in the labial area. Her cervix was normal, no vaginal discharge and uterus and ovaries were normal to palpation. Routine labs were sent off as part of her physical exam and a viral and bacterial culture of the labia were sent of as well. Her viral/HSV culture returned positive for herpes simplex virus and type specific testing documented HSV-2.

The patient was contacted, counseled and educated about her diagnosis and offered treatment.

Genital HSV Infections

Types of genital HSV infections

Genital herpes is a chronic viral infection and can be associated with serious morbidity.

In primary genital HSV infection, the patient has an initial exposure to HSV and no type-specific antibodies to either HSV-1 or HSV-2 exist at the time of the infection. Lesions may appear 2 to 14 days after exposure and, without antiviral therapy, may persist for an average of 20 days[1]. Lesions begin as tender vesicles that may rupture and ulcerate. Additional symptoms associated with primary infections may include intense pain, dysuria, itching, lymphadenopathy, fever, headache, nausea, malaise, and myalgia. Women may have vaginal discharge. Approximately 75 percent of patients with primary genital HSV infection are asymptomatic[1]. Viral shedding lasts an average of 12 days and ceases before complete resolution of lesions, if present. Antibody response occurs 2 to 12 weeks after the infection and is life-long. Unlike protective antibodies to other viruses, antibodies to HSV do not prevent local recurrences[1].

A non-primary first-episode infection is the first genital HSV infection in an individual who has heterologous HSV antibodies. For example, if an individual acquires a non-primary first-episode HSV-2 infection, he/she would have antibodies against HSV-1 at the time of the genital infection. Because of the partial protection of the preexisting antibodies, symptoms may be fewer and of shorter duration, however, this varies. The duration of lesions in a non-primary first-episode averages 15 days, and shedding lasts for approximately 7 days. The clinical presentation of a primary infection cannot be reliably distinguished from a non-primary first-episode infection. The diagnosis is based on type-specific culture and type-specific serology[1].

Recurrent infections may be symptomatic or asymptomatic. Although genital HSV is a chronic infection, the frequency of symptomatic reactivation decreases over time in the majority of individuals. Most symptoms are localized and can include lesions, pain, itching, and, in women, vaginal discharge. Lesions from recurrent infections are present for approximately 7 days with viral shedding for 4 days[1].

Prevalence/Incidence

The prevalence of genital HSV-2 infection is greater than 20% among adults in the United States[2]. It has been estimated that at least 50 million people in the United States have been infected with HSV-2[3]. Studies of HSV-2 incidence suggest that most infections are acquired in the third decade of life[4]. However, HSV-2 seroprevalence has quintupled in white teenagers and has doubled among young adults in their 20s over the past two decades[4].

Presentation

The genital lesions can be caused by both HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2. Numerous studies have revealed that the majority of HSV-2 infections are undiagnosed[4]. Often people have mild symptoms, do not recognize symptoms to be that of the herpes virus or are asymptomatic. Therefore most genital herpes infections are transmitted by people who are unaware that they have it. Following the initial genital infection, HSV becomes latent in the sacral nerve ganglia and can reactivate to cause recurrent genital lesions[4]. Approximately 85% of women and nearly all men with symptomatic acquisition of genital HSV-2 infection will have a recurrence within the first year at an average rate of 4 to 5 episodes per year[4].

The clinical diagnosis of genital herpes is both nonsensitive and nonspecific. The typical clinical presentation of genital herpes includes painful, multiple vesicular or ulcerative lesions, genital ulcers, tender inguinal lymphadenopathy and possibly constitutional signs[2]. But many patients do not present in such a straightforward manner. Atypical presentations include skin splitting in the genital area, fissures, erythema and pain[2]. HSV-1 is causing an increasing proportion of first episodes of genital herpes in some populations. Recurrences and subclinical shedding are much less frequent for genital HSV-1 than HSV-2. Subclinical virus shedding is up to three times more frequent in the first 3 months after acquisition of genital herpes than in later months[4]. Subclinical HSV-1 shedding occurs with less than one-third the frequency of HSV-2 shedding[4]. Data from daily sampling studies suggest that one-half to two-thirds of subclinical HSV shedding episodes occur within a week before or after an episode of clinically recognized, symptomatic HSV[4].

Diagnosis of genital HSV

Prognosis and counseling depends on the type of HSV, so viral and serologic testing to determine whether a patient has been exposed to HSV-1 or HSV-2 or both is important[3]. Diagnosis of genital HSV-2 based on history and clinical exam alone has poor sensitivity. The predictive value of a genital herpes diagnosis based on clinical signs alone is about 40 %[2]. Laboratory methods of diagnosis are important in diagnosing genital herpes.

Virologic tests

Viral culture is the the preferred HSV test for persons presenting with possible HSV[1]. Viral culture is considered the "gold standard." Specificity is 100% for both HSV-1 and HSV-2 but up to 50% of cultures are negative[2]. Results are available in two to three days and along with PCR, it is the only test that identifies the type of herpetic infection (HSV-1 vs. HSV-2). At UCLA when a HSV culture is sent to the lab it is recorded as a positive culture for herpes but you need to request type specificity at the time of submission or shortly after the positive result. PCR assays for HSV DNA are more sensitive and increasingly used in many settings but are expensive and not used routinely. The prior tests are direct methods because the sample is taken from the lesion at or near the genital site. Sampling should be taken early in the course of genital herpes outbreak and in multiple areas if possible[2].

Type Specific Serologic tests

Type specific serologic tests are also available to diagnose HSV. IgM testing for HSV is not useful because the IgM tests are not type specific and might be positive during recurrent episodes of herpes[3]. Because nearly all HSV-2 infections are sexually acquired, the presence of type specific HSV-2 antibody implies anogenital infection[3]. The presence of HSV-1 antibody alone is more difficult to interpret. Most persons with HSV-1 antibody have oral HSV infection acquired during childhood, which may have been asymptomatic, however, HSV-1 is increasingly the cause of genital HSV infections. Lack of symptoms in an HSV-1 seropositive person does not distinguish anogenital from orolabial infection and these people remain at risk for HSV-2. The serology does not differentiate between oral and genital infection[2].

Recommendations for HSV Serologic testing

Antibodies testing can diagnose infection when culture, antigen detection, or PCR are impractical or negative[4]. HSV serologic testing should be considered for persons presenting for a STD evaluation (especially for those with multiple sex partners) and persons with HIV infection[3]. The USPSTF does not recommend screening for the general population Neonatal herpes can occur when the mother develops primary infection late in pregnancy. Some specialists believe that type specific serologic tests are useful to establish the

susceptibility of the mother to acquire a genital herpes infection during the third trimester particularly in women with partners with HSV infection[2,3].

Management of genital herpes

Management of genital herpes includes systemic antiviral drugs as well as counseling regarding the natural history of genital herpes, sexual and perinatal transmission and methods to reduce transmission.

Three antiviral medications provide clinical benefit from genital herpes: acyclovir, valacyclovir and famcyclovir. These drugs are selective for cells infected with HSV and stop viral replication[1]. These drugs can partially control the signs and symptoms of herpes episodes when used to treat a first clinical episode or a recurrence or when used as daily suppressive therapy[3]. Patients should be counseled that these medications neither eradicate latent virus nor affect the risk, frequency or severity of recurrences after the drug is discontinued[3].
Valacyclovir and famcyclovir have enhanced absorption after oral administration and have a high oral bioavailability. Topical formulations are available but these offer minimal clinical benefit and its use is discouraged[3].

First Clinical Episode of genital herpes

Newly acquired genital herpes can cause a prolonged clinical illness with severe genital ulcerations and even neurologic involvement. All patients should be treated with antiviral therapy[3].

Recommended Regimens (reprinted from CDC article)[3]*

Acyclovir 400 mg orally three times a day for 7–10 days

OR

Acyclovir 200 mg orally five times a day for 7–10 days

OR

Famciclovir 250 mg orally three times a day for 7–10 days

OR

Valacyclovir 1 g orally twice a day for 7–10 days

*Treatment can be extended if healing is incomplete after 10 days of therapy.

Common side effects of these antivirals include headaches, nausea and diarrhea.

Established HSV-2 Infection

Most patients with symptomatic first episode genital HSV-2 infection usually develop recurrent episodes. Knowing which type of HSV a patient has been infected with is important for counseling as recurrences are less frequent after initial hsv-1 genital infection. Intermittent asymptomatic shedding occurs in patients with longstanding or clinically silent disease[3]. Antiviral therapy can be given as suppressive therapy to reduce the frequency of recurrences or episodically to shorten the duration of lesions during an outbreak. Suppressive therapy has the added benefit of decreasing the risk for genital HSV-2 transmission to susceptible partners[3].

Suppressive therapy reduces frequency of genital herpes recurrences by 70-%-80% in patients who have frequent recurrences[3]. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years and with valacyclovir or famcyclovir for 1 year[3]. There is dramatic improvement in quality of life. The frequency of recurrent genital herpes outbreaks decreases over time in many patients, so providers should discuss the need to continue therapy. Treatment with valacyclovir 500 daily decreases the rate of HSV-2 transmission in discordant heterosexual couples in which the source partner has a history of genital HSV-2 infection. Suppressive therapy should be considered in those couples in addition to condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy can also reduce transmission when used by persons with multiple sexual partners and those who are HSV-2 seropositive without a history of HSV[3].

Recommended Regimens (reprinted from CDC article)[3]*

Acyclovir 400 mg orally twice a day

OR

Famciclovir 250 mg orally twice a day

OR

Valacyclovir 500 mg orally once a day*

OR

Valacyclovir 1 g orally once a day

* Valacyclovir 500 mg once a day might be less effective than other Val acyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).

All antivirals appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding[3].

To treat genital HSV episodes effectively therapy with one of the antivirals should start within one day of lesion onset or during the prodrome that precedes some outbreaks[3].

Recommended Regimens (Reprinted from CDC article)*[3]

Acyclovir 400 mg orally three times a day for 5 days

OR

Acyclovir 800 mg orally twice a day for 5 days

OR

Acyclovir 800 mg orally three times a day for 2 days

OR

Famciclovir 125 mg orally twice daily for 5 days

OR

Famciclovir 1000 mg orally twice daily for 1 day

OR

Famciclovir 500 mg once, followed by 250 mg twice daily for 2 days

OR

Valacyclovir 500 mg orally twice a day for 3 days

OR

Valacyclovir 1 g orally once a day for 5 days

Counseling

The goals of educating infected individuals and their sexual partners are to assist them in coping with recurrent symptoms and to prevent sexual and perinatal transmission. Common concerns regarding genital herpes include the severity of the initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners and ability to bear healthy children[3].

Specific educational messages recommended by the Centers for Disease Control and Prevention (CDC) include[3]:

1) Patients diagnosed with genital herpes should be educated about the natural history of the disease, the potential for recurrence, asymptomatic viral shedding and risks of sexual transmission

2) Patients with a first episode of genital herpes should know about antiviral treatment and its use in both treating acute outbreaks and recurrences and well as to provide suppression to decrease frequency of future outbreaks.

3) All patients with genital HSV should be encouraged to notify their sexual partners that they have genital herpes and to inform future partners before initiating sex.

4) Sexual transmission of HSV can occur during asymptomatic periods and asymptomatic viral shedding is more frequent in genital HSV-2 infection than genital HSV-1 and is most frequent during the first 12 months after acquiring HSV.

5) All patients with genital herpes should remain abstinent from sexual activity with uninfected partners when lesions or prodromal symptoms are present.

6) The risk for HSV-2 sexual transmission can be decreased by daily use of valacyclovir. Episodic therapy does not reduce the risk of transmission. A 2004 study in The New England Journal of Medicine found that valacyclovir reduced the risk of herpes transmission in monogamous couples where one partner was infected. The other two medications are

likely to do the same, and all three are considered safe for consistent use.

7) Latex condom use when used properly can reduce the risk of transmission.

Sex partners of infected persons should be advised that they might be infected with HSV even if they have no symptoms. CDC recommends type specific serologic testing of the asymptomatic partner of persons with genital HSV is recommended to determine whether such partners are already HSV seropositive or whether risk for acquiring HSV exists. (The USPSTF does not recommend screening in asymptomatic patients.)[1,3]

8) The risk for neonatal HSV infection should be explained to all persons including men.

9) Pregnant women and women of childbearing age who have genital herpes should inform their care providers during pregnancy. Pregnant women who are not known to be infected with HSV-2 should be advised to abstain from intercourse with men who have genital herpes during the third trimester of pregnancy.

10) Asymptomatic patients diagnosed with HSV-2 infection by type specific serologic testing should receive the same counseling messages as persons with symptomatic infection.

11) When exposed to HIV, HSV-2 seropositive persons are at increased risk for HIV acquisition. Patients should be informed that suppressive antiviral therapy (for HSV) does not reduce the increased risk for HIV acquisition associated with HSV-2 infection.

By educating the patient about the disease process, the physician can help empower the patient to manage the disease. That should be our goal as providers in addition to offering medical treatment.

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3. Diseases characterized by genital, anal, or perianal ulcers, sexually transmitted treatment guidelines. 2010. CDC
4. **Ashley RL, Wald A**. Genital herpes: review of the epidemic and potential use of type-specific serology. *Clin Microbiol Rev*. 1999 Jan;12(1):1-8. Review. PubMed PMID: 9880471; PubMed Central PMCID: PMC88903.

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Table: Resources for Patients with Genital Herpes Infection (from American Family Physician October 15, 2005

American Social Health Association	Web site: http://www.ashastd.org
Centers for Disease Control and Prevention	Web site: http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm
Herpes Web	Web site: http://www.herpesweb.net
International Herpes Management Forum	Web site: http://www.ihmf.org/Patient/PatientResources.asp
National Herpes Hotline	Telephone: (919) 361–8488 (9 a.m. to 6 p.m. EST, Monday through Friday)
National STD & AIDS Hotline	Telephone: (800) 227-8922 or (800) 342-2437 (24 hours per day, 7 days per week)En Espa ñol: (800) 344-7432 (8 a.m. to 2 a.m. EST, 7 days per week)