



Is herpes simplex a systemic disease?



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Abstract Orofacial herpes simplex virus infections are usually caused by herpes simplex virus 1 (HSV-1), and HSV-2 infections have been accepted as a sexually transmitted disease. HSV establishes a latent infection in the dorsal root ganglia of the host and remains there for the rest of life. HSV affects mainly skin and genitalia, although in immunocompromised patients it may cause local infection with vast skin involvement, chronic herpetic ulcers, or widespread mucous membrane damage, as well as systemic infections localized in the central and peripheral nervous systems, gastrointestinal tract, and ocular system. Usually, HSV infections are in the domain of dermatology, but the accumulating facts for localization of the disease in many systems of the human body give us the possibility to pose the question: Is herpes simplex a systemic disease?

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Herpes simplex virus 1 and 2 (HSV-1 and HSV-2), also known as human herpesvirus 1 and 2 (HHV-1 and HHV-2), are two members of the herpesvirus family, Herpesviridae, that infect humans. Both viruses are ubiquitous and contagious. HSV infection is known for its main predisposition toward skin and mucous membranes, but as medicine progresses, the incidence of the disease has been found to include other tissues, representing a viral infection able to damage several systems of the human body.

Herpes simplex virus infection of the skin

The clinical course of herpes simplex infection on the skin counts on many factors: viral type, primary or secondary infection, immune status of the patient, and lesion localization.

Virus type

Herpes simplex viruses are categorized into two types: herpes type 1 (HSV-1) and herpes type 2 (HSV-2). Most commonly, HSV-1 causes orofacial disease, whereas HSV-2 is usually associated with genital and anal involvement but not always. In Europe, differences in viral prevalence are noted for HSV-1, where its seroprevalence is higher in Bulgaria (83.9%) and the Czech Republic (80.6%) and lower in Belgium (67.4%), the Netherlands (56.7%), and Finland (52.4%). HSV-2 seropositivity is widely distributed in European patients older than 12. Again, Bulgaria has a high (23.9%) HSV-2 seroprevalence relative to other European countries, such as Germany (13.9%) and Finland (13.4%).¹ In the United States, case reports for HSV-2 are not available, but there have been several surveys based on initial physicians' assessments, pointing out 16.2% as an average rate of seroprevalence.² HSV-2 is the most common in sub-Saharan Africa, the highest rates of HSV infection in

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the world. Up to 82% of women and 53% of men in sub-Saharan Africa are seropositive for HSV-2.³

Primary infections

Most primary HSV infections are asymptomatic. Some studies suggest that only 10-12% of children who are infected have signs or symptoms severe enough to be remembered.⁴

Acute herpetic gingivostomatitis and acute herpetic pharyngotonsillitis are the common manifestations of primary HSV-1 infection. HSV-2 can cause acute primary herpetic gingivostomatitis by oral-genital or oral-oral contact.

Acute herpetic gingivostomatitis occurs mostly in children aged 6 months to 5 years but can affect people of any age. Adults may also suffer from acute gingivostomatitis, but it is less severe and associated more often with posterior pharyngitis. The mode of transmission is through infected saliva from another child or adults. The incubation period is not fixed, extending from a few days to 3 weeks.⁵ Usually, mucosal signs are preceded by fever, anorexia, and apathy. The disease involves the buccal and gingival mucosa. Gingivitis presents with erythematous, swollen, and fragile gums. The oral mucosa, lips, and tongue are edematous and erythematous with many vesicles that rupture, coalesce, and form erosions. Perioral skin may be involved due to contamination with the infected saliva. Regional lymphadenopathy may be present. Although a self-limiting disease, this oral infection can cause significant mouth discomfort, burning pain around the blisters, and difficulty with eating and drinking. Acute herpetic gingivostomatitis lasts 5 to 7 days, and the findings subside within 2 weeks. Viral shedding from the saliva may continue for 3 weeks or more.

Acute herpetic pharyngotonsillitis occurs mostly in adults. The clinical sign is preceded by high temperature, headache, and malaise. Vesicles appear on the tonsils and pharyngeal mucosa, coalesce, and form painful erosions and ulcerations.³

Primary genital herpes (also termed herpes progeneralis)

Primary genital herpes due to HSV-2 infection occurs 3 to 14 days after sexual contact. The primary lesions consist of small grouped vesicles localized on a man's or woman's genitalia. Sometimes they appear in the perigenital skin area.

Acute herpetic vulvovaginitis

Acute herpetic lesions of the cervix, vagina, and vulva are characteristic for primary infection with HSV-2 but can be caused also by HSV-1. The incubation period ranges from 3 to 7 days. In acute gingivostomatitis, the vesicles and erosions on the vulvar and vaginal mucosa are preceded by severe and prolonged systemic and local symptoms. Increased vaginal discharge may be accompanied by discomfort when urinating, including burning, fever, and malaise. Herpetic vesicles can appear on the external genitalia, labia majora, labia minora, vaginal vestibule, and introitus. In moist areas, the vesicles rupture, leaving exquisitely tender ulcers. The vaginal mucosa is inflamed and edematous. The cervix is

involved in 70-90% of cases and is characterized by ulcerated to cervical mucosa.

Acute balanitis and urethritis

In acute balanitis and urethritis, herpetic vesicles commonly appear on the glans penis, the prepuce, and the shaft. Rarely, vesicles and erosions can be observed on the scrotum, thighs, and buttocks. Herpetic urethritis occurs in 30-40%, and its main characteristics are dysuria and mucoid discharge. The perianal area and rectum may also be involved in men who have sex with men (MSM) with the clinical representation of herpetic proctitis.

Secondary infections

Pain, burning, or tingling at the site often precedes clinical symptoms. In a demarcated area, a small group of vesicles with clear contents appears on top of an erythematous base. After a few days, the vesicles gradually darken and dry out to become crusts.

The most common reemergence of the infection is in the perioral region, in the same area each time for HSV-1. HSV-2 reemergence is found around the genital area. In female patients lesions are usually localized on the labia majora, labia minora, or perineum. In men lesions are focused on the glans, the prepuce, or the shaft of the penis. They can be localized on the scrotum, thighs, and buttocks, though this is rare.

Herpes simplex virus infection with neurologic manifestations

HSV-1 and HSV-2 form a latent infection in the dorsal root ganglia. The main characteristic of these viruses is their ability to establish latency, maintain it for the entire lifespan of the host, and reactivate and cause primary and recurrent disease. HSV-1 in relation to the nervous system is responsible for almost all cases of HSV encephalitis and several peripheral disorders; HSV-2 infection may manifest also with acute generalized encephalitis in the neonatal period, more typically with aseptic meningitis and sometimes with a polyradiculitis or myelitis in adults.^{6,7}

The most important viral encephalitis with a treatable causative agent is HSV. The HSV encephalitis is, by far, the most common encephalitis, accounting for almost 10% of all cases in the United States. This type of encephalitis has gained importance not only for its frequency but also for its severe clinical representation and sometimes serious neurologic sequelae. Between 30% and 70% are fatal, and most of the surviving patients are left with a serious neurologic deficit. About 90% of cases are caused by HSV-1. Approximately 10% are due to HSV-2, which is usually the cause of herpes simplex encephalitis in immunocompromised individuals and neonates with a disseminated infection.^{8,9} HSV encephalitis occurs sporadically throughout the year and can affect patients of all ages in all parts of the world.⁷

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