7- Herpesviruses

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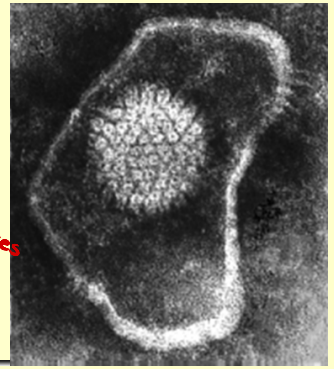
Objectives

- Discuss the morphology, epidemiology, pathogenesis, clinical presentation, laboratory diagnosis and management of:

1. Herpes Simplex virus Type 1 (HSV-1)
2. Herpes Simplex virus Type 2 (HSV-2)
3. Epstein Barr virus (EBV)
4. Cytomegalovirus (CMV)
5. Varicella Zoster virus (VZV)
6. Human Herpes virus 6 (HHV-6)
7. Human Herpes virus 8 (HHV-8)

Most important ones

Introduction



- Herpes Viruses are a leading cause of human viral diseases, second only to influenza and cold viruses
- The outstanding property of herpesviruses is their ability to establish lifelong persistent (Latent) infections in their hosts and to undergo periodic reactivation
- Reactivation is more likely to take place during periods of immunosuppression and in the elderly
- All herpesviruses have identical morphology and cannot be distinguished from each other under electron microscopy.

Classification

Different in clinical characteristics

Group	Biological characteristics	Members
Alpha herpesviruses	fast-growing, cytolytic (Cell Lysis), establish latent infections in neurons	HSV-1, HSV-2, VZV
Beta herpesviruses	slow growing, cytomegalic (Hypertrophy), become latent in secretory glands and kidneys	CMV, HHV-6, HHV-7 (Won't be studied)
Gamma herpesviruses	Variable, lymphoproliferative, e latent in lymphoid cells (e.g. B cells)	EBV, HHV-8

General properties

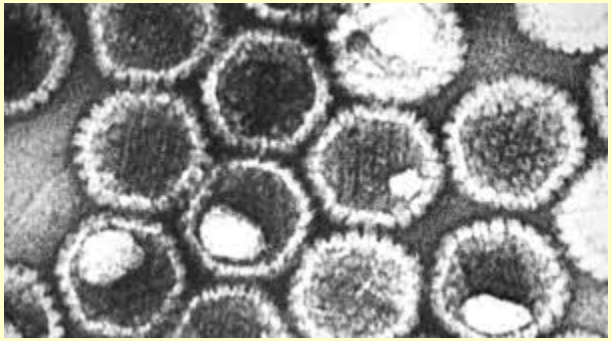


TABLE 33-1 Important Properties of Herpesviruses

Virion: Spherical, 150–200 nm in diameter (icosahedral)
Genome: Double-stranded DNA, linear, 125–240 kbp, reiterated sequences
Proteins: More than 35 proteins in virion
Envelope: Contains viral glycoproteins, Fc receptors
Replication: Nucleus, bud from nuclear membrane
Outstanding characteristics:
Encode many enzymes
Establish latent infections
Persist indefinitely in infected hosts
Frequently reactivated in immunosuppressed hosts
Some cause cancer

Big

Quite large genome

Also large

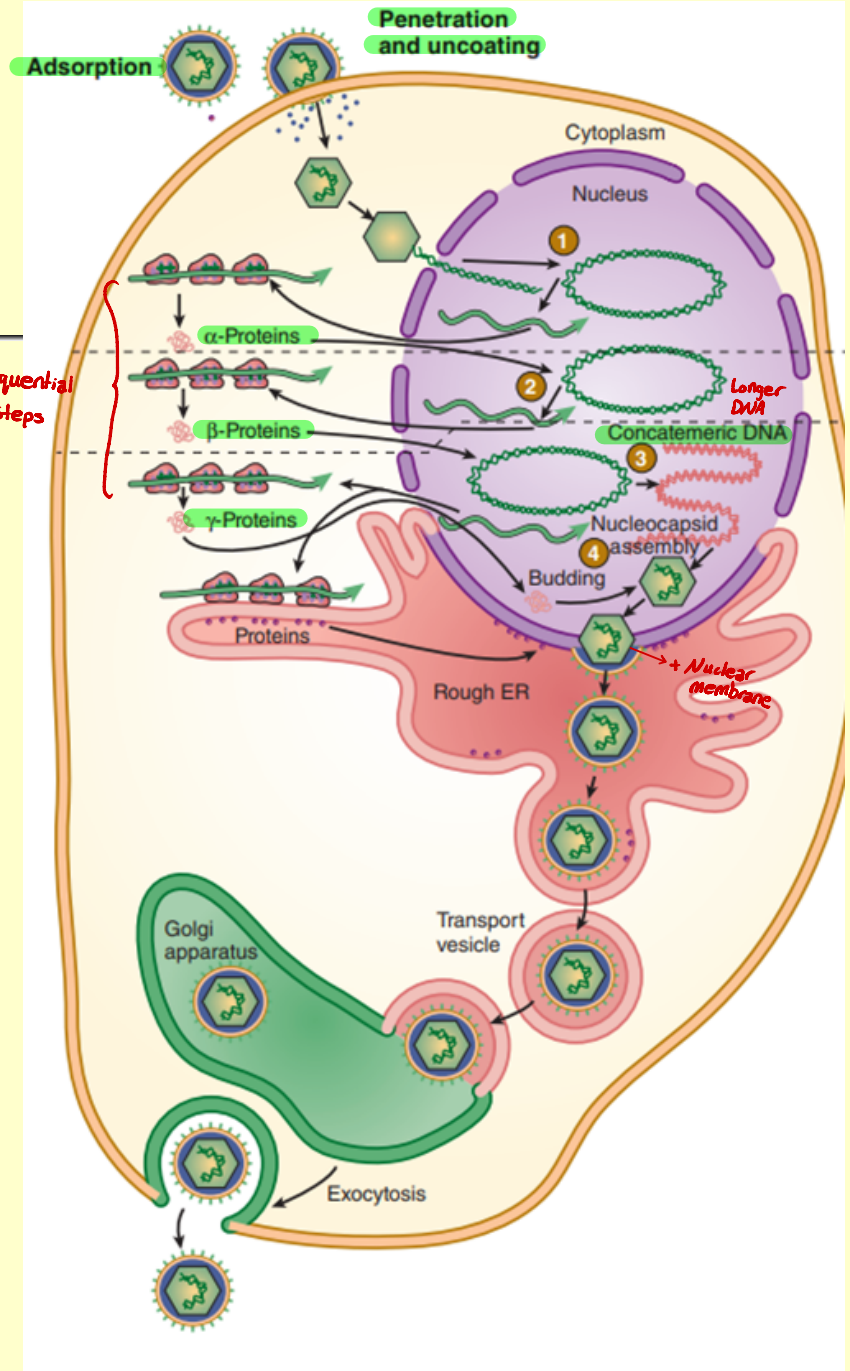
Uses pores for entry & takes part of the nuclear membrane when getting out

e.g. EBV

Replication

1. α-Proteins, products of immediate-early genes, stimulate transcription of early genes.
2. β-Proteins, products of early genes, function in DNA replication, yielding concatemeric DNA.
3. γ-Proteins, products of late genes and consisting primarily of viral structural proteins, participate in virion assembly

They encode a large number of enzymes/proteins (70-200)

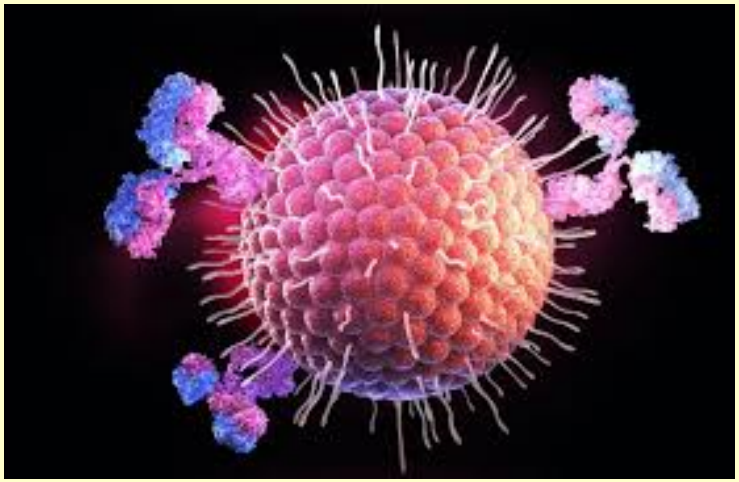


Important clinical viruses

- There are 25 families in the Herpeotoviridae but only 7 of them infect man:
  - Herpes Simplex virus Type 1 (HSV-1)
  - Herpes Simplex virus Type 2 (HSV-2)
  - Epstein Barr virus (EBV)
  - Cytomegalovirus (CMV)
  - Varicella Zoster virus (VZV)
  - Human Herpes virus 6 (HHV-6)
  - Human Herpes virus 8 (HHV-8)

1- Herpes Simplex Viruses (HSV)

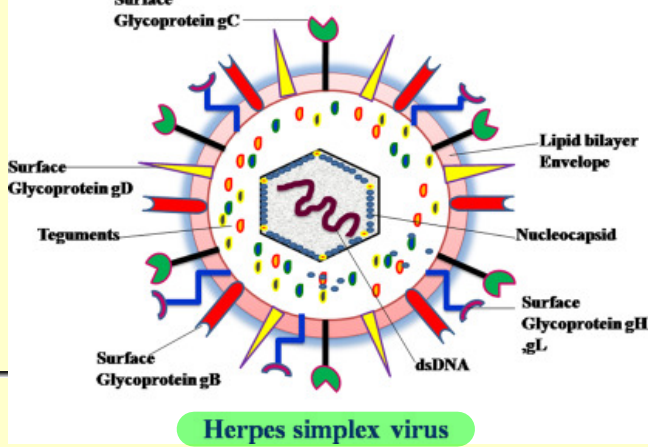
α



Properties

An epitope or antigenic determinant is a group of amino acids or other chemical groups exposed on the surface of a molecule, frequently a protein, which can generate an antigenic response and bind antibody.

Notes regarding the last point ←



Herpes simplex virus

- Belong to the alpha herpesvirus subfamily of herpesviruses
- HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons
- Type 1 is associated with oropharyngeal lesions (above the belt) while Type 2 infects the genital mucosa (below the belt), though the anatomical specificity of these viruses is diminishing

  1 → Below
  2 → Above
  } Possible
- Classically, HSV-1 is spread by contact with infected saliva and HSV-2 is transmitted sexually
- The genome of HSV-1 and HSV-2 share 50 - 70% homology.
- They also share several cross-reactive epitopes with each other.

Epidemiology

- HSV is spread by contact, as the virus is shed in saliva, tears, genital and other secretions.
- By far the most common form of infection results from a kiss given to a child or adult from a person shedding the virus.
- There are 2 peaks of incidence, the first at 0 - 5 years and the second in the late teens when sexual activity commences.
- About 10% of the population acquires HSV infection through the genital route and the risk is concentrated in young adulthood.
- Following primary infection, 45% of orally infected individuals and 60% of patients with genital herpes will experience recurrences.

90% → Oropharyngeal → More common

Higher recurrence

Pathogenesis and Pathology

- Because HSV causes cytolytic infections, pathologic changes are due to necrosis of infected cells and inflammation
- During the primary infection, HSV spreads locally and a short-lived viraemia occurs. Spread to the craniospinal ganglia (trigeminal or sacral ganglia) through retrograde axonal flow and establishes latency.
- Virus resides in latently infected ganglia in a nonreplicating state and persists for life
- Reactivation/recurrence is triggered by physical or psychological stress, infection, fever, or ultraviolet and sunlight
- The virus transits via axons back to the peripheral site, and replication proceeds at the skin or mucous membranes

Clinical Manifestations

HSV is involved in a variety of clinical manifestations which includes;-

1. Acute gingivostomatitis
2. Herpes Labialis (cold sore) } Most common
3. Ocular Herpes
4. Herpes Genitalis → HSV-2 mostly
5. Meningitis/Encephalitis → Especially in cases of immunosuppression
6. Neonatal herpes Mother to baby

Oral-facial Herpes (HSV-1)

- **Acute Gingivostomatitis**
  - The commonest manifestation of primary herpetic infection.
  - The patient experiences pain and bleeding of the gums. 1 - 8 mm ulcers with necrotic bases are present. Neck glands are commonly enlarged accompanied by fever.
  - Usually a self-limiting disease that lasts around 13 days.
- **Herpes labialis (cold sore)**
  - Following primary infection, 45% of orally infected individuals will experience reactivation.
  - Herpes labialis (cold sore) is a recurrence of oral HSV.
  - A prodrome of tingling, warmth, or itching at the site usually heralds the recurrence. About 12 hours later, redness appears followed by papules and then vesicles. With fluids discharge

Secondary

Cold Sore

Ocular herpes

- HSV infections may occur in the eye, producing severe keratoconjunctivitis
- Recurrent lesions of the eye are common and appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids
- With recurrent keratitis permanent opacification and blindness might occur

Due to cell lysis

Can sometimes be a result of the recurrence of HSV

Genital Herpes (HSV-2)

- Genital herpes is characterized by vesiculoulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female
- lesions are very painful and may be associated with fever, malaise, dysuria, and inguinal lymphadenopathy.
- The lesions of genital herpes are particularly prone to secondary bacterial infection
- 60% of patients with genital herpes will experience recurrences.
- Recurrent lesions in the perianal area tend to be more numerous and persists longer.

Herpes Simplex Encephalitis

Cell lysis of brain cells

- Herpes Simplex meningitis or encephalitis is one of the most serious complications of herpes simplex disease. There are two forms:

1. Neonatal – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100%. Transmission of virus during delivery through infected genital secretions from the mother

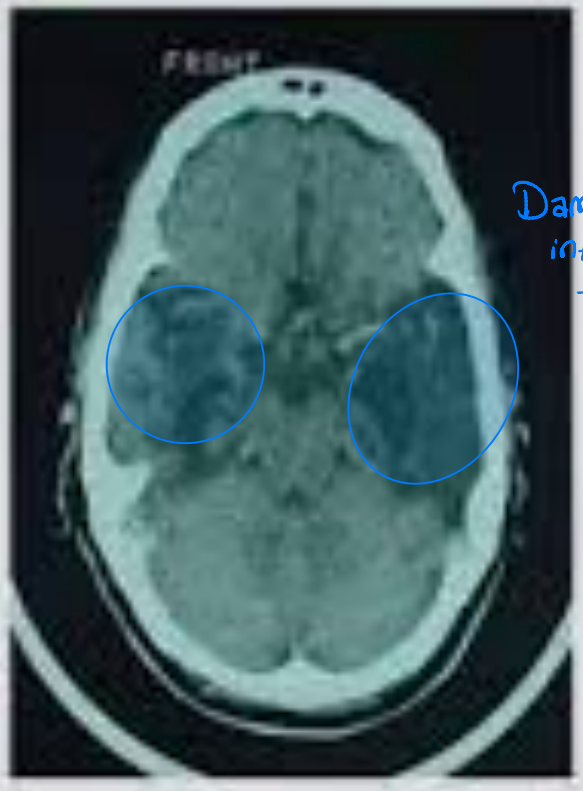
C-section is the solution

2. Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults. It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.

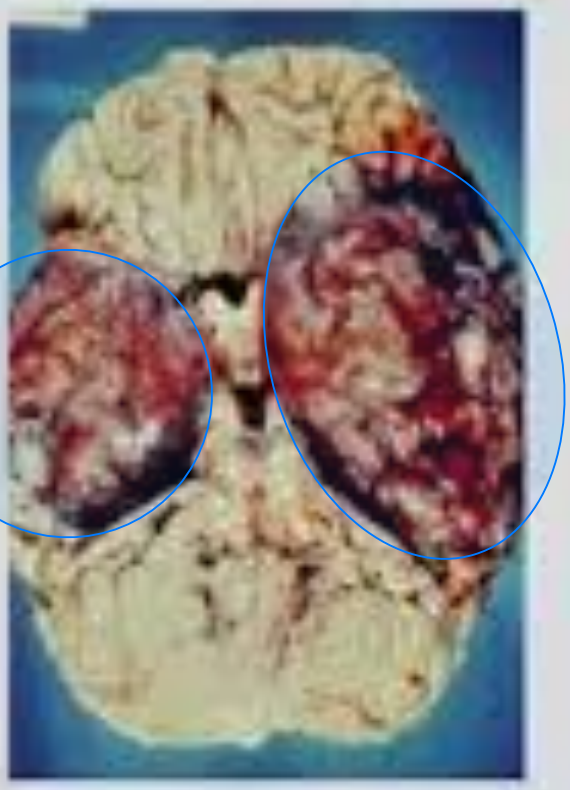
- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given in all cases of suspected HSE before laboratory results are available.

Neurological symptoms are always present

Herpes Simplex Encephalitis



Damaged/ infected tissue



CT Scan

Autopsy

Figure 1

Figure 2

1) CSF Sample → + → reached the brain
2) PCR

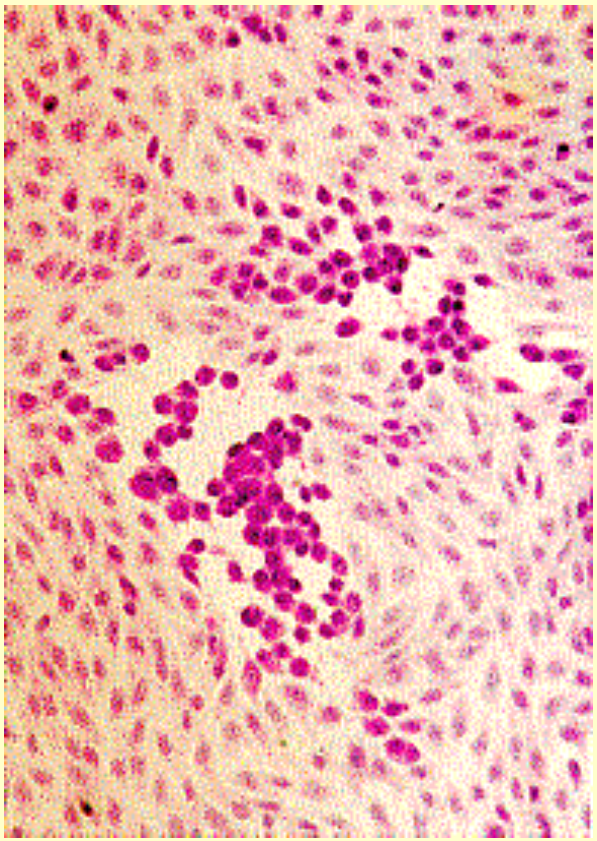
Trigeminal/Sacral → + → Latent but hasn't reached the brain

Laboratory Diagnosis

- Direct Detection
  - Electron microscopy of vesicle fluid - rapid result but cannot distinguish between HSV and VZV
  - Immunofluorescence of skin scrappings - can distinguish between HSV and VZV
  - PCR - now used routinely for the diagnosis of herpes simple encephalitis
- Virus Isolation
  - HSV-1 and HSV-2 are among the easiest viruses to cultivate. It usually takes only 1 - 5 days for a result to be available.
- Serology
  - Not that useful in the acute phase because it takes 1-2 weeks before antibodies appear after infection.

IgM ↑

- Cytopathology
  - Multinucleated giant cells and ballooning of cells. → Necrosis



Cytopathic Effect of HSV in cell culture: Note the ballooning of cells.

Fig. 3, HSV-infected epithelial cell from skin lesion (DFA)

Positive immunofluorescence test for HSV antigen in epithelial cell.

Multinucleated giant cells and ballooning of cells

Management and prevention

- At present, there are only a few indications of antiviral chemo-therapy:

1. the primary infection is especially severe
2. dissemination
3. sight is threatened → Ocular
4. herpes simplex encephalitis → IV acyclovir is a must

* Preventive measures:
1) Hygienic measures
2) Avoid kissing
3) Safe sexual contact

X → Prevent reactivation
↓ Stress UV, ...

Failure of preventing the virus

- Acyclovir – this is the drug of choice.
- Prevention

5. Avoiding contact with individuals with lesions; however, virus may be shed asymptomatically
6. Safe sexual practices
7. Cesarean section delivery to minimize contact of the infant with infected maternal genital secretions

2- Varicella- Zoster Virus (VZV)

Causes chickenpox + shingles

Epidemiology

- Primary varicella is an endemic disease. Varicella is one of the classic diseases of childhood, with the highest prevalence occurring in the 4 - 10 years old age group.
- Varicella is highly communicable, with an attack rate of 90% in close contacts. → isolation is recommended → Can be transmitted before isolation
- Most people become infected before adulthood but 10% of young adults remain susceptible.

Pathogenesis

- The virus is thought to gain entry via the respiratory tract and spreads shortly after to the lymphoid system.
- After an incubation period of 14 days, the virus arrives at its main target organ, the skin. Skin rash → Main clinical manifestation
- Following the primary infection, the virus remains latent in the cerebral or posterior root ganglia. In 10 - 20% of individuals, a single recurrent infection occurs after several decades. 50 years after the primary infection. Recurrence: Shingles
- The virus reactivates in the ganglion and tracks down the sensory nerve to the area of the skin innervated by the nerve, producing a varicellaform rash in the dermatome distribution.

Varicella (chickenpox)

- Primary infection results in varicella (chickenpox)
- Incubation period of 14-21 days
- Presents fever, lymphadenopathy, a widespread vesicular rash.
- The rash appears first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa
- Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles, and crusts may be seen at one time
- The features are so characteristic that a diagnosis can usually be made on clinical grounds alone. No need for any diagnostic tests
- Complications are rare and may include viral pneumonia, encephalitis, and hemorrhagic chickenpox.

Herpes Zoster (Shingles)

- Herpes Zoster mainly affect a single dermatome of the skin.
- It may occur at any age but the vast majority of patients are more than 50 years of age.
- The latent virus reactivates in a sensory ganglion and tracks down the sensory nerve to the appropriate segment.
- There is a characteristic eruption of vesicles in the dermatome which is often accompanied by intensive pain which may last for months (postherpetic neuralgia)
- Herpes zoster affecting the eye and face may pose great problems.
- As with varicella, herpes zoster in a far greater problem in immunocompromised patients in whom the reactivation occurs earlier in life and multiple attacks occur as well as complications.
- Complications are rare and include encephalitis and disseminated herpes zoster.

Eyes are compromised

Skin rash is exactly above the nerve

Extreme pain because nerves are targeted

Post-herpetic neuralgia

Laboratory Diagnosis

The clinical presentations of varicella or zoster are so characteristic that laboratory confirmation is rarely required. Laboratory diagnosis is required only for atypical presentations, particularly in the immunocompromised.

- Virus Isolation - rarely carried out as it requires 2-3.
- Direct detection – electron microscopy for vesicle fluids and immunofluorescence on skin scrappings.
- Serology – The presence of VZV IgM is indicative of a recent primary infection. IgG is indicative of past infection and immunity.
- PCR
- Cytopathology: multinucleated giant cells

Management and prevention

- Uncomplicated varicella is a self-limited disease and requires no specific treatment. However, acyclovir has been shown to accelerate the resolution of the disease.
- Acyclovir should be given promptly to immunocompromised individuals with varicella infection and normal individuals with serious complications such as pneumonia and encephalitis.
- A live attenuated vaccine is available. Recent data suggests that the vaccine is safe usually offered to those above 50 years who got infected
- Where urgent protection is needed, passive immunization should be given. Zoster immunoglobulin (ZIG) is the preparation of choice but it is very expensive.