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Virology

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In this sheet, we will introduce Herpesvirus family, so let's get started:

General view:

Herpesviruses are important viral pathogens with a wide spectrum of diseases (meaning that, having different species induces different diseases).

They are able to **establish lifelong persistent infections** in their hosts and **to undergo periodic reactivation** (the symptoms are similar or different from the disease caused by the primary infection), with serious health complications in case of reactivation in immunosuppressed patient.

Herpesviruses possess a large number of genes, some of which with protein products that are **susceptible to antiviral chemotherapy**.

Some of the members in Herpesviridae family are considered as onco-viruses.

Onco-viruses: Is a virus that is associated with cancer.

The herpesviruses that commonly infect humans include HSV-1, HSV-2, Varicella zoster virus (VZV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV) -causes the kissing disease, herpesviruses 6 and 7, and Kaposi's sarcoma-associated herpesvirus (KSHV).

Herpes B virus of monkeys can also infect humans. There are nearly 100 viruses of the herpes group that infect many different animal species.

Structure:

Herpesviruses share architectural details and are indistinguishable by EM.

Herpes viruses are enveloped, with a very large genome, encoding for large number of enzymes (called potential viral proteins, located in the tegument- that can be targeted by antiviral therapy).

All herpesviruses have a core of ds-DNA (125–240 kbp) that is linear, surrounded by a capsid of icosahedral symmetry with 162 capsomeres. The envelope is derived from the nuclear membrane and contains viral glycoprotein spikes about 8 nm long.

NOTE: all enveloped viruses take their envelope from cytoplasmic membrane except Herpesviridae family, they take their envelope from the cell's nuclear membrane.

Herpesvirus genome is large and encodes at least 100 different proteins. Of these, more than 35 polypeptides are involved in the structure of the virus particle and at least 10 are part of the viral envelope.

Many herpesvirus genes appear to be viral homologs of cellular genes.

Herpesviruses encode an array of virus-specific enzymes involved in nucleic acid metabolism, DNA synthesis, gene expression, and protein regulation (DNA polymerase, helicase-primase, thymidine kinase, transcription factors, protein kinases).

They have a tegument; an area between the envelope and the capsid, filled with viral proteins.

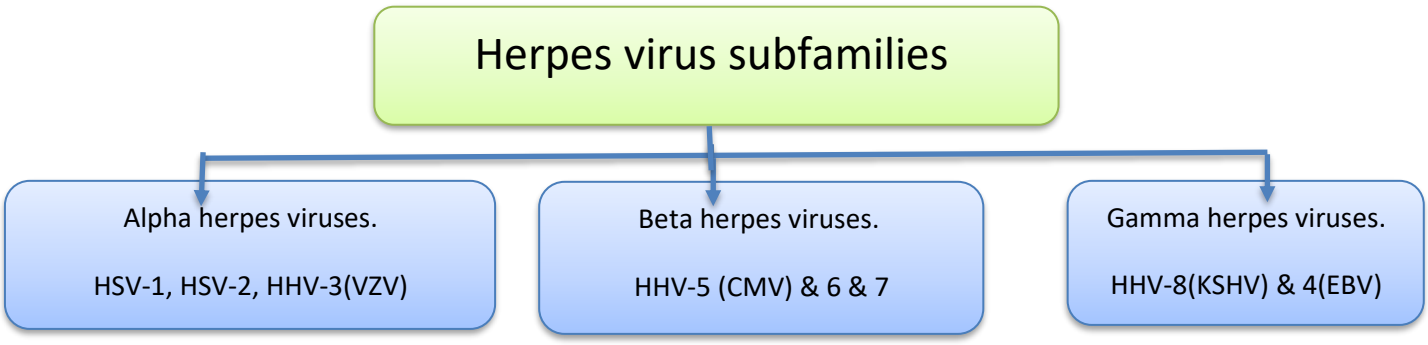
DNA polymerase is targeted by antivirals to stop the replication of the virus. However, this will affect normal cells' replication because they also have DNA polymerase. Virus-specific enzymes come to the rescue, since they are only found in viruses, we can design pro-drugs that are only activated by these viral enzymes (e.g. thymidine kinase), therefore, normal tissue is not affected.

Here are some important properties summarized in this table:

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

Now let's introduce each subfamily with the most important notes mentioned by the doctor:

Herpesviridae family was divided to different subfamilies according to different features that are associated with each, e.g. the clinical manifestations, target cells and the cellular receptors:



1. **α-herpesviruses:** are fast-growing, cytolytic viruses (lyse the cells), that tend to establish latent infections in **neurons**.
2. **β-herpesviruses** are slow-growing and may be cytomegalic (increase in cell size) and become latent in **secretory glands and kidneys.** (HHV-6 is also called the sixth disease).
3. **χ-herpesviruses**, exemplified by Epstein–Barr virus also known as (EBV, HHV 4, Lymphocryptovirus), infect and become latent in lymphoid cells. KSHV, designated as HHV-8, is classified in the Rhadinovirus genus.

There is little antigenic relatedness among members of the herpesvirus group. Only HSV-1 and HSV-2 share a significant number of common antigens. HHV-6 and HHV-7 exhibit a few cross-reacting epitopes. (explained further below).

Side notes:

- In latent infections, the virus resides in latently infected ganglia in a non-replicating state
- It is predicted that viral microRNAs are important in regulating entry into or exit from (or both) the latent phase of the virus life cycle.

And here is another table that introduces some differences between the subfamilies:

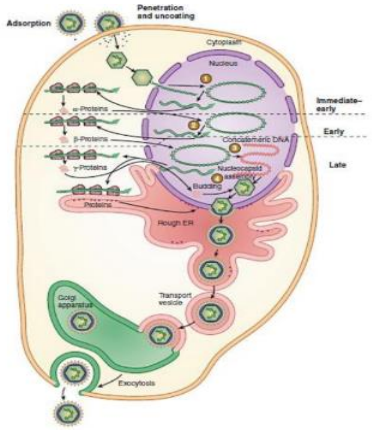
	Biologic Properties			Examples	
Subfamily ("-herpesvirinae")	Growth Cycle and Cytopathology	Latent Infections	Genus ("-*virus*")	Official Name ("Human Herpesvirus")	Common Name
Alpha	Short, cytolytic	Neurons	*Simplex*	1	Herpes simplex virus type 1
				2	Herpes simplex virus type 2
			Varicello	3	Varicella-zoster virus
Beta	Long, cytomegalic	Glands, kidneys	*Cytomegalo*	5	Cytomegalovirus
	Long, lymphoproliferative	Lymphoid tissue	*Roseolo*	6	Human herpesvirus 6
				7	Human herpesvirus 7
Gamma	Variable, lymphoproliferative	Lymphoid tissue	*Lymphocrypto*	4	Epstein-Barr virus
			Rhadino	8	Kaposi sarcoma-associated herpesvirus

Replication of viruses: (details are not required)

common rule for all viruses:

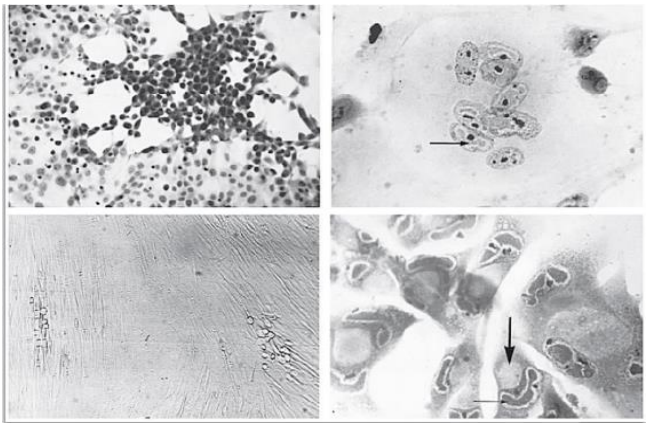
1-early stage of replication that involves the replication of the viral proteins and enzymes that are responsible for replication.

2-late stage, for the replication of the structural proteins.



The cytopathic effects:

We have different methods for diagnosis of viral infections, including molecular diagnosis (PCR), serological methods, culture (that involves the viral isolation).



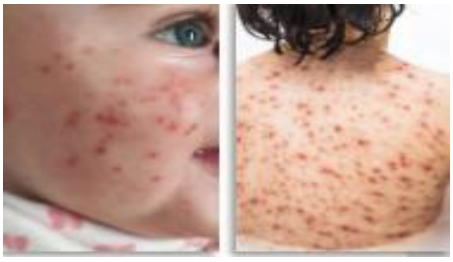
The definitive diagnosis of herpes virus is performed by cell culture and looking for cytopathic effects under the light microscope. (remember we cannot see virus particles with the light microscope, we only see the pathologic effect of the virus on the cells).

Cytopathic effects include ballooning of infected cells, production of Cowdry type A intranuclear inclusion bodies (intracellular because it's a DNA virus, the RNA viruses usually produce inclusion bodies in the cytoplasm where the RNA usually exists), margination of chromatin, and formation of multinucleated giant cells.

Several herpesviruses bind to cell surface glycosaminoglycans, principally **heparansulfate** in addition to co-receptors from the integrins family and immunoglobulins. (details are not required).

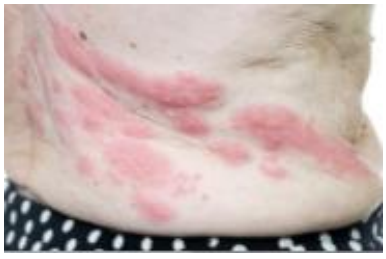
1. **Varicella zoster virus:**

   Varicella (chickenpox) is a mild, highly contagious disease, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes.



(Vesicles are small lesions have a diameter less than 1 cm and filled with clear fluid, whereas the bullae- that are associated with autoimmune diseases- have a diameter of more than 1 cm).

Zoster (shingles) is a sporadic, incapacitating disease of elderly or immunocompromised individuals that is characterized by pain and rash limited in distribution to the skin innervated by a single sensory ganglion (dermatome). The lesions are similar to those of varicella.



Dermatome distribution: is a cutaneous area that is supplied by a single spinal nerve root.

Both diseases are caused by the same virus. Whereas varicella is the acute disease that follows primary contact with the virus, zoster is the response of the partially immune host to reactivation of varicella virus present in latent form in neurons in sensory ganglia.

(Immunity against VZV: Previous infection with varicella can confer lifelong immunity to **varicella.)**

So, if a person does not get chickenpox in his life, he will never get zoster vesicle, because the occurrence of zoster disease is dependent on previous infection with chickenpox.

For HSV-1 & 2, their primary and recurrent infections give the **same** manifestations-vesicles-, while the VZV's primary infection is chickenpox then latency period and the reactivation appears as zoster).

Zoster appear as lesions that spread among 1 dermatome.

About the treatment of the VZV infection:

- Varicella in normal children requires no treatment.
- Neonates and immunocompromised patients with severe infections should be treated.

2. **Herpes simplex virus,** it's the most common in the population. And it actually has two types; 1 and 2.

HSVs are widespread in the human population. They establish latent infections in nerve cells; recurrences are common.

They differ in their mode of transmission. Where HSV-1 is spread by contact, usually involving infected saliva, HSV-2 is transmitted sexually or from a maternal genital infection to a newborn (vertical transmission).

Among viral late gene products, (gpD) is the most potent inducer of neutralizing antibodies. gpC is a complement (C3b)-binding protein, and gpE is an Fc receptor, binding to the Fc portion of immunoglobulin G (IgG).

The site of latency for HSV-1 is the trigeminal ganglia (cranial nerves), explaining why their effects are associated with lesions in oral cavity, head and neck area, whereas HSV-2 is in the sacral ganglia, with manifestations associated with the genital area .

(because of the latency site in the dorsal root ganglia, the disease appears in the skin, since the dorsal root ganglia are sensors).

Pathologic changes are due to necrosis of infected cells with inflammatory response. Lesions induced in the skin and mucous membranes by HSV-1 and HSV-2 are the same and resemble those of VZV. Changes induced by HSV-1 and HSV-2 are similar for primary and recurrent infections.

The age of primary infection in HSV-1 is among young children, while HSV-2 more among adults.

The HSV-1 & 2 are 50% cross-reactive

Cross reactivity: Cross-reactivity between **antigens** occurs when an antibody raised against one specific **antigen** has a competing high affinity toward a different **antigen**. This is often the case when two **antigens** have similar structural regions that the antibody recognizes.

i.e. if you're infected with herpes simplex type 1, obviously you will have antibodies against it, these antibodies can react with 50% of the herpes simplex type 2 antigens.

This cross reactivity can only be found between types 1 and 2 and between 6 and 7 of all the herpes family.

Usually, the primary infection of HSV is asymptomatic; meaning that a virus may, enter your body, replicate, undergo shedding, and even go into latency without you feeling the slightest thing.

NOTE: asymptomatic infections are still contagious to others.

Type 1: most symptoms are observed on the upper part of the body, specifically the face.

oral lesions like cold sores and gingivostomatitis (lesions in oral cavity and gums), pharyngitis, keratoconjunctivitis (infection in the conjunctiva of the eye), keratitis (infection of the cornea).

Type 2: most symptoms are observed on the lower part of the body, specifically the genitals.

Characteristics	HSV-1	HSV-2
Clinical		
Primary infection:		
Gingivostomatitis	+	–
Pharyngotonsillitis	+	–
Keratoconjunctivitis	+	–
Neonatal infections	±	+
Recurrent infection:		
Cold sores, fever blisters	+	–
Keratitis	+	–
Primary or recurrent infection:		
Cutaneous herpes		
Skin above the waist	+	±
Skin below the waist	±	+
Hands or arms	+	+
Herpetic whitlow	+	+
Eczema herpeticum	+	–
Genital herpes	±	+
Herpes encephalitis	+	–
Herpes meningitis	±	+

Transmission:

Infection in type 1 is mainly transmitted by oral secretion or direct contact through epithelial cells of skin and mucous membranes.

For an infection to occur through the skin, we need the epithelial cells to be disturbed by trauma, or anything that causes abrasions. -you know we have micro-abrasions that we cannot see. However, infections through mucous membranes can happen even if they were intact.

Okay, so we said type1 mainly affects the face. But do you think it can cause genital lesions?

Yes, and it's on an increasing trend because of oral-sexual practices.

Here's another one: can type2 cause oral lesions?

Also, yes, but it's highly infrequent compared to type1.

Type2: is really dangerous in pregnant women because it's one of the congenital TORCH diseases.

TORCH: diseases that are transmitted from the mother to the fetus.

T: toxoplasma

O: others (like measles, HIV, syphilis, varicella-zoster)

R: rubella

C: cytomegalovirus (CMV)

H: herpes simplex virus

However, most common is CMV

The HSV growth cycle proceeds rapidly, requiring 8–16 hours for completion

Site of latency: dorsal root ganglia

Type1: trigeminal ganglia, it makes sense because it innervates the face.

Type2: sacral ganglia, because it innervates the genitals obviously.

Clinical manifestations:

Type1: gingivostomatitis, pharyngitis, eczema herpeticum. HSV infection on top of a previous atopic dermatitis will create conventional eczema. Herpetic whitlow (lesions on fingers), is most common in dentists due to direct contact with oral microbes.

The incubation period is very variable in HSV-1, it ranges from 2 days to 12 days, but why??

Because the incubation period depends on the inoculum size (viral dose), the more incubation period the lesser inoculum size and vice versa.

Herpes labialis: starts with pain and erythema around and on the lips, then a papule appears which turns into vesicles and eventually become ulcers that will form crusts.

Pharyngitis: throat infection, 70% caused by viral infections. Herpes type 4 (EBV) and type 5 (CMV) can also cause pharyngitis.

Encephalitis, specifically sporadic (irregular and scattered).

Why sporadic ?? because there's another type which is epidemic encephalitis which is caused by arboviruses; arthropod borne. They're viruses carried by insects and mosquitoes.

Severe keratoconjunctivitis, which appears as dendritic keratitis or corneal ulcers or as vesicles on the eyelids, it can cause blindness. HSV-1 infections are the second cause of corneal blindness in the US.

Can be diagnosed by slit lamp examination; staining the eye which lets the ophthalmologist see the typical ulcers of HSV. Actually, these dendritic ulcers are pathognomonic for herpes simplex keratitis.

Pathognomonic? Means that these signs and symptoms cannot be seen in any other disease; when I see dendritic ulcers, I would say this is definitely HSV keratitis.

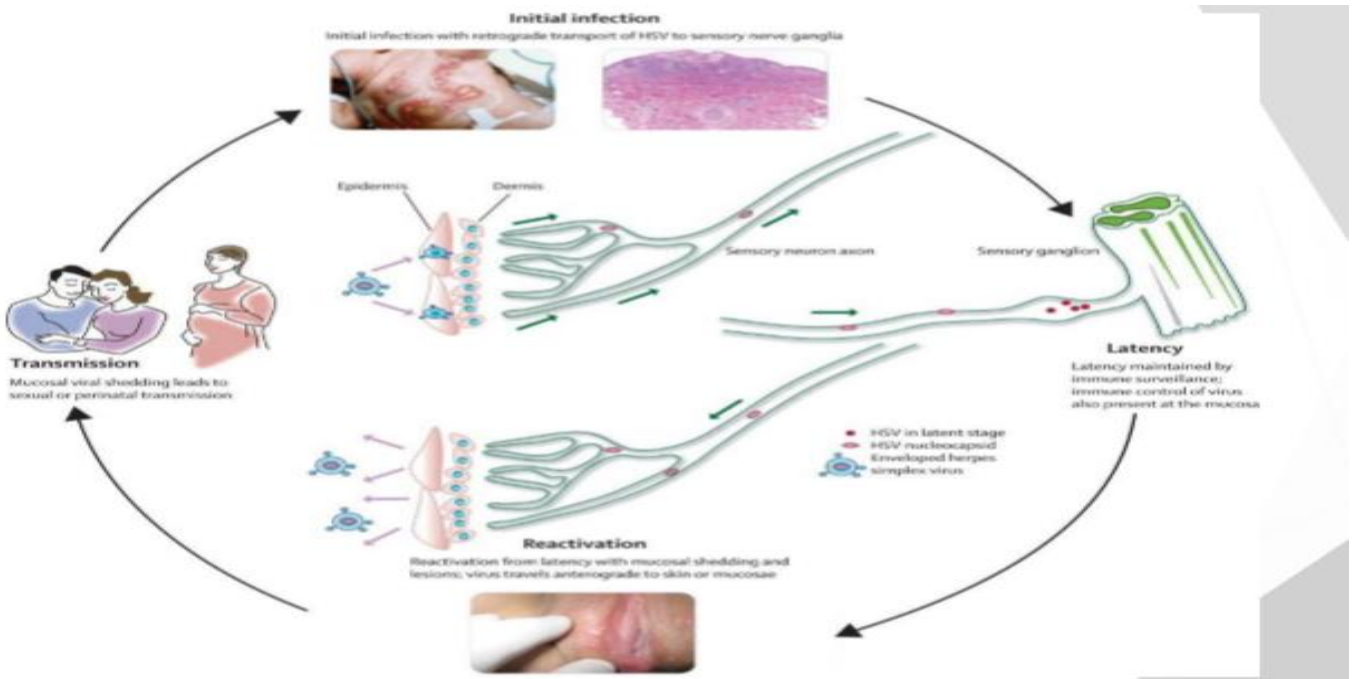
Type2: lesions on the genitals; vulva, vagina, cervix, and perineum in females. On the penis and skin of inguinal area (extragenital) in males. Complications include extragenital lesions (~20% of cases) and aseptic meningitis (~10% of cases).

Meningitis: infection of the protective membranes surrounding the brain and the spinal cord. It can be caused by bacterial infection (septic meningitis) which is really dangerous and fatal. Or by viral infection (aseptic meningitis), the aseptic meningitis has a better outcome and it's less dangerous than that caused by bacteria, and patients will recover completely without any complications.

Pathogenesis:

Upon transmission of the virus, it goes and disturb the epithelial cells (either skin or mucous membranes), then it invades local nerve endings and is transported to dorsal root ganglia by a mechanism called **retrograde axonal flow**, where latency is established.

Provocative stimuli can reactivate virus from the latent state, including axonal injury, fever, physical or emotional stress, and exposure to ultraviolet light. The virus follows axons back to the peripheral site by **anterograde axonal flow**, and replication proceeds at the skin or mucous membranes. Spontaneous reactivations occur despite HSV specific humoral and cellular immunity in the host. However, this immunity limits local viral replication, so that recurrent infections are less extensive and less severe. Which tells you that the primary and secondary manifestations are similar in the HSV infection despite the severity difference.

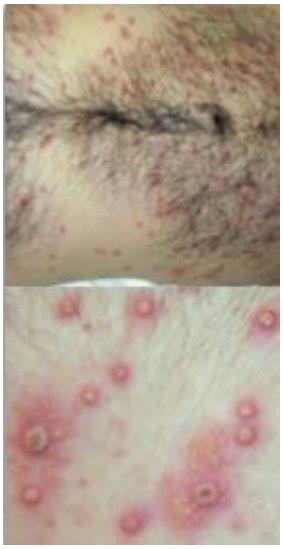


Many recurrences are asymptomatic, reflected only by viral shedding in secretions. Although symptomatic episodes of recurrent HSV-1 infection are usually manifested as cold sores (fever blisters) near the lip, more than 80% of the human population harbor HSV-1 in a latent form, but only a small portion experience recurrence.

HSV-1 infection is considered to be more asymptomatic (sub-clinical) than HSV-2 infection.

Infection in immunocompromised people:

The primary manifestations in immunocompromised people is very rare, most are reactivations. Lesions are usually disseminated all over the body.



It can affect areas other than skin, e.g. respiratory tract, esophagus, and intestinal mucosa.

These pictures were taken from a case study of an AIDS patient, just focus on the fact that it is more disseminated.

Immunity to herpes simplex virus:

The period of greatest susceptibility to primary herpes infection occurs between ages 6 months and 2 years. WHY?

Half-life of antibodies, strictly speaking IgG antibodies is around 3 weeks; so, we need nearly 6 months for all these antibodies to disappear, thus becoming susceptible.

Treatment of herpes simplex viruses:

Several antivirals are effective against HSV infections, including acyclovir, valacyclovir, and vidarabine. All are inhibitors of viral DNA synthesis.

Acyclovir, a nucleoside analog, is monophosphorylated by the **HSV thymidine kinase**. The acyclovir triphosphate is efficiently incorporated into viral DNA by the HSV polymerase, where it then prevents chain elongation.

The drugs may suppress clinical manifestations, shorten time to healing, and reduce recurrences of genital herpes. However, HSV remains latent in sensory ganglia. Drug-resistant virus strains may emerge.

Good luck