

Herpes simplex virus

General properties:

Herpes simplex virus (HSV) is a DNA virus belonging to Herpesviridae family of viruses. The virus occurs worldwide and produces various illnesses in neonates as well as adults. The name herpes comes from the Latin *herpes* which, in turn, comes from the Greek word *herpein* which means to creep, which reflects the creeping or spreading nature of the skin lesions caused by many herpes virus types.

Classification:

The family Herpesviridae is divided into three sub-families Alphaherpesvirinae, Betaherpesvirinae and Gammaherpesvirinae based on their location in the latent state. Although there are more than 100 viruses in this family, only eight are known to produce disease in human. Humans are the only natural reservoirs, and no vectors are involved in transmission.

Sub-family	Site of latency	Members
Alphaherpesvirinae	Neural ganglia	Herpes simplex-1 (HSV-1), Herpes simplex-2 (HSV-2), Varicella Zoster virus (VSV)
Betaherpesvirinae	Lymphocytes/monocytes	Cytomegalovirus (CMV), Herpes lymphotropic virus, Human herpes virus-7 (HHV-7)
Gammaherpesvirinae	Lymphocyte/unknown	Epstein-Barr Virus (EBV), human herpesvirus 8 (HHV-8 including Kaposi's sarcoma associated herpes virus [KSHV])

Morphology:

Herpes simplex viruses are spherical (150-200 nm) with a capsid of icosahedral symmetry. The nucleocapsid is surrounded by a membrane that is derived from host's nuclear membrane and contains viral glycoprotein spikes. The genome is made of double stranded DNA. HSV-1 and HSV-2 have 50% sequence homology.

Viral replication:

The virus binds to the target cells via specific cellular receptors and other coreceptors. It then enters the cell by fusing with the target cell membrane. After fusion, the nucleocapsid is transported through the cytoplasm to a nuclear pore and enters the DNA enters the nucleus after uncoating. The linear DNA then forms a closed circle. Transcription of several early genes occurs and their proteins are produced. This is followed by DNA replication. Host's own DNA and protein synthesis is blocked. Newly synthesized DNA is packaged into preformed empty nucleocapsids in the nucleus. Maturation occurs by budding of nucleocapsids through the nuclear membrane. The enveloped virus particles are transported to the cell surface and released. Host cells are invariably killed. The replication cycle is approximately 8-16 hours.

Pathogenesis:

Infection occurs by direct contact involving mucous membranes or abraded skin with infectious materials such as saliva and genital secretions. HSV tends to infect cells of ectodermal origin. HSV-1 infections are usually limited to oropharynx and virus is spread by respiratory droplets or direct contact with infected saliva. HSV-2 is usually transmitted by contact with infected genital secretions.

Initial viral replication occurs at the site of entry in the skin or mucus membrane. It invades the local nerve endings in the epidermal and dermal cells and starts replicating. Virions travel from the initial site of infection via retrograde axonal flow to sensory dorsal root ganglion, where further replication occurs. Then, the viral genome becomes latent, clinical latency is established and the infection persists for life. Viral particles are not produced during latency. While HSV-1 establishes latency in trigeminal ganglia, HSV-2 establishes latency in lumbosacral ganglia.

A stimulus such as physical or emotional stress, fever, ultraviolet light, extremes in temperature, immunosuppression, or hormonal fluctuations reactivates the virus in the sensory ganglia leading to clinical disease. The virus follows axons back to the peripheral site and replication proceeds at the skin or mucus membrane. The reactivation can lead to multiple episodes of diseases. Viral shedding occurs during primary infection or during subsequent recurrences, and may lead to possible transmission. People with asymptomatic infections also shed the virus in their secretions.

Histopathology:

HSV exhibit broad host range and are able to replicate in many cell types. They grow rapidly and are highly cytolytic. Because of cytolytic nature of these viruses, pathological changes are due to necrosis of infected cells together with the inflammatory response. Characteristic histopathologic changes include ballooning of infected cells, production of Cowdry Type A intranuclear inclusion bodies, margination of chromatin, and formation of multinucleated giant cells (due to cell-to-cell fusion).

Clinical findings:

Primary HSV infections are usually mild or asymptomatic. In rare cases, the initial replication may lead to disease and life-threatening infection such as encephalitis. Widespread organ involvement can occur in immunocompromised individuals. Spontaneous reactivations are known to occur despite specific immunity in the host. Many recurrences are asymptomatic.

- a) Oropharyngeal disease
- b) Keratoconjunctivitis
- c) Genital herpes
- d) Skin infections
- e) Encephalitis
- f) Neonatal herpes
- g) Infections in immunocompromised hosts

Oropharyngeal disease:

These are often caused by HSV-1 and involve buccal and gingival mucosa of the mouth. Most infections are asymptomatic but symptomatic diseases occur in small children. The incubation period is about 3-5 days and the illness may last 2-3 weeks. Symptoms include fever, sore throat, vesicular and ulcerative lesions, gingivostomatitis, submandibular lymphadenopathy and malaise. In adults it produces pharyngitis and tonsillitis. Recurrent disease is

characterized by a cluster of vesicles (fever blisters/ cold sores/ herpes labialis) commonly at the border of lip. Intense pain occurs at the outset but fades over 4-5 days. The lesions may recur several times at the same location.

Keratoconjunctivitis:

HSV-1 infection can produce severe keratoconjunctivitis. It manifests with an acute onset of pain, watery discharge, itching, blurred vision, lid swelling, and conjunctival injection. Recurrent lesions appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids. Blindness can follow recurrent keratitis.

Genital herpes:

Genital disease is mainly caused by HSV-2. HSV-2 is usually acquired as a sexually transmitted disease. Primary infections can be severe and is characterized by vesiculoulcerative lesions of the penis of the male, or of the cervix, vulva, vagina and perineum of the female. These painful lesions are associated with fever, malaise, dysuria and inguinal lymphadenopathy. Illness may last for three weeks. Aseptic meningitis may be a complication. Recurrences are common but are usually mild. A limited number of vesicles appear and heal in 10 days.

Skin infections:

Abrasions that are contaminated with infected material containing HSV-1 or HSV-2 result in localized lesions (vesicles). These lesions are seen in the fingers of dentists and hospital personnel (herpetic whitlow). They are also seen on the bodies of wrestlers (herpes gladiatorum). In patients with burns or eczema, the skin infections tend to become severe. Eczema herpeticum is seen in patients with chronic eczema.

Encephalitis:

HSV encephalitis may be a manifestation of primary or recurrent infection with the virus. The infection may have an insidious or an abrupt onset. Headache and fever may be followed by behavioral changes. Seizures, hemiparesis, aphasia, visual-field defects, and paresthesias may also occur. Aseptic meningitis caused by herpes simplex virus can occur after primary genital HSV-2 infection. Patients with herpes simplex virus meningitis present with headache, fever, stiff neck, and photophobia. Symptoms usually begin 3-12 days after the onset of genital lesions. In rare cases, HSV-1 or HSV-2 may cause viral meningitis without genital herpes simplex virus involvement.

Neonatal herpes:

HSV infection of the newborn may be acquired in utero, during birth or after birth. The mother is often the source of infection. Post natal infections can occur by exposure to HSV-1 or HSV-2. Babies with neonatal herpes exhibit three categories: a) lesions localized to eyes, mouth and skin; b) encephalitis with or without skin lesions and c) disseminated disease involving multiple organs including CNS. Viral pneumonitis or intravascular coagulopathy is often the cause of death in disseminated disease.

Infections in the immunocompromised host:

Malnourished individuals as well as patients with deficient cellular immunity are high risk to developing severe HSV infections. Organ transplant recipients, patients suffering from hematologic malignancies and AIDS are also at high risk to severe and disseminated infections. Widespread dissemination of herpes simplex virus may cause signs of specific organ dysfunction progressing to a picture of sepsis and death.

Immunity:

Passively received maternal antibodies lasts only for first six months of life and are not totally protective against infection. During primary infection, IgM antibodies appear transiently and are followed by IgG and IgA, which persists for long periods. Antibodies appear in 4-7 days after infection and reach peak in 2-4 weeks and persist for the rest of life. Antibody levels may rise with recurrences. CMI is more useful in controlling primary as well as recurrent infections. Reactivation and reinfection may occur even in the presence of antibodies.

Laboratory diagnosis:

Various types of specimen that can be collected include specimen from the lesion, throat washings, blood, and CSF. Smear made from scrapings taken from the base of the vesicle may show multinucleated giant cells when stained with Giemsa's stain. Tzank smear is also helpful in cytological study. Immunoperoxidase techniques may be used to distinguish HSV-1 and HSV-2 antigens in formalin-fixed tissue samples. Virus can be isolated from CSF, throat washings as well as from lesions by culturing on monolayer cell culture. It is subsequently identified by neutralization test or immunofluorescence. Viral nucleic acid can be detected by molecular method such as PCR. Antibodies may be detected by ELISA tests but since HSV-1 and HSV-2 antigens cross react, definitive identification is difficult.

Treatment:

Several antiviral drugs are effective against HSV infections. These include acyclovir, valacyclovir, famciclovir and vidarabine. These drugs may suppress clinical manifestations, shorten time to healing, and reduce recurrences of genital herpes. Latent viruses are not affected by the drugs. Commercially available topical treatments for herpes are much less effective than oral therapy. Acyclovir-resistant HSV strains have been identified, and treatment with intravenous foscarnet or cidofovir may be used in such cases. Vaccine against HSV infections is not yet available.

(Created on 05-01-2010)